NSJ: Spinal Intramedullary Tumor
Special Issue

Neurospine

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Featured Articles

The Posterior Cranial Vertical Line: A Novel Radiographic Marker for Classifying Global Sagittal Alignment
Paul J. Park, Fthimnir M. Hassan, Xavier E. Ferrer... Lawrence G. Lenke

Simultaneous Single-Position Lateral Lumbar Interbody Fusion Surgery and Unilateral Percutaneous Pedicle Screw Fixation for Spondylolisthesis
Hui Lv, Yu Sheng Yang, Jian Hong Zhou... Ze Hua Zhang

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Seung-Ho Seo, Seung-Jae Hyun, Jae-Koo Lee... On Behalf of the Korean Spinal Deformity Society

Outcomes of Surgical Treatment for Patients With Mild Scoliosis and Age-Appropriate Sagittal Alignment With Minimum 2-Year Follow-up
Justin K. Scheer, Justin S. Smith, Peter G. Passias... The International Spine Study Group

The Official Journal of
- ASIA SPINE
- The Korean Spinal Neurosurgery Society
- The Neurospinal Society of Japan
- Taiwan Neurosurgical Spine Society

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Aims and Scope

Neurospine provides spine clinicians and researchers with peer-reviewed articles on basic and clinical investigation of spine and spinal cord to enhance patient management, education, clinical or experimental research, and professionalism. The journal will consider submissions in areas on craniocervical to lumbosacral spine including the followings: neuroscience and pain research, bone and mineral research, disc and joint research, bio and industrial technology, pathophysiology, risk factors, symptomatology, imaging, treatment, rehabilitation of spine, spinal cord and peripheral nerve diseases. Specifically, basic and technology researches include the most influential research papers from all fields of science and technology, revolutionizing what physicians and researchers practicing the art of spinal neurosurgery worldwide know. Thus, we welcome valuable basic and translational technology research articles to introduce cutting-edge research of fundamental sciences and technology in clinical spinal neurosurgery. Clinical or basic research articles, review articles, case reports, technical notes, and letters to the editor written in English will be accepted.

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Publisher Korean Spinal Neurosurgery Society
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Tel: +82-2-585-5455 • Fax: +82-2-523-6812 • Email: ksns1987@gmail.com

Editorial Office
Department of Neurosurgery, CHA Bundang Medical Center, CHA University School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
Tel: +82-31-780-1914 • Fax: +82-31-780-5269 • Email: theneurospine@gmail.com

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From the Editor-in-Chief: Featured Articles in the September 2023 Issue

Inbo Han
Department of Neurosurgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

Among the papers published in the September issue of Neurospine, the featured articles selected by editors are as follows.

“The Posterior Cranial Vertical Line: A Novel Radiographic Marker for Classifying Global Sagittal Alignment” by Park et al.²

The study introduces a new radiographic measurement called the posterior cranial vertical line (PCVL) to better understand global sagittal alignment in adults. A multicenter review of 334 asymptomatic volunteers aged 20–79 was conducted, and the PCVL was classified into 3 grades based on its relation to other anatomical points. Most subjects (83%) were grade 1, followed by grade 2 (15%), and only 3% were grade 3. The study found that higher PCVL grades correlated with aging and specific alignment changes. The PCVL is easy to implement and interpret, and it also incorporates cervical alignment parameters like C2–7 sagittal vertical axis. Overall, the PCVL provides a meaningful marker for assessing global sagittal alignment.

“Simultaneous Single-Position Lateral Lumbar Interbody Fusion Surgery and Unilateral Percutaneous Pedicle Screw Fixation for Spondylolisthesis” by Lv et al.¹

The study compares the effectiveness of 2 surgical methods for treating lumbar spondylolisthesis: lateral lumbar interbody fusion with lateral single screw-rod and unilateral percutaneous pedicle screw fixation (LLIF-LSUP) and minimally invasive transforaminal lumbar interbody fusion with bilateral pedicle screw fixation (MIS-TLIF-BPS). The LLIF-LSUP procedure resulted in shorter operating times, less hospital stay, and lower blood loss compared to MIS-TLIF. Both methods provided significant pain relief, with no statistical differences in visual analogue scale and Oswestry Disability Index (ODI) scores or in complication rates. LLIF-LSUP had advantages in certain postoperative radiographic measurements. The fusion rate was higher for LLIF-LSUP at 3 months but similar to MIS-TLIF at longer follow-up intervals. Overall, both methods yielded satisfactory results with few complications.

“Surgical Outcomes of Symptomatic Intramedullary Spinal Cord Cavernous Malformations: Analysis of Consecutive Cases in a Single Center” Cai et al.³

The study focuses on intramedullary spinal cavernous malformations (ISCMS), rare vascular spinal cord lesions. It examined 29 patients who underwent microsurgical treatment, documenting symptoms, lesion size, and surgical outcomes. Most patients presented with
bowel/bladder dysfunction, followed by sensory deficits and gait issues. Postsurgery, 65.5% improved, 13.8% remained stable, and 20.7% worsened. The annual hemorrhage risk was 2.1% per patient-year. Patients with larger lesions and previous hemorrhages faced increased risk of rehemorrhage. The study concludes that the risk of rehemorrhage is significant in symptomatic ISCM patients.

“Selection of Optimal Lower Instrumented Vertebra for Adolescent Idiopathic Scoliosis Surgery” by Seo et al.4

The study focuses on adolescent idiopathic scoliosis (AIS), a condition affecting about 2% of adolescents. The aim of AIS surgery is to stop curve progression, correct the spinal deformity, and preserve spinal mobility. Despite advancements in surgical algorithms and classification systems, choosing the right fusion level remains a debated issue. The study reviews existing literature on fusion level selection and presents current concepts about selecting the lower instrumented vertebra for AIS surgery.

“Outcomes of Surgical Treatment for Patients With Mild Scoliosis and Age-Appropriate Sagittal Alignment With Minimum 2-Year Follow-up” by Scheer et al.5

The study aimed to assess the surgical outcomes in patients with mild scoliosis and age-appropriate sagittal alignment. A retrospective review of a prospective adult spinal deformity database was conducted, including 151 patients (82.8% women; average age, 56.4 years). The Mild Scoli group (27.8% of the total) had significantly worse baseline leg pain, ODI, and physical composite score scores but showed significant improvement in all health-related quality of life measures 2 years postsurgery. The study concluded that despite a high complication rate, including a 35.7% reoperation rate, patients with mild scoliosis benefited from surgical correction and stabilization at the 2-year follow-up.

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To Seek Appropriate Management for Intramedullary Spinal Cord Tumor: Commentary on Special Issue “Spinal Intramedullary Tumor”

Toshiyuki Takahashi1, Tomoo Inoue2

1Spinal Disorders Center, Fujieda Heisei Memorial Hospital, Fujieda, Japan
2Department of Neurosurgery, Saitama Red Cross Hospital, Oomiya, Japan

Spinal intramedullary tumors are known as one of the most complicated diseases to manage within the central nervous system (CNS). This is because the eloquent area is more concentrated in a small area than that of brain tumors. Therefore, there is a heightened concern for potential risks of neurological sequelae and complications following surgical removal and postoperative adjuvant therapies. Additionally, the lack of definitive evidence compounds the challenge of determining appropriate treatment strategies due to the infrequent occurrence and varied nature of these tumors. The critical factors in surgically removing spinal intramedullary tumors are the histological malignancy of tumors and invasiveness into the spinal cord. In cases of well-circumscribed tumors, complete removal is essential to expect recurrence-free period and increased survival expectancy. Conversely, when dealing with invasive tumors, preserving neurological function takes priority. Various intraoperative support tools and methods have been developed to facilitate the safe and thorough removal of these tumors. These tools include neuromonitoring, echo-imaging, dye-injection, and more. Therefore, surgeons must adopt smart and flexible concepts that carefully balance efficacy and the risk of complications in their surgical management. The necessity of postoperative adjuvant therapy should also be considered.

Recently multicenter studies that have analyzed a large number of cases have provided cumulative data on the prevalence and characteristics of spinal intramedullary tumors.1-3 The updated classification of CNS tumors by World Health Organization in 2021 offers valuable insights for better management of spinal intramedullary tumors based on genetic profiles of the tumors.4 Methylome profiling is a promising new technique for CNS tumor classification, and it has been validated by multiple studies.5-7 Some authors have even suggested that environmental factors, such as socioeconomic status and residential location, can influence the quality of intensive care and treatment facilities.8,9 The accumulation of this knowledge will gradually lead to better management of spinal intramedullary tumors.

This special issue focuses on spinal intramedullary tumor, which still remain relatively unknown and controversial in terms of appropriate management. In particular, this special issue compiles data and provides therapeutic insights for the rarest type of intramedullary tumors. Many of the articles in this special issue present results from the subanalysis of multicenter studies on spinal intramedullary tumors in Japan. These articles are expected to
shed light on appropriate management strategies for these tumors, for which treatment options can be challenging to determine. Another crucial aspect of the surgical treatment of spinal intramedullary tumors is the surgical skill and strategy employed, which have a direct impact on patient outcomes. Surgeons tasked with removing spinal intramedullary tumors must continually be aware of and strive to improve their surgical techniques to achieve excellence.

The management of spinal intramedullary tumors is a complex and challenging task, but recent advances in research have offered new hope for patients. This journal's ongoing series of special issues provides a comprehensive overview of the latest findings and their implications for clinical practice. The findings of these special issues have important implications for the future of research and treatment of spinal intramedullary tumors. By understanding the genetic and molecular basis of these tumors, we can develop more targeted and effective therapies. This will lead to improved outcomes for patients and a better quality of life.

- **Conflict of Interest:** The authors have nothing to disclose.

**REFERENCES**


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Spinal Cord Subependymoma: A Subanalysis of the Neurospinal Society of Japan’s Multicenter Study of Intramedullary Spinal Cord Tumors

Takashi Yagi, Masaki Mizuno, Hiroto Kageyama, Kotaro Tatebayashi, Toshiki Endo, Yasuhiro Takeshima, Motoyuki Iwasaki, Ryu Kurokawa, Keisuke Takai, Misao Nishikawa, Kazutoshi Hida; for the Neurospinal Society of Japan Investigators of Intramedullary Spinal Cord Tumors

Department of Neurosurgery, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan

Department of Minimally Invasive Neurospinal Surgery, Mie University, Mie, Japan

Department of Neurosurgery, Hyogo Medical University, Hyogo, Japan

Division of Neurosurgery, Tohoku Medical and Pharmaceutical University, Sendai, Japan

Department of Neurosurgery, Nara Medical University, Nara, Japan

Department of Neurosurgery, Hokkaido University, Hokkaido, Japan

Department of Neurosurgery, Dokkyo Medical University, Tochigi, Japan

Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan

Department of Neurosurgery, Moriguchi-Ikuno Memorial Hospital, Osaka, Japan

Department of Neurosurgery, Sapporo Azabu Neurosurgical Hospital, Sapporo, Japan

Objective: This study aimed to analyze the clinical characteristics, treatment strategies, and surgical outcomes of subependymoma patients from the 2022 Neurospinal Society of Japan multicenter intramedullary spinal cord tumor study.

Methods: Twenty-six patients with spinal cord subependymoma who were included in the index study of 1,033 patients were retrospectively analyzed.

Results: Mean patient age was 49.4 years. Seventeen patients were men and 9 were women. Sensory disturbance was reported in 22 patients and motor weakness in 18. Median duration of symptoms was 24 months. The tumor was eccentrically located in 19 patients (73.1%) and unilateral in 17 (65.4%). Gross total resection was achieved in 6 patients (23.1%). The same rate for ependymoma patients in the index study was significantly higher (74.8%). Median follow-up was 40.5 months (interquartile range, 18–68 months). In 2 patients who underwent only partial resection, reoperation was required owing to progression 68 and 90 months after surgery, respectively. No recurrence occurred in patients who underwent gross total resection. Five patients experienced neurological worsening after surgery.

Conclusion: Although spinal cord subependymoma can be difficult to distinguish from other intramedullary spinal cord lesions before surgery, it is characterized by an indolent clinical course and eccentric location. Surgical treatment should prioritize functional preservation because the prognosis is good even after subtotal resection.

Keywords: Glioma, Spinal cord neoplasm, Subependymoma, Treatment outcome

INTRODUCTION

Subependymomas are rare, slow-growing, benign central nervous system tumors which predominantly occur in the fourth and lateral ventricles of the brain. Approximately 11% occur in the spinal cord. Only 113 cases of spinal cord subependymoma have been reported since 1954; therefore, data regarding appropriate treatment, surgical outcomes, and long-term prog-
nosis are limited. Although this tumor is a histologically benign lesion and can be cured by complete surgical resection, a surgical strategy that considers the preservation of neurological function is required at the same time. To date, both reports recommending complete resection and safe maximal resection preserving neurological function have been reported, but standard surgical strategies have not been established due to the limited number of patients. In 2022, the Neurospinal Society of Japan (NSJ) published the results of a retrospective multicenter cohort study of patients with intramedullary spinal cord tumors who underwent surgical treatment. We aimed to analyze the clinical characteristics, treatment strategies, and surgical outcomes of the patients from this study who harbored a spinal cord subependymoma.

MATERIALS AND METHODS

The NSJ study was approved by the institutional review board of the Tohoku University Hospital (2021-1-130) and 57 participating centers (listed in Acknowledgments section). The requirement for written informed consent was waived because the study was retrospective in design. Public notification of the study was provided on the websites of the individual centers. Data were recorded from 1,033 consecutive patients who underwent surgical treatment for an intramedullary spinal cord tumor from 2009 to 2020 in 58 facilities across Japan.

For this subanalysis, we retrospectively reviewed the data of 26 patients in the NSJ study who were pathologically diagnosed with subependymoma. Clinical presentation, duration of symptoms, magnetic resonance imaging (MRI) findings, neurological function before surgery, extent of surgical resection, diagnostic accuracy of intraoperative frozen pathology, adjuvant treatment, postoperative neurological function, tumor recurrence or progression, and surgical complications were recorded. Neurological function was assessed using the modified McCormick scale before surgery, immediately after, 6 months after, and at last follow-up (Table 1). The following MRI tumor characteristics were recorded: location and length, signal intensity, and enhancement pattern. Presence of tumor calcification on computed tomography was also recorded.

All tumors were resected via laminectomy using intraoperative neuropathological monitoring. Surgery was performed by 17 surgeons certified by the NSJ from 17 institutions in Japan. Extent of resection was determined by each surgeon and classified as gross total resection (GTR), subtotal resection (STR; defined as ≥ 95% resection), partial resection (PR; defined as < 95% resection), or biopsy (Remove only a piece of tissue for pathological diagnosis). Tumor recurrence was defined as regrowth of the tumor on MRI after GTR. Tumor progression was defined in patients who underwent STR, PR, or biopsy as regrowth on MRI in conjunction with clinical deterioration.

Categorical variables are presented as numbers with percentage and were compared using the chi-square test or Fisher exact test as appropriate; multiple comparisons were performed after factor analysis using the chi-square test. Continuous variables are expressed as means with standard deviation or medians with interquartile range (IQR) and were compared using the t-test or Wilcoxon rank-sum test as appropriate; multiple comparisons were performed after factor analysis using analysis of variance or the Kruskal-Wallis test as appropriate. Statistical analyses were conducted using JMP Pro 16.0 software (SAS Institute Inc., Cary, NC, USA). All test were two-tailed. A p-value of < 0.05 was considered significant.

RESULTS

1. Patient Characteristics

Patient characteristics are shown in Table 2. Seventeen patients were men and 9 were women. Median age was 49.4 years (range, 21–75 years). Median duration of symptoms was 24 months (IQR, 8.25–120 months). The most common symptoms were numbness in 22 patients (84.6%), motor weakness in 18 (69.2%), gait disturbance in 16 (61.5%), and pain in 13 (50%). Seven patients (26.9%) reported back pain and 7 reported bladder and/or bowel dysfunction. Modified McCormick grade at presentation was as follows: grade I, 5 patients; grade II, 9 patients; grade III, 9 patients; and grade IV, 3 patients. Median follow-up was 40.5 months (IQR, 18–68 months).

2. Radiological Findings

Radiological findings are summarized in Table 3. Tumor location was cervical spine in 10 patients, cervicothoracic in 6,
Table 2. Summary of demographics and clinical presentations of 26 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)/sex</th>
<th>Duration of symptom (mo)</th>
<th>Presentation</th>
<th>Surgical methods</th>
<th>McCormick grade</th>
<th>F/U (mo)</th>
<th>Recurrence or progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36/M</td>
<td>3</td>
<td>Leg pain and numbness, bilateral leg weakness, bladder dysfunction</td>
<td>Biopsy</td>
<td>Pre 2 Post 2 6M 2 Last 40</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>53/F</td>
<td>3</td>
<td>Back pain, upper limb numbness</td>
<td>Biopsy</td>
<td>Pre 1 Post 4 6M 3 Last 93</td>
<td>93</td>
<td>Progression, 90 months reoperation</td>
</tr>
<tr>
<td>3</td>
<td>37/F</td>
<td>156</td>
<td>Upper limb numbness and pain, leg weakness</td>
<td>PR</td>
<td>Pre 3 Post 3 6M 4 Last 40</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>71/M</td>
<td>120</td>
<td>Bil-lower limb numbness</td>
<td>PR</td>
<td>Pre 2 Post 2 6M 2 Last 60</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
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<td>42/M</td>
<td>60</td>
<td>Upper limb numbness, leg weakness, bladder dysfunction</td>
<td>PR</td>
<td>Pre 4 Post 4 6M 3 Last 97</td>
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<td>-</td>
</tr>
<tr>
<td>6</td>
<td>57/F</td>
<td>10</td>
<td>Leg pain and weakness</td>
<td>PR</td>
<td>Pre 3 Post 3 6M 3 Last 6</td>
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<td>-</td>
</tr>
<tr>
<td>7</td>
<td>67/M</td>
<td>1</td>
<td>Leg numbness</td>
<td>PR</td>
<td>Pre 1 Post 1 6M 1 Last 16</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>31/M</td>
<td>108</td>
<td>Leg numbness and weakness, gait disturbance</td>
<td>PR</td>
<td>Pre 3 Post 3 6M 3 Last 99</td>
<td>99</td>
<td>Progression, 68 months reoperation</td>
</tr>
<tr>
<td>9</td>
<td>30/M</td>
<td>24</td>
<td>Upper limb numbness, leg weakness, bladder dysfunction</td>
<td>PR</td>
<td>Pre 3 Post 3 6M 2 Last 16</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>50/F</td>
<td>120</td>
<td>Upper limb pain and numbness, leg weakness, bladder dysfunction</td>
<td>PR</td>
<td>Pre 3 Post 3 6M 3 Last 34</td>
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<tr>
<td>11</td>
<td>61/F</td>
<td>24</td>
<td>Limb pain and numbness, leg weakness</td>
<td>PR</td>
<td>Pre 3 Post 3 6M 3 Last 108</td>
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<td>-</td>
</tr>
<tr>
<td>12</td>
<td>57/M</td>
<td>12</td>
<td>Leg pain and numbness</td>
<td>STR</td>
<td>Pre 1 Post 4 6M 3 Last 13</td>
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<td>-</td>
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<tr>
<td>13</td>
<td>75/F</td>
<td>192</td>
<td>Leg weakness, gait disturbance</td>
<td>STR</td>
<td>Pre 3 Post 3 6M 3 Last 27</td>
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<td>-</td>
</tr>
<tr>
<td>14</td>
<td>66/M</td>
<td>192</td>
<td>Upper limb numbness and pain, leg weakness</td>
<td>STR</td>
<td>Pre 3 Post 3 6M 3 Last 42</td>
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<tr>
<td>15</td>
<td>32/M</td>
<td>12</td>
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<td>STR</td>
<td>Pre 3 Post 3 6M 3 Last 19</td>
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<tr>
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<td>46/M</td>
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<td>STR</td>
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<tr>
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<td>66/M</td>
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<td>Leg numbness and gait disturbance, bladder dysfunction</td>
<td>STR</td>
<td>Pre 4 Post 4 6M 4 Last 12</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>21/M</td>
<td>15</td>
<td>Leg numbness and weakness</td>
<td>STR</td>
<td>Pre 1 Post 3 6M 1 Last 60</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>48/M</td>
<td>120</td>
<td>Upper limb numbness and weakness</td>
<td>STR</td>
<td>Pre 2 Post 2 6M 2 Last 127</td>
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<tr>
<td>20</td>
<td>43/M</td>
<td>96</td>
<td>Leg weakness and gait disturbance</td>
<td>STR</td>
<td>Pre 2 Post 4 6M 3 Last 36</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>64/M</td>
<td>12</td>
<td>Back pain and numbness</td>
<td>GTR</td>
<td>Pre 2 Post 2 6M 2 Last 92</td>
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<tr>
<td>22</td>
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<td>GTR</td>
<td>Pre 2 Post 2 6M 2 Last 32</td>
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</tr>
<tr>
<td>23</td>
<td>53/F</td>
<td>12</td>
<td>Upper limb pain and numbness</td>
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<td>GTR</td>
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<td>Upper limb pain and weakness</td>
<td>GTR</td>
<td>Pre 1 Post 2 6M 2 Last 17</td>
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<td>-</td>
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<tr>
<td>26</td>
<td>35/M</td>
<td>120</td>
<td>Leg pain and weakness, bladder dysfunction</td>
<td>GTR</td>
<td>Pre 2 Post 3 6M 2 Last 60</td>
<td>60</td>
<td>-</td>
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6M, 6 months; F/U, follow-up; GTR, gross total resection; PR, partial resection; STR, subtotal resection.
Table 3. Summary of radiological findings of 26 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Level</th>
<th>Length (mm)</th>
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<th>MRI findings</th>
<th>Calcification on CT</th>
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<td>Iso</td>
<td>High Heterogeneous</td>
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<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>C0–T5</td>
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<td>Iso</td>
<td>Iso Heterogeneous</td>
<td>Solid</td>
</tr>
<tr>
<td>4</td>
<td>C3–4</td>
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<td>Iso</td>
<td>High Heterogeneous</td>
<td>Mixed</td>
</tr>
<tr>
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<td>C4–6</td>
<td>23</td>
<td>Lateral</td>
<td>Iso</td>
<td>High Heterogeneous</td>
<td>Solid</td>
</tr>
<tr>
<td>6</td>
<td>T11–12</td>
<td>35</td>
<td>Lateral</td>
<td>Iso</td>
<td>High Poor</td>
<td>Mixed</td>
</tr>
<tr>
<td>7</td>
<td>T10–11</td>
<td>36</td>
<td>Lateral</td>
<td>Iso</td>
<td>High Heterogeneous</td>
<td>Solid</td>
</tr>
<tr>
<td>8</td>
<td>C5–T5</td>
<td>122</td>
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<td>Iso</td>
<td>High Heterogeneous</td>
<td>Solid</td>
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<tr>
<td>9</td>
<td>C4–T3</td>
<td>100</td>
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<td>High Poor</td>
<td>Solid</td>
</tr>
<tr>
<td>10</td>
<td>C1–4</td>
<td>26</td>
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<td>Iso</td>
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<td>Solid</td>
</tr>
<tr>
<td>11</td>
<td>C2–T2</td>
<td>110</td>
<td>lateral</td>
<td>Iso</td>
<td>High Poor</td>
<td>Solid</td>
</tr>
<tr>
<td>12</td>
<td>T6–7</td>
<td>26</td>
<td>Lateral</td>
<td>Low</td>
<td>Iso Heterogeneous</td>
<td>Solid</td>
</tr>
<tr>
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<td>107</td>
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<tr>
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<td>Lateral</td>
<td>Iso</td>
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</tr>
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<tr>
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<td>Low</td>
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<td>Solid</td>
</tr>
<tr>
<td>17</td>
<td>T6–10</td>
<td>91</td>
<td>Lateral</td>
<td>Iso</td>
<td>High Heterogeneous</td>
<td>Solid</td>
</tr>
<tr>
<td>18</td>
<td>T11–12</td>
<td>63</td>
<td>Dorsal</td>
<td>Low</td>
<td>High Poor</td>
<td>Solid</td>
</tr>
<tr>
<td>19</td>
<td>C2–6</td>
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<td>Iso</td>
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<td>Solid</td>
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<td>Mixed</td>
</tr>
<tr>
<td>21</td>
<td>T1</td>
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<td>Cystic</td>
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<td>C2–3</td>
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<td>Iso</td>
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</tr>
<tr>
<td>23</td>
<td>C7–T1</td>
<td>27</td>
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<td>Low</td>
<td>High Poor</td>
<td>Solid</td>
</tr>
<tr>
<td>24</td>
<td>T12–L1</td>
<td>63</td>
<td>Central</td>
<td>Low</td>
<td>High Poor</td>
<td>Mixed</td>
</tr>
<tr>
<td>25</td>
<td>C5–7</td>
<td>34</td>
<td>Lateral</td>
<td>Iso</td>
<td>High Poor</td>
<td>Solid</td>
</tr>
<tr>
<td>26</td>
<td>T5–9</td>
<td>145</td>
<td>Central</td>
<td>Iso</td>
<td>High Heterogeneous</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; Gd, gadolinium (+); CT, computed tomography; Dx., diagnosis; NA, not available.

and thoracic in 10. Median tumor length was 60.5 mm (IQR, 26.8–101.8 mm). The tumor was located centrally in the spinal cord in 7 patients (26.9%) and eccentrically in 19 (73.1%). Seventeen tumors were unilateral (65.3%). Tumor signal was iso- to hypointense on T1-weighted imaging (T1WI); 18 tumors (69.2%) were isointense. On T2-weighted imaging (T2WI), the tumor signal was iso- to hyperintense; 24 tumors (92.3%) were hyperintense. Gadolinium enhancement was poor in 13 tumors (50%) and partial or slight in 13 (50%). Tumor consistency based on MRI was solid in 18, mixed in 7, and cystic in 1. Only 15 tumors (57.7%) were diagnosed as subependymoma before surgery. Three of the 7 centrally located tumors (42.9%) and 12 of the 17 unilateral tumors (70.6%) were correctly diagnosed as subependymoma before surgery. Among the 11 tumors that were not correctly diagnosed before surgery, 4 were diagnosed as astrocytoma and 2 as ependymoma.

3. Surgical Findings

Median surgeon experience was 30 years (IQR, 23–34.3 years). Extent of resection was GTR in 6 patients (23.1%), STR in 9, PR in 9, and biopsy in 2.

4. Postoperative Neurological Function

Fig. 1 shows time course of modified McCormick scale by extent of resection. Modified McCormick grade improved after surgery in 2 patients who underwent GTR. Postoperative worsening occurred in 6 patients overall (23.1%). By extent of resection, postoperative worsening occurred in 2 of the 6 patients...
Surgical Outcomes of Spinal Cord Subependymoma

who underwent GTR (33.3%), 3 of the 9 who underwent STR (33.3%), and 1 of 2 who underwent biopsy. All 9 patients who underwent PR experienced no postoperative neurological deterioration. The only postoperative complication was a single case of cerebrospinal fluid leakage. No patient received additional radiotherapy for residual tumor. Compared with that before surgery, the modified McCormick grade 6 months after surgery improved in 4 patients (2 of the 9 patients who underwent PR and 2 of the 6 patients who underwent GTR) and worsened in 5 (1 of the 2 who underwent biopsy, 1 of the 9 who underwent PR, 2 of the 9 who underwent STR, and 1 of the 6 who underwent GTR).

Compared with that 6 months after surgery, the modified McCormick scale at last follow-up had improved in 4 patients, worsened in 5, and remained unchanged in 17. Neurological outcome 6 months after surgery did not significantly differ based on neurological function before surgery (modified McCormick grade ≤ 2 vs. grade ≥ 3), tumor size (< 3 cm vs. ≥ 3 cm), location (cervical vs. other), nor extent of surgical resection (GTR vs. other). However, the proportion of patients who experienced neurological improvement 6 months after surgery was significantly higher in patients with preoperative bladder and/or bowel dysfunction than in those who did not (42.9% vs. 5.3%; crude odds ratio, 13.5; 95% confidence interval, 1.1–166, p = 0.047) (Table 4).

Three patients required multiple surgeries. Case 2 initially underwent biopsy and laminoplasty but the residual tumor grew 90 months later and was partially resected. Case 3 had a tumor extending from the pons to T5 and resection was performed in 2 stages 4 months apart. In case 8, neurological function remained stable after PR of a tumor extending from C5 to T5; reoperation was required 5.5 years later because of progression.

5. Pathological Findings

Intraoperative frozen-section pathology was performed in 18 cases (69.2%). The frozen section and final pathological diagnoses agreed in 9 (50%). Among the 9 cases in which these diagnoses differed, the frozen-section diagnosis was nonspecific (e.g., low-grade glioma) in 8 and 1 was incorrectly diagnosed as ependymoma. The Ki-67 labeling index was measured in 22 tumors and was less than 1% in 18.

6. Illustrative Cases

1) Case 24

A 40-year-old woman presented with a 1-month history of progressive back pain and bilateral leg numbness. Neurological examination showed 4+/5 strength on manual muscle testing in both lower extremities and bladder and bowel dysfunction. Modified McCormick grade was IV. MRI revealed a centrally located intramedullary mass lesion with 63 mm long in the spi-
Table 4. Prognostic factors for neurological function 6 months after surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subependymoma</th>
<th></th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 26)</td>
<td>Improved (n = 4)</td>
<td>Stable (n = 17)</td>
<td>Worsened (n = 5)</td>
<td></td>
</tr>
<tr>
<td>Preoperative neurological findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Modified MS grade I/II</td>
<td>14 (53.9)</td>
<td>1 (25)</td>
<td>9 (52.9)</td>
<td>4 (80)</td>
<td></td>
</tr>
<tr>
<td>Modified MS grade III/IV/V</td>
<td>12 (46.2)</td>
<td>3 (75)</td>
<td>8 (47.1)</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>7 (26.9)</td>
<td>2 (50)</td>
<td>4 (23.5)</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>19 (73.1)</td>
<td>2 (50)</td>
<td>13 (76.5)</td>
<td>4 (80)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Cervical lesion</td>
<td>10 (38.5)</td>
<td>1 (25)</td>
<td>8 (47.1)</td>
<td>1 (20)</td>
<td></td>
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<tr>
<td>Noncervical lesion</td>
<td>16 (61.5)</td>
<td>3 (75)</td>
<td>9 (52.9)</td>
<td>4 (80)</td>
<td></td>
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<td>The extent of surgical resection</td>
<td></td>
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<td>0.38</td>
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<tr>
<td>GTR</td>
<td>6 (23.1)</td>
<td>2 (50)</td>
<td>3 (17.7)</td>
<td>1 (20)</td>
<td></td>
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<tr>
<td>Non-GTR</td>
<td>20 (76.9)</td>
<td>2 (50)</td>
<td>14 (82.4)</td>
<td>4 (80)</td>
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<tr>
<td>Preoperative appearance of bladder and bowel dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04**</td>
</tr>
<tr>
<td>Bladder and bowel dysfunction</td>
<td>7 (26.9)</td>
<td>3 (75)</td>
<td>4 (23.5)</td>
<td>0</td>
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<tr>
<td>Nonbladder and bowel dysfunction</td>
<td>19 (73.1)</td>
<td>1 (25)</td>
<td>13 (76.5)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).
MS, McCormick scale; GTR, gross total resection.
*p < 0.05, statistically significant differences.

Fig. 2. Preoperative magnetic resonance imaging in case 24 showed an intramedullary mass with cystic component at T12-L1. The mass was hypointense on T1-weighted images (A) and exhibited partial enhancement (B). (C) It was hyperintense on T2-weighted images. (D) Axial T2-weighted images showed a centrally located intramedullary cystic mass. (E) Sagittal T2-weighted imaging 6 months after surgery demonstrated complete removal.

Nal cord extending from T12 to L1. The lesion was hypointense on T1WI and hyperintense on T2WI. An area of focal enhancement was noted in the cranial portion (Fig. 2). The patient underwent T12 and L1 laminectomies for resection using a midline approach. The tumor contained cystic components and extended posteriorly and laterally from the central canal. The dissection plane was relatively clear. The intraoperative frozen pathology diagnosis was pilocytic astrocytoma. After the opera-
tion, her paraplegia was relieved but the sensory disturbance persisted; she was able to walk independently. The final histopathological diagnosis was subependymoma. In over 9 years of follow-up, she has remained recurrence-free and her neurological function has remained modified McCormick grade II.

2) Case 19

A 48-year-old man presented with a 10-year history of low back pain followed by numbness of the right leg. Six months being referred to our hospital, the patient developed neck pain, numbness and muscle weakness of the left arm. MRI showed an eccentric intramedullary mass extending longitudinally from C2 to C6 with 80 mm long. The lesion was isointense on T1WI and hyperintense on T2WI with poor gadolinium enhancement (Fig. 3). Neurological examination showed muscle weakness involving the left arm and leg. Modified McCormick scale was II. The patient was diagnosed with subependymoma based on the gradually progressive clinical course and the specific radiological findings.

After C1 laminectomy and C2–7 laminotomy, the tumor was removed in a piecemeal fashion via the left dorsal root entry zone under motor evoked potential monitoring. The solid tumor extended from the central to the left lateral side. The tumor was elastic and demarcated; however, multiple small feeders from the pia mater precluded GTR. After maximal resection while preserving neurological function under monitoring, the surgery was aborted in STR because the intraoperative frozen-section diagnosis was subependymoma. Postoperatively, the patient developed weakness in the left deltoid and biceps muscles and thermohypesthesia in the trunk on the right side. The left deltoid muscle weakness and thermohypesthesia partially recovered but the biceps muscle weakness did not. The permanent section diagnosis was subependymoma. In the 127 months of follow-up, there has been no tumor progression and the pa-
tient has remained independent with modified McCormick scale II.

**DISCUSSION**

1. **Patient Characteristics**

Central nervous system subependymoma accounts for less than 1% of all intracranial tumors. Spinal cord subependymoma is even rarer—only 113 surgical cases have been reported to date in numerous case reports and series. Subependymomas are more common in middle-aged men in the fourth decade of life (mean age, 46 years) and frequently occur in the fourth and lateral ventricles. In 2 recent case series of spinal cord subependymoma, most patients were men in their 40s and cervical and cervicothoracic sites were most common. In this series of 26 subependymoma patients from the 2022 NSJ study of intramedullary spinal cord tumors, the male-to-female ratio was 1.9:1, mean age was 49.4 years, and 65.4% of tumors were located in the cervical or cervicothoracic cord, consistent with previous reports. The corresponding values for patients with spinal ependymoma (1.2:1, 50.9 years, and 69.5%, respectively) and spinal astrocytoma (1.5:1, 43.9 years, and 55.2%, respectively) in the NSJ study were similar. However, mean duration of symptoms was significantly longer in subependymoma patients (57.7 months) than patients with ependymoma (25.2 months, \( p < 0.001 \)) or astrocytoma (14.9 months, \( p < 0.001 \)). Analysis of our study indicated that subependymoma is the slowest growing among all intramedullary spinal cord gliomas.

In the patients of this series, numbness in the extremities was the most frequent symptom (84.6%), followed by motor paralysis (69.2%), and gait disturbance (61.5%), which is consistent with previous case series. However, modified McCormick grade before surgery was I or II in almost all patients in 2 of these series; in contrast, modified McCormick grade was I or II in slightly more than half of patients in this series.

2. **Radiological Findings Before Surgery**

An accurate preoperative diagnosis based on MRI findings and clinical course is helpful when selecting the surgical strategy for treatment of an intramedullary spinal cord tumor. Spinal cord subependymoma is iso- to hypointense on T1WI, hyperintense on T2WI, and poorly or partially enhances. Because these findings are similar to those of ependymoma, the 2 are difficult to distinguish. However, subependymoma is frequently located eccentrically and rarely calcifies, which can aid with differentiation. In this series, 18 subependymomas (69.2%) were isointense on T1WI, 24 (92.3%) were hyperintense on T2WI, and half poorly enhanced. Furthermore, location was eccentric in 19 (73.0%), and calcifications were present in only 3 of the 23 cases (13.0%) in which computed tomography was performed. Despite these characteristic findings, only 57.7% were correctly diagnosed with subependymoma before surgery. Diagnostic accuracy was 63.2% in tumors with eccentric location and 42.9% in those located centrally. The low accuracy may be explained by the rarity of subependymoma and the fact that other intramedullary lesions appear similar on MRI. To improve diagnostic accuracy for subependymoma, clinicians should consider both clinical course and lesion location.

3. **Intraoperative Frozen Pathology**

Subependymomas are histologically benign and classified as World Health Organization grade 1. Histological features that distinguish it from ependymoma or astrocytoma are: (1) well-demarcated and multinodular mass; (2) low or moderate cellularity; (3) microlobular pattern; and (4) small clusters of neoplastic cells. Ependymomas are classified as grade 2 and characterized by perivascular pseudorosettes with long fibrillary processes. Because the extent of surgical resection is associated with progression-free survival in patients with ependymoma, accurate intraoperative diagnosis with frozen pathology is ideal. Previously reported accuracy rates of intraoperative diagnosis for spinal cord ependymoma and astrocytoma are 72% and 71%, respectively, which are considerably lower than those for brain tumors (83%–97%). In this study, the accuracy rate was only 50%, which is even lower. One tumor was incorrectly diagnosed as ependymoma and 8 were rendered a nonspecific diagnosis, such as low-grade glioma. Possible reasons for the low accuracy rates include frozen-section artifact, small sample size, and limited pathologist experience with subependymoma. In this study, GTR was achieved in only 22.2% of the tumors correctly diagnosed as subependymoma during surgery. The reasons for the low GTR rate include poorly defined tumor-spinal cord interface and tumor location near the pyramidal tract. Surgeons should consider that the accuracy of intraoperative diagnosis for intramedullary spinal cord tumors is low when selecting surgical strategy.

4. **Surgical Strategy and Outcomes**

Surgical excision of subependymoma is expected to result in good clinical outcomes with low risk of recurrence or progression. Radiation is not recommended as adjuvant therapy. The basic surgical strategy for spinal cord subependymoma is to re-
Surgical Outcomes of Spinal Cord Subependymoma

In a series of 6 patients with spinal cord subependymoma in whom GTR was achieved, Jallo et al. reported neurological deterioration in all; however, 5 recovered within 6 months. They recommend aggressive surgical excision because GTR is expected to be curative. However, Yuh et al. reported their experience with 10 surgical cases and noted that the tumor did not always detach easily from the spinal cord and only half could be completely resected. Because subependymoma is an indolent tumor, they recommended that preservation of neurological function should be prioritized and that STR is a reasonable option. In this series of subependymoma patients from the 2022 NSJ study, GTR was achieved in only 23.1%, which was higher than 10.7% in astrocytoma patients but significantly lower than the 74.8% rate achieved in the ependymoma patients. Among the 6 GTR cases, the tumor was centrally located in 3. Only 3 of the 19 eccentrically located tumors were completely resected. As described above, the tumor in case 24 progressed from the central canal toward the posterior columns with minimal invasion of the anterior and lateral columns and was completely resected. In addition, the tumor's cystic component and clear demarcation from the spinal cord were factors that contributed to the favorable outcome. In contrast, in case 19, the longitudinally extensive eccentric tumor with multiple small feeders precluded GTR; therefore, the resection was limited to preserve neurological function. One of the probable reasons for the low spinal subependymoma GTR rate is tumor location or extension adjacent to the pyramidal tract. The extent of resection must be restricted to preserve neurological function.

Neurological function before surgery, tumor extension, and extent of resection are factors reportedly associated with functional outcome in patients with spinal ependymoma. In this study, preoperative neurological function and tumor extension were not associated with better functional outcome 6 months after surgery; however, preoperative bladder and/or bowel dysfunction was. It is not possible to clarify why the presence of preoperative bladder and bowel dysfunction is associated with favorable surgical outcomes, as multiple factors may be involved. One speculation is that cases with bladder and bowel dysfunction in this series were younger (42.7 years vs. 51.9 years) and had shorter duration of symptoms (47 months vs. 61.7 months) than those without bladder and bowel dysfunction, which may have contributed to postoperative good recovery. Based on the results of our study, early surgical excision is recommended for spinal subependymoma cases with bladder and bowel dysfunction because functional improvement can be expected with surgery.

In this series, recurrence did not occur in any of the patients in whom GTR was achieved (mean follow-up, 60 ± 37.3 months), indicating that resection is curative. In 2 patients who underwent PR and biopsy, respectively, progression occurred after 68 and 90 months, respectively, and re-resection was indicated. Both patients recovered to their preoperative state. Five patients experienced neurological worsening after surgery and 4 of these had improved at last follow-up; however, functional outcome did not significantly differ between GTR and lesser extents of resection. Favorable long-term outcome after STR has also been reported for spinal subependymoma in another study. We recommend aiming for GTR but not at the cost of causing loss of neurological function, which should be monitored electrophysiologically during surgery. For tumors with a poorly defined tumor-spinal cord interface, STR or less is acceptable to avoid the risk of causing a neurological deficit. Because radiotherapy is not recommended for residual subependymoma, careful follow-up is necessary after partial removal. A second surgery should be considered if progression occurs.

5. Study Limitations

The major limitations of this study include its small sample size and relatively short follow-up period. In addition, because it was retrospective in design and included data from patients treated in 58 centers, the experience and skill of the numerous radiologists, pathologists, and surgeons involved was variable. Furthermore, the particular experience of these individual physicians and surgeons with spinal cord subependymoma is limited because it is so rare. Because this study comprises the largest case series reported to date and all patients were diagnosed and treated by experienced surgeons certified by the NSJ, we are convinced that it will be useful for guiding diagnosis and treatment of patients with spinal subependymoma.

CONCLUSION

Spinal cord subependymoma is an indolent tumor which is frequently located eccentrically, a characteristic that is useful to differentiate it from other intramedullary spinal cord tumors. Although GTR is curative and should be the aim of surgical treatment, many subependymomas are not completely resectable without causing a neurological deficit. PR to preserve neurological function is acceptable in cases in which the tumor-spinal cord interface is poorly defined.
NOTES

Conflict of Interest: The authors have nothing to disclose.

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ORCID
Takashi Yagi: 0000-0002-5162-3959
Masaki Mizuno: 0000-0002-1761-344X
Hiroti Kageyama: 0000-0002-6796-9313
Kotaro Tatebayashi: 0000-0003-2239-0102
Toshiki Endo: 0000-0002-5609-200X
Yasuhiro Takeshima: 0000-0002-5438-6098
Motoyuki Iwasaki: 0000-0001-5401-0325
Ryu Kurokawa: 0000-0002-8336-8366
Keisuke Takai: 0000-0002-7439-9849
Misao Nishikawa: 0000-0002-0808-390X
Kazutoshi Hida: 0000-0003-4789-8375

REFERENCES


Intramedullary Schwannoma of the Spinal Cord: A Nationwide Analysis by the Neurospinal Society of Japan

Takeshi Hara1,2, Masaki Mizuno3, Kazutoshi Hida4, Toru Sasamori4, Yasuyuki Miyoshi5, Hisaaki Uchikado6, Hiroki Ohashi7, Taku Sugawara8, Yasuhiro Takeshima9, Yukoh Ohara1,2, Akhide Kondo2, Toshiki Endo10; for the Investigators of Intramedullary Spinal Cord Tumors in the Neurospinal Society of Japan

Objective: This study was aimed to report the clinical characteristics of intramedullary schwannomas and discuss imaging findings and treatment strategies.

Methods: The inclusion criterion was consecutive patients with intramedullary schwannomas who were surgically treated at 8 centers between 2009 and 2020. Clinical characteristics included age, sex, clinical presentation, disease duration, and follow-up period. The modified McCormick scale was used to compare the preoperative and postoperative conditions. Pre- and postoperative magnetic resonance images (MRI) of each case were analyzed.

Results: The mean age of the total 11 patients at the operation was 50.2 years. The mean duration of the symptoms was 23 months, with limb paresthesia being the most common clinical presentation. The cervical spine was the most common localization level of the tumor in 6 cases. The mean follow-up duration was 49.4 months. Gross total resection (GTR) and subtotal resection (STR) was achieved in 9 and 2 cases, respectively. According to the modified McCormick scale at 6 months postoperatively, 7 cases (63.6%) had improved and 4 cases (36.3%) had unchanged grades. Typical MRI findings of the intramedullary schwannoma included ring-like enhancement, syringomyelia, cystic formation, intramedullary edema, and hemosiderin deposition. Gadolinium enhancement was homogenous in 8 cases (72.7%). The tumor margins were well demarcated in all cases.

Conclusion: Intramedullary schwannoma should be considered when sharp margins and well-enhanced tumors are present at the cervical spine level and the initial symptoms are relatively mild, such as dysesthesia. When GTR cannot be achieved, STR for tumor decompression is recommended.

Keywords: Intramedullary schwannoma, Magnetic resonance imaging, Gross total resection, Subtotal resection, Preoperative diagnosis

INTRODUCTION

Intramedullary schwannomas are rare tumors that contribute to 1.1% of spinal schwannomas and 0.3% of all intraspinal neoplasms.1,3 Histologically, it is a benign tumor with a good prognosis if...
surgically removed. However, it is sometimes difficult to distin-
guish it from other intramedullary tumors, especially epende-
ymomas and astrocytomas. In addition, there are cases in which
intraoperative pathological examination does not reveal schwan-
noma, but the final pathological diagnosis reveals schwannoma.¹
These challenges make the determination of treatment strategy
difficult.

Due to its rarity, the pathogenesis of intramedullary schwan-
noma is poorly understood. We report 11 cases of intramedul-
lar schwannoma and discuss imaging findings and treatment
strategies.

MATERIALS AND METHODS

This was a multicenter cohort study authorized by the Neu-
rospine Society of Japan. This study is a subanalysis of previous
research and was approved by the Institutional Review Board of
Tohoku University Hospital and the Ethics Committee (2021-
1-130) of the relevant institution. This is a multicenter cohort
study of 11 cases from 8 centers.

The inclusion criterion was consecutive patients with intra-
medullary schwannoma who were surgically treated at 8 cen-
ters between 2009 and 2020. Intramedullary schwannomas were
defined as tumors that are pathologically diagnosed as schwan-
noma and present within the spinal cord, which can be identi-
fied on imaging; tumors with areas of exophytic extramedullary
extension are also included.

Clinical characteristics included age, sex, clinical presentation,
disease duration, and follow-up period. The modified McCor-
mick scale was used to compare preoperative and postoperative
conditions; mainly grades at discharge and 6 months postoper-
atively, were compared with those observed before surgery. Ra-
diological data were collected from preoperative and postoper-
ative images, lesion levels, and magnetic resonance imaging (MRI)
findings. The degrees of excision and complications were eval-
uated from surgical records.

RESULTS

1. Patient Demographics

Eleven patients were identified. The mean patient age at the
time of operation was 50.2 years (range, 13–73 years). The pa-
tient demographics are summarized in Table 1. Of the 11 pa-
tients, 5 (45%) were male and 6 (55%) were female. The mean
duration of symptoms was 23 ± 18.8 months, with limb pares-
thesia (90.9%) being the most common clinical presentation,
followed by limb weakness (66.6%), gait disturbance (63.6%),
limb pain (45.4%), head, neck, or back pain (27.2%), and blad-
der and/or bowel disturbance (27.2%).

2. Tumor Levels, Surgical Treatment, and Postoperative
Course

The localization level of the tumor was the cervical spine in 6
cases (46.1%), cervicothoracic spine in 1 case (7.6%), thoracic
spine in 2 cases (15.3%), and thoracolumbar spine in 2 cases
(15.3%), and the cervical spine being the most common site. The
affected nerve root could be identified intraoperatively in 8 pa-
tients, all of whom were considered to have a posterior root origin.

In 4 of these cases, the affected nerve root was confirmed to have
been resected. Of these patients, 3 had postoperative improvement
of neurological symptoms, and none had deterioration.

Surgical resection was performed in all cases: 9 patients (81.8%)
underwent gross total resection (GTR) and 2 (18.1%) underwent
subtotal resection (STR). In 5 cases, the nerve root of origin of
the tumor was resected intraoperatively, and there were no cas-
es of postoperative worsening of symptoms. In the case of the
patient who failed to achieve STR, the motor evoked potential
disappeared intraoperatively, and tumor removal was abandoned.
In the other case, the tumor was strongly adherent near the dor-
sal root entry zone on the spinal cord surface, and there was po-
tential for neurological symptoms after removal, so STR was
performed.

Immediately post operation, symptoms improved from the
preoperative state in 5 patients (45.4%), remained unchanged
in 2 patients (18.8%), and worsened in 4 patients. Three of them
had tumors without extramedullary lesions, and one had a tu-
mor with extramedullary lesions that was strongly intramedul-
lary embedded. On the modified McCormick scale, the grade
improved in 2 cases (18.8%), remained unchanged in 7 cases
(63.6%), and worsened in 2 cases (18.8%).

On the same scale at 6 months postoperatively, 7 (63.6%) and
4 (36.3%) cases showed improved and unchanged grades, re-
spectively. The grades on the modified McCormick scale tempo-
arily worsened in some patients immediately after surgery
(at discharge); however, these patients showed functional im-
provement at 6 months postoperatively. The patients’ grades on
the McCormick scale are shown before, immediately after, and
6 months after surgery. Complications occurred in 1 case, and
the patient underwent reoperation due to postoperative intra-
medullary hemorrhage. The patients with postoperative intra-
medullary hemorrhage were those with a hemosiderin cap on
preoperative MRI. One patient underwent STR at the time of
<table>
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<th>No.</th>
<th>Age (yr)/sex</th>
<th>Duration of illness (mo)</th>
<th>Symptom</th>
<th>Surgery</th>
<th>Modified McCormick scale Pre</th>
<th>Post</th>
<th>Last FU</th>
<th>Location/origin of tumor</th>
<th>FU (mo)</th>
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<th>NF</th>
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<td>T12–L1/NA</td>
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<td>1</td>
<td>1</td>
<td>C1–2/dorsal root</td>
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<td>Schwannoma</td>
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<td>2</td>
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<td>48/F</td>
<td>13</td>
<td>Limb paresthesia, limb weakness</td>
<td>STR</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>C4–6/NA</td>
<td>40</td>
<td>Schwannoma</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>47/M</td>
<td>36</td>
<td>Headache, neck and back pain, limb paresthesia, limb weakness, gait disturbance</td>
<td>GTR</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>C3–5/dorsal root</td>
<td>38</td>
<td>Extramedullary tumor</td>
<td>No</td>
</tr>
<tr>
<td>10†</td>
<td>37/M</td>
<td>14</td>
<td>Neck and back pain, limb pain, limb paresthesia, limb weakness, gait disturbance, bladder/bowel disturbance</td>
<td>GTR</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>T9–10/intradural</td>
<td>70</td>
<td>Ependymoma</td>
<td>NF2</td>
</tr>
<tr>
<td>11</td>
<td>73/F</td>
<td>7</td>
<td>Limb paresthesia, limb weakness, gait disturbance</td>
<td>GTR</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>T10–11/NA</td>
<td>23</td>
<td>Ependymoma</td>
<td>No</td>
</tr>
</tbody>
</table>

FU, follow-up; NF, neurofibromatosis; NA, not available; GTR, gross total resection; STR, subtotal resection.

*N= Neurofibromatosis type 1. †= Neurofibromatosis type 2.
initial surgery experienced local recurrence and underwent re-operation (Table 2).

### 3. MRI Findings (Table 3)

T1-weighted MRI scans showed iso intensity in 7 cases (63.6%) and a mixture of low to iso and high intensity in 2 cases (18.1%). T2-weighted images showed mixed iso-to high intensity in 9 cases (81.8%) and high intensity in 2 cases (18.1%). Tumor length (including cystic lesions) was 1 vertebra in 5 cases (45.4%), 2 vertebrae in 3 cases (27.2%), 3 vertebrae in 2 cases (18.1%), and 5 vertebrae in 1 case (5.5%). The border with the surrounding spinal cord was clear in all the cases. Gadolinium enhancement was homogenous in 8 cases (72.7%), heterogeneous enhancement in 1 (9.0%), and ring-like enhancement in 1 (9.0%).

Associated syringomyelia was found in 2 cases (18.1%), cystic lesions in 8 (72.7%), intramedullary edema in 6 (54.5%), and hemosiderin deposition in 2 cases (18.1%). In the 2 cases with syringomyelia, the syringomyelia shrank with removal of the tumors. The extramedullary component of the tumor was found in 7 cases (63.6%), and the remaining 4 cases (36.3%) had an intramedullary component of the tumor (Fig. 1).

Preoperative diagnosis of schwannoma was possible in 6 cases, and 4 cases were diagnosed as ependymoma. These tumors were enhanced with gadolinium and were accompanied by cystic lesions, syringomyelia, and hemosiderin deposition, which are also seen in ependymomas. All 6 patients with preoperative diagnosis of schwannoma had extramedullary regions on preoperative MRI. Three patients diagnosed with ependymoma did not have exophytic lesions (Fig. 2, Table 1).

Clinical features of all cases are shown in Table 1.

### DISCUSSION

Intramedullary schwannomas have a frequency of 0.3% in all intraspinal neoplasms and 1.1% in spinal schwannomas, mak-

### Table 2. Postoperative course and complications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom at discharge</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>5 (45.4)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>2 (18.8)</td>
</tr>
<tr>
<td>Worsened</td>
<td>4 (36.3)</td>
</tr>
<tr>
<td>Modified McCormick scales at discharge</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>2 (18.8)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Worsened</td>
<td>2 (18.8)</td>
</tr>
<tr>
<td>Modified McCormick scales 6 months</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>4 (36.3)</td>
</tr>
<tr>
<td>Worsened</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Surgical complication</td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid leak</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Postoperative hematoma</td>
<td>1 (9.0)</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>1 (9.0)</td>
</tr>
</tbody>
</table>

### Table 3. Summary of magnetic resonance imaging findings of 11 cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>T1</th>
<th>T2</th>
<th>Enhancement</th>
<th>Edema</th>
<th>Cystic lesion</th>
<th>Extramedullary lesion</th>
<th>Hemosiderin deposition</th>
<th>Syringomyelia</th>
<th>Tumor length (vertebral segment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Iso</td>
<td>Iso-high</td>
<td>Homogenous</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Iso</td>
<td>Iso-high</td>
<td>Homogenous</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Iso</td>
<td>Iso-high</td>
<td>Homogenous</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>4*</td>
<td>Iso</td>
<td>High</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Iso</td>
<td>High</td>
<td>Homogenous</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Low-iso</td>
<td>Iso-high</td>
<td>Ring-like</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Low-high</td>
<td>Iso-high</td>
<td>Heterogenous</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>N/A</td>
<td>Iso-high</td>
<td>Homogenous</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Iso</td>
<td>Iso-high</td>
<td>Homogenous</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>10'</td>
<td>Iso</td>
<td>Iso-high</td>
<td>Homogenous</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>N/A</td>
<td>Iso-high</td>
<td>Homogenous</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

N/A, not available.
*Neurofibromatosis type 1. †Neurofibromatosis type 2.
Intramedullary Schwannoma of the Spinal Cord

Hara T, et al.

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Intramedullary schwannoma of the spinal cord is a very rare tumor.\(^1\,^3\) They occur more frequently in men at a ratio of 3:1, and the average age of onset is reported to be 40 years, with very few pediatric cases.\(^3\,\,^5\) The most common site of occurrence is the cervical spine, followed by the thoracic and lumbar spine.\(^6\) In this study, the mean patient age at the operation was 50.2 years. The number of female patients (55%) was slightly different from that in previous reports, as 6 (55%) were predominant. The present study is a subanalysis of a previous multicenter study\(^7\) which included 1,033 cases of intramedullary tumors. Among the 1,033 intramedullary spinal cord tumors, intramedullary schwannomas accounted for 1.06% of tumors during the same period. Based on previous reports, Ross et al.\(^1\) estimated the frequency of intramedullary schwannomas to be 0.3% of all intramedullary neoplasms and 1.1% of all spinal cord schwannomas. The present study is significant because it directly presents the frequency of intramedullary schwannomas among spinal intramedullary tumors.

The unique feature of this study was not to report the status of treatment at a single institution, but to identify the actual treatment and status of intramedullary schwannoma in neurosurgical facilities in Japan, and to reveal the treatment and incidence of this disease currently being performed in Japan. Treatment results were generally comparable to previous reports, and the treatment system was considered to be basically well maintained on a nationwide basis.

The possible association between neurofibromatosis (NF) and intramedullary schwannoma has been reported from Japan, where it occurred in 2.2% of cases of NF type 1 (NF1).\(^8\) In addition, a literature review reported 13.6% of those occurring in NF1 and NF type 2 (NF2).\(^7\) In the present study, 1 case was observed in NF1 and 1 case in NF2, which suggests that intramedullary schwannoma can occur in NF as well as other types of schwannoma.

The pathogenesis of intramedullary schwannoma remains unclear. The following developmental mechanisms are thought to be responsible for the development of Schwann cell-derived tumors that exist in peripheral nerves within the spinal cord and central nervous system.

1. Conversion of pial mesodermal cells into neuroectodermal Schwann cells.\(^10\)
2. Schwannoma arises from Schwann cells in the dorsal root entry zone and extends intramedullary.\(^11\,\,^12\)
3. Schwannoma arises from Schwann cells under the perivascular nerve plexus of spinal cord vessels, resulting in subpial extension.\(^13\)
4. Schwannosis occurs in proximity of the anterior spinal artery.\(^14\)
5. Schwannomas occur due to the intrusion of neural crest cells during embryogenesis.\(^15\)
6. They result from inadequate regeneration of the spinal cord after trauma or chronic disease.\(^16\)

Fig. 1. Representative magnetic resonance imaging findings of intramedullary schwannoma reviewed in this study. (A) Ring-like enhancement. (B) Cyst formation. (C) Hemosiderin. (D) Edema. (E) Syringomyelia. (F) Exophytic lesion.
The localization and extension of the tumors in the cases included in this study can be divided into 2 main types: those that are completely intramedullary. One was completely intramedullary and the other was intramedullary to extramedullary extension. Considering these developmental mechanisms and tumor localization, each type may have a different developmental mechanism. The location within the spinal cord where the above mechanisms occur may determine the morphology of the tumor. That is, tumors that arise near the surface of the spinal cord are thought to have exophytic lesions, while tumors that arise in more central areas of the spinal cord are thought to have intramedullary lesions (Fig. 3).

One of the problems in the treatment of intramedullary schwannomas is the difficulty of preoperative diagnosis. The problem with preoperative MRI is its inability to differentiate schwannomas from other intramedullary tumors, such as ependymomas and astrocytomas, which are relatively more common among intramedullary tumors. Since the surgical strategies for these tumors are different from those for schwannoma, it is worthwhile to identify imaging differentiators. In addition, owing to
Intramedullary Schwannoma of the Spinal Cord

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Fig. 3. Classification of tumor form based on the location of tumor origin. (A) Tumor originates from the superficial layer within the spinal cord. (B) Tumor originates near the center within the spinal cord. Red area, tumor; brown area, gray matter; yellow area, white matter; gray area, root.

The histological and structural characteristics of the tumor (Antony type A and type B), spinal schwannomas present various magnetic resonance (MR) appearances, such as cystic formation and ring-like enhancement. In a report by Gupta et al., MRI findings were a mixture of T2 hyperintensity changes and T2 isointense tumors. The tumor was strongly enhanced with the use of gadolinium. In addition, a cyst formed caudally to the tumor, which could be considered as a differential diagnosis for ependymomas or astrocytomas. The tumor was completely intramedullary, with edema around the tumor. Sekar et al. reported a case of cervical intramedullary schwannoma with a hemosiderin cap sign that was difficult to distinguish from that observed in ependymoma. The causes of bleeding in schwannoma include spontaneous thrombosis of vessels with distal tumor necrosis, traction of vascular attachments to the nerve roots, neovascularization, and central ischemic necrosis. In the present study, hemosiderin deposition was observed in 2 cases. This finding also makes differentiation from other intramedullary tumors difficult. Wu et al. compared imaging findings and clinical symptoms in 8 intramedullary schwannoma cases and 243 glioma (ependymoma and astrocytoma) cases treated at the same time. In schwannomas, hypointensity on T1-weighted images, hyperintensity or mixed intensity on T2-weighted images, and associated syringomyelia and cysts were observed. However, these findings showed no significant differences between gliomas and intramedullary schwannomas. The authors suggest that the initial presentation of somatic pain or root pain is significantly common in patients with intramedullary schwannoma and that a preoperative diagnosis should be made based on the imaging findings and clinical course of the disease. In the present case series, as in previous reports, 90.9% of the cases showed limb paresthesia as the initial symptom. Many of our cases showed T1 iso intensity and T2 mixed iso-to high intensity on MRI. Similarly, syringomyelia and cystic formation were seen in some cases, and in addition, hemosiderin deposition was seen in some cases. These are common findings in ependymoma, thus the many similarities in imaging findings may be a factor that contributes to the difficulty in differentiating ependymoma from intramedullary schwannoma. On the other hand, most of the tumor lengths including cystic lesions in the present study cases are less than 3 vertebral, and even shorter if only the enhanced region is considered. Ependymoma has been reported to have a tumor length of 3–4 vertebral levels, and the relatively short tumor length may be a point of differentiation between intramedullary schwannomas and ependymomas. We believe that the tumor is detected at a relatively small stage because schwannoma is a benign tumor and develops slowly, reflecting the nature of benign tumors. Tumors with extramedullary lesions may involve nerve roots relatively early in the process of tumor development and may develop and be diagnosed with dysesthesia or pain.

The characteristic findings of intramedullary schwannoma include a clear border between the tumor and the surrounding spinal cord on MRI and a strong enhancing effect. In addition to intramedullary tumors, some studies have reported that contrast-enhanced MRI findings of enlarged roots contiguous with the tumor may be helpful in the diagnosis of intramedullary schwannoma. Because schwannoma is a benign tumor, the dissection plane is usually clear, and GTR is likely to be achieved. If there is a strong adhesion between the tumor and the surrounding nerves or spinal cord, additional neurological symptoms may be exacerbated postoperatively if the tumor is removed for GTR. Therefore, if the dissection plane is unclear, STR should also be an option to avoid surgical complications. For large tumors, staged operations should be considered to minimize the occurrence of postoperative neurological deficit. In our case, one patient who underwent STR showed symptomatic improvement and one patient's neurological symptoms remained unchanged postoperatively. As observed in the present study, long-term follow-up is important because of the possibility of recurrence.
and symptom relapse in patients who underwent STR. Postoperative chemotherapy or radiation therapy is not recommended, and tumor resection is considered if the residual tumor progresses or symptoms develop.

**CONCLUSION**

Intramedullary schwannoma presents with a variety of imaging findings, making a preoperative diagnosis from imaging difficult, especially in the absence of exophytic lesions, which makes its differentiation from other intramedullary tumors difficult. Therefore, a differential diagnosis must be considered based on the clinical course and symptoms.

Schwannomas should be considered, especially when sharp margins and well-enhanced tumors are present at the level of the cervical spine and the initial symptoms are relatively mild, such as pain or dysesthesia. Schwannomas are benign tumors, and a good clinical outcome can be expected if GTR is achieved. However, it is possible to control the tumor without worsening neurological symptoms, even with STR; therefore, it is important to limit the treatment to STR if GTR is not feasible.

**NOTES**

**Conflict of Interest:** The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: TH, MM, TE; Formal Analysis: TH; Methodology: TH, MM, TE; Project Administration: MM, KH, TE; Data curation: Toru S, YM, HU, HO, Taku S, YT, TE; Writing – Original Draft: TH; Writing – Review & Editing: MM, KH, Toru S, YM, HU, HO, Taku S, YT, YO, AK, TE.

**ORCID**

Takeshi Hara: 0000-0002-5124-5329
Masaki Mizuno: 0000-0002-1761-344X
Kazutoshi Hida: 0000-0003-4789-8375
Toru Sasamori: 0000-0002-5852-6297
Yasuyuki Miyoshi: 0000-0002-8082-4709
Hisakki Uchikado: 0000-0002-6082-0911
Hiroki Ohashi: 0000-0003-3484-9734
Taku Sugawara: 0009-0001-9610-7464

Yasuhiro Takeshima: 0000-0002-5438-6098
Yukoh Ohara: 0000-0002-1816-0219
Akihide Kondo: 0000-0003-1729-4490
Toshiki Endo: 0000-0002-5609-200X

**REFERENCES**

Comparison of the Recurrence and Surgical Outcome of Spinal Hemangioblastoma in Sporadic and Von Hippel-Lindau Diseases: A Subanalysis of a Nationwide Study by the Neurospinal Society of Japan

Yasuhiro Takeshima1, Hirokazu Takami2, Toshiki Endo3, Masaki Mizuno4, Kazutoshi Hida5; for the Investigators of Intramedullary Spinal Cord Tumors in the Neurospinal Society of Japan

1Department of Neurosurgery, Nara Medical University, Kashihara, Japan
2Department of Neurosurgery, Faculty of Medicine, The University of Tokyo Hospital, Tokyo, Japan
3Department of Neurosurgery, Tohoku Medical and Pharmaceutical University, Sendai, Japan
4Department of Minimum-Invasive Neurospinal Surgery, Mie University, Tsu, Japan
5Department of Neurosurgery, Sapporo Azabu Neurosurgical Hospital, Sapporo, Japan

Objective: This study aimed to clarify the relationship between recurrence and the extent of resection in surgery for intramedullary spinal hemangioblastoma (sHB) and its impact on von Hippel-Lindau (vHL) disease.

Methods: Data on sHB cases followed up for at least 6 months after surgery were extracted from a nationwide registry of 1,033 consecutive spinal intramedullary tumors surgically treated between 2009 and 2020, and were retrospectively categorized into a sporadic or vHL group. The diagnosis of vHL disease was made at each institution based on clinical findings.

Results: A total of 168 patients (sporadic group, 101; vHL group, 67) were included in the study. Compared with the sporadic group, the vHL group had a younger onset (45.4 ± 16.8 years vs. 39.6 ± 14.1 years, p = 0.02), more preoperative motor (47.5% vs. 68.7%, p < 0.01) and gait (37.6% vs. 61.2%, p < 0.01) impairments, and more patients with worsening neurological symptoms at discharge (p = 0.02). The gross total resection (GTR) rates and the recurrence rates were not statistically different between the sporadic and the vHL groups. GTR significantly improved recurrence-free survival compared to non-GTR in all patient analysis (p < 0.01) but this trend was not observed in the sporadic group. Physical functional improvement from discharge to 6 months after surgery was observed in the sporadic group (p < 0.01) but not in the vHL group.

Conclusion: A high GTR rate may sufficiently decrease susceptibility to recurrence, especially in patients with sHB with vHL. In sporadic sHB, postoperative functional improvement can be expected, and the long-term functional prognosis is favorable.

Keywords: Hemangioblastoma, Recurrence, Intramedullary spinal cord neoplasms, Treatment outcome, Spinal cord, Von Hippel-Lindau disease

INTRODUCTION

Spinal hemangioblastoma (sHB) is a common spinal intra-medullary tumor accounting for 10%–20% of spinal cord tumors.1-3 sHB is characterized by a highly vascularized and slow-growing tumor with a benign character, often accompanied by
cysts and syringomyelia; it may occur sporadically or in association with von Hippel-Lindau (vHL) disease in 25%–33% of cases in adults and more frequently in children, and often involves multiple tumors. vHL disease is one of the most common hereditary diseases and is responsible for the development of neoplasia in multiple organ systems including not only central nervous hemangioblastomas but renal cell carcinoma, pancreatic tumors, adrenal tumors, and epididymal cystadenomas. The multiplicity accounts for the varied natural history of vHL-associated sHBs, complexities in their management, and uncertainties associated with the long-term functional outcome.

Although surgical removal of sHB is closely related to recurrence and postoperative functional prognosis, the degree of removal varies widely among reports, and its relation to recurrence has not been sufficiently investigated. Recurrence can occur even after achieving gross total resection (GTR). Additionally, there is disagreement in the literature as to whether there is a difference in recurrence between solitary cases and those associated with vHL disease. The outcome of sHB cannot be discussed without ignoring vHL disease, which can adversely affect life expectancy by progressively worsening neurological function and is secondary to hemangioblastoma in the central nervous system (CNS) or other malignancies.

We recently constructed a nationwide registry of spinal intramedullary tumors and reported the clinical data. Although excellent treatment results at a single center are important, collecting data from multiple centers in a national region will reveal real-world treatment results for sHB that can be used in daily clinical practice. Therefore, we extracted and investigated data from this registry for sHBs.

This study aimed to clarify the relationship between recurrence and the extent of resection in surgery for intramedullary sHB and its relation to vHL disease, as well as to reveal the differences in clinical and radiological characteristics and surgical outcomes of sHB between sporadic and vHL diseases by analyzing data from a large number of cases collected from many facilities.

MATERIALS AND METHODS

1. Ethics Statements
This was a subanalysis of a multicenter cohort study authorized by the Neurospinal Society of Japan. The study protocol was approved by the Institutional Review Board of Tohoku University Hospital (2021-1-130) and the participating centers. As this was a retrospective, noninvasive study, the requirement for written informed consent was waived. Instead, a public notice that provided information on this study was published on individual center’s websites.

2. Study Population
This study included patients with pathologically diagnosed sHB, who were extracted from the nationwide registry of 1,033 consecutive spinal intramedullary tumor cases surgically treated at 58 Japanese centers between 2009 and 2020. Exclusion criteria were insufficient data, surgery for locally recurrent lesions after prior treatment, and a follow-up interval of < 6 months.

3. Data Collection
Clinical characteristics, including age, sex, body mass index (BMI), medical history (including vHL disease, brain tumor, and spinal surgery), clinical presentations, and duration of illness, were anonymously extracted from the patients’ medical records. Modified McCormick scales (grade I, normal gait; grade II, mild gait disturbance not requiring support; grade III, gait with support; grade IV, assistance required; and grade V, wheelchair needed) were periodically analyzed, allowing comparisons between patients’ preoperative and postoperative statuses. Radiological data were collected from preoperative and postoperative images, including the tumor location at the spinal level, tumor length measured the long diameter of the enhancing portion on sagittal images, and morphological type classified as cystic, solid or mixed on magnetic resonance imaging (MRI) (Supplementary Fig. 1). The surgical approach, degree of excision, operative time, blood loss, and complications were recorded from the surgical records. Tumor recurrence was defined as the reappearance of the tumor at the same site after GTR or tumor regrowth after partial removal. Information regarding the postoperative clinical course, including adjuvant radiotherapy, the presence of recurrence, and duration to recurrence or final follow-up after surgery was also recorded. To investigate short-term functional improvement after surgery, the change in the modified McCormick scale between the preoperative period and discharge was evaluated in each case: “improved” and “deteriorated” were defined as improvement or deterioration in at least one of the grades, respectively. The diagnosis of vHL disease was made at each institution based on the clinical findings.

The patients were classified into 2 groups, sporadic and vHL, based on the presence or absence of a diagnosis of vHL disease. The diagnosis of vHL disease was made at each institution based on clinical findings. The collected data were retrospectively compared between the 2 groups.

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4. Statistical Analysis

All data were analyzed for completeness and accuracy, and anonymized prior to scrutiny. Recurrence-free survival (RFS) was determined in each case and was defined as the time from surgery to the last follow-up in patients without tumor recurrence; the time from surgery to the first-time recurrence was observed in patients with recurrence.

Continuous variables among the clinical characteristics and radiological variables were compared using the unpaired t-test or Welch t-test based on equal variances in the population. Binary and nominal variables among the clinical characteristics and radiological variables were compared using the Pearson chi-square test. To evaluate the relationship between GTR and recurrence, Kaplan-Meier plots for RFS of all patients stratified by the presence of vHL disease and extent of resection were created and compared using the log-rank test. To investigate whether there were differences between the 2 groups, Kaplan-Meier plots for RFS in each group were created and compared using the log-rank test. To clarify the differences in changes in the physical functional status during the perioperative period, trends in the modified McCormick scales over time were compared in each group using 1-way analysis of variance with repeated measures. Statistical analysis of each recent change and the change from the preoperative period to the time of the last follow-up was performed.

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as numbers and percentages. Statistical significance was defined as p < 0.05. All statistical analyses were performed using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Study Population

Of the 1,033 spinal intramedullary tumor registry cases, 195 (18.9%) were diagnosed as sHB. One case with insufficient data, one reoperation case due to local recurrence after prior treatment, and 25 cases with a follow-up duration < 6 months were excluded. Finally, 168 patients treated at 39 centers were included. There were 75 male and 93 female patients aged 8–80 years (43.1 ± 16.0 years at the time of surgery), and 101 (60.1%) and 67 cases (39.9%) were categorized into the sporadic and vHL groups, respectively.

2. Clinical and Radiological Characteristics

Detailed clinical characteristics of the patients in each group are presented in Table 1. There were significant differences between the 2 groups in terms of age (45.4 ± 16.8 years vs. 39.6 ± 14.1 years, p < 0.02), BMI (22.8 ± 3.8 kg/m² vs. 21.4 ± 3.1 kg/m², p = 0.02), cigarette smoking (31.7% vs. 14.9%, p = 0.02), history of brain tumor (1.0% vs. 70.1%, p < 0.01), spinal surgery (3.0% vs. 29.9%, p < 0.01), motor weakness (47.5% vs. 68.7%, p < 0.01), and gait disturbance (37.6% vs. 61.2%, p < 0.01). In summary, patients in the vHL group were younger, thinner, less likely to smoke, more likely to have a history of brain tumor or spinal surgery, and more often affected by motor dysfunction than those in the sporadic group.

The detailed radiological characteristics and preoperative functional statuses of the patients in each group are presented in Table 2. More than 90% of the tumors in both groups were found in the cervical and thoracic spine, and the distribution of tumor locations showed no statistically significant difference between the 2 groups (p = 0.36). The most common morphological type on MRI was the solid type in both groups, and there was no statistically significant difference in morphological type

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sporadic group (n = 101)</th>
<th>vHL group (n = 67)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.4 ± 16.8</td>
<td>39.6 ± 14.1</td>
<td>0.02*</td>
</tr>
<tr>
<td>Male sex</td>
<td>50 (49.5)</td>
<td>25 (37.3)</td>
<td>0.12b</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.8 ± 3.8</td>
<td>21.4 ± 3.1</td>
<td>0.02*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (13.9)</td>
<td>7 (10.0)</td>
<td>0.52b</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (5.0)</td>
<td>6 (9.0)</td>
<td>0.31b</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (7.9)</td>
<td>12 (17.9)</td>
<td>0.05b</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>32 (31.7)</td>
<td>10 (14.9)</td>
<td>0.02b</td>
</tr>
<tr>
<td>Past history; brain tumor</td>
<td>1 (1.0)</td>
<td>47 (70.1)</td>
<td>&lt; 0.01b</td>
</tr>
<tr>
<td>Past history; spinal surgery</td>
<td>3 (3.0)</td>
<td>20 (29.9)</td>
<td>&lt; 0.01b</td>
</tr>
<tr>
<td>Duration of illness (mo)</td>
<td>20.3 ± 47.9</td>
<td>33.1 ± 74.6</td>
<td>0.22a</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). vHL, von Hippel-Lindau disease. *p < 0.05. aUnpaired t-test. bChi-squared test.
between the groups (p = 0.57). The tumor length was 16.4 ± 11.3 mm in the sporadic group and 14.0 ± 7.3 mm in the vHL group, with no statistically significant difference between the groups (p = 0.10). The distribution of the preoperative modified McCormick scale in each group demonstrated that the preoperative functional status tended to be worse in the vHL group than in the sporadic group, but the difference was not statistically significant (p = 0.24).

### 3. Surgical Details and Results

In the evaluation of all patients, the mean follow-up period was 53.6 ± 37.7 months, and GTR and recurrence rates were 92.9% and 3.6%, respectively. The surgical details and results of the 2 groups are presented in Table 3. GTR was performed in 94.1% and 91.0% of patients in the sporadic and vHL groups, respectively; however, there was no statistical difference in the degree of tumor removal between the groups (p = 0.15). The posterior approach was used in most patients in both groups. The operative time tended to be longer in the vHL group than in the sporadic group, but the difference was not statistically significant (p = 0.07). There were also no statistically significant differences in intraoperative blood loss (p = 0.51) or postoperative complications including cerebrospinal fluid leakage (p = 1.00), postoperative hematoma (p = 0.41), or surgical site infection (p = 0.22) between the 2 groups. There was one case in each group in which postoperative irradiation was performed for lesions that could not achieve GTR, without any statistical significance. The follow-up periods were not significantly different between the groups (p = 0.33). The recurrence rate tended to be higher in the vHL group (6.0%) than in the sporadic group (2.0%), but there was no significantly different (p = 0.17).

### 4. Relationship Between the Extent of Resection and RFS

The Kaplan-Meier plot of RFS after tumor resection stratified based on the extent of tumor removal was used to evaluate the relationship between the extent of resection and RFS. The results showed that the patients who achieved GTR had a significantly longer RFS compared to those who did not achieve GTR (p = 0.02).

---

**Table 2. Radiological characteristics and preoperative functional status of the 2 groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sporadic group (n = 101)</th>
<th>vHL group (n = 67)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>48 (47.5)</td>
<td>35 (52.2)</td>
<td>0.36b</td>
</tr>
<tr>
<td>Cervicothoracic</td>
<td>3 (3.0)</td>
<td>6 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>43 (42.6)</td>
<td>23 (34.3)</td>
<td></td>
</tr>
<tr>
<td>Thoracolumbar</td>
<td>3 (3.0)</td>
<td>2 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>4 (4.0)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Morphological type on MRI</td>
<td></td>
<td></td>
<td>0.57b</td>
</tr>
<tr>
<td>Cystic</td>
<td>15 (14.9)</td>
<td>9 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td>49 (48.5)</td>
<td>38 (56.7)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>37 (36.6)</td>
<td>20 (29.9)</td>
<td></td>
</tr>
<tr>
<td>Length of the tumor (mm)</td>
<td>16.4 ± 11.3</td>
<td>14.0 ± 7.3</td>
<td>0.10a</td>
</tr>
<tr>
<td>Preoperative modified McCormick scale</td>
<td></td>
<td></td>
<td>0.24b</td>
</tr>
<tr>
<td>I</td>
<td>21 (19.8)</td>
<td>12 (17.9)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>58 (57.4)</td>
<td>31 (46.3)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>13 (12.9)</td>
<td>18 (26.9)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>8 (7.9)</td>
<td>5 (7.5)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>1 (1.0)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. vHL, von Hippel-Lindau disease; MRI, magnetic resonance imaging.

**Table 3. Surgical details and results of the 2 groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sporadic group (n = 101)</th>
<th>vHL group (n = 67)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor removal</td>
<td></td>
<td></td>
<td>0.15b</td>
</tr>
<tr>
<td>Gross total removal</td>
<td>95 (94.1)</td>
<td>61 (91.0)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>2 (2.0)</td>
<td>5 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>4 (4.0)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Surgical approach</td>
<td></td>
<td></td>
<td>0.34b</td>
</tr>
<tr>
<td>Anterior</td>
<td>1 (1.0)</td>
<td>2 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>100 (99.0)</td>
<td>65 (97.0)</td>
<td></td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>365.6 ± 174.9</td>
<td>415.9 ± 170.7</td>
<td>0.07a</td>
</tr>
<tr>
<td>Intraoperative blood loss (mL)</td>
<td>197.3 ± 340.4</td>
<td>166.1 ± 167.4</td>
<td>0.51a</td>
</tr>
<tr>
<td>Surgical complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid leakage</td>
<td>3 (3.0)</td>
<td>2 (3.0)</td>
<td>1.00b</td>
</tr>
<tr>
<td>Postoperative hematoma</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
<td>0.41b</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>0 (0)</td>
<td>1 (1.5)</td>
<td>0.22b</td>
</tr>
<tr>
<td>Short-term functional improvement after surgery</td>
<td></td>
<td></td>
<td>0.02b</td>
</tr>
<tr>
<td>Improved</td>
<td>52 (51.5)</td>
<td>22 (32.8)</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>23 (22.8)</td>
<td>28 (41.8)</td>
<td></td>
</tr>
<tr>
<td>Deterioriated</td>
<td>26 (25.4)</td>
<td>17 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Postoperative irradiation</td>
<td>1 (1.0)</td>
<td>1 (1.5)</td>
<td>0.77b</td>
</tr>
<tr>
<td>Duration to the final follow-up (mo)</td>
<td>51.2 ± 35.7</td>
<td>57.1 ± 40.5</td>
<td>0.33a</td>
</tr>
<tr>
<td>Recurrence</td>
<td>2 (2.0)</td>
<td>4 (6.0)</td>
<td>0.17b</td>
</tr>
<tr>
<td>After the gross total removal</td>
<td>2 (2.0)</td>
<td>2 (5.0)</td>
<td></td>
</tr>
<tr>
<td>After the non-gross total removal</td>
<td>0 (0)</td>
<td>2 (5.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. vHL, von Hippel-Lindau disease.

a) Unpaired t-test. b) Chi-square test. *Welch t-test.
by the presence of vHL disease demonstrated no significant difference between the groups (p = 0.27) (Fig. 1A). In contrast, the Kaplan-Meier plot of RFS stratified by the extent of resection indicated that GTR significantly improved RFS (p < 0.01) (Fig. 1B).

In a stratified comparison that focused on the extent of resection in each group, Kaplan-Meier plots for RFS showed a trend toward shorter RFS in the non-GTR cases than in the GTR cases in the vHL group (Fig. 1D), but this trend was not observed in the sporadic group (Fig. 1C).

5. Perioperative Changes in the Physiological Functional Status

Regarding short-term functional improvement after surgery, most of the patients in the sporadic group improved after the surgery (51.5%), whereas most of the patients in the vHL group remained unchanged (41.8%), indicating a lack of functional improvement between the preoperative period and discharge in the vHL group compared to the sporadic group, which was statistically significantly different (p = 0.02). Changes in the physical functional status during the perioperative period in each group are shown in Fig. 2. There were statistically significant differences in the distribution of modified McCormick grades between discharge and 6 months postoperatively (p < 0.01), and between the preoperative period and final follow-up (p < 0.01) (Fig. 2A). In other words, the sporadic group showed functional recovery from discharge to the sixth postoperative month and at the last follow-up compared with the preoperative period. In contrast, the vHL group showed no improvement (Fig. 2B).

From 6 months postoperatively to the final follow-up, the per-
percentage of patients with modified McCormick grade was maintained in all grades I (42.6% to 45.5%), II (46.5% to 46.5%), III (7.9% to 5.0%), IV (1.0% to 1.0%), and V (2.0% to 3.0%) in the sporadic group. In contrast, in the vHL group, the percentage of patients with grade I remained the same (37.3% to 38.8%), those of grades II (32.8% to 25.4%) and III (16.4% to 13.4%) decreased, and those of grades IV (10.4% to 14.9%) and V (3.0% to 7.5%) increased, indicating that physical function tended to deteriorate without a significant difference (p = 0.54).

DISCUSSION

1. Main Findings

This study evaluated the relationship between recurrence and the extent of resection in surgery for sHB and its association with vHL disease. This study’s results showed that a high GTR rate of 92.9% resulted in a low recurrence rate of 3.6% during a mean follow-up of 52.9 months, and GTR tended to improve RFS in the vHL group, unlike in the sporadic group. An improvement in physical function up to 6 months after surgery was observed in the sporadic group but not in the vHL group.

2. Impact of the Extent of Resection on Tumor Recurrence

The GTR rate of sHB is generally high and partial resection is associated with tumor recurrence. In a literature review, total, subtotal, and partial resection rates of 83.52%, 9.17%, and 3.5%, respectively. There have been several reports illustrating the GTR rates and recurrence rate of sHB concurrently, but the relationship has been inconsistent. Prokopienko et al. reported 12 cases and demonstrated that GTR was achieved in all patients with no tumor recurrence during a mean follow-up period of 5 years. Conversely, Yousef et al. reported on 42 cases; GTR was achieved in 80.5%, and recurrence was observed in 41.4% of the cases during the mean follow-up of 20.9 months. Herein, we analyzed data of the 168 cases and reported a GTR rate of 92.9% and a recurrence rate of 3.6%. This GTR rate is considerably higher than that reported in a recent literature review. As a result, the recurrence rate was also found to be lower despite >50 months of follow-up.

In previous studies, the GTR rate of sHB tended to be slightly lower in vHL cases than in sporadic cases, and it cannot be ruled out that this may also affect the recurrence rate. Siller et al. reported the GTR rates of 100% for sporadic lesions and 90% for...
vHL lesions. Yousef et al.\textsuperscript{18} reported the GTR rates achieved in 86.4% for sporadic lesions and 70.0% for vHL lesions, with no statistical difference. In a literature review, Jankovic et al.\textsuperscript{15} also reported the recurrence rates of 7.9% in sporadic lesions and 22% in vHL lesions. However, few reports focused on the details of recurrence in sHB.

Only 2 reports investigating the impact of the presence of vHL disease and the degree of tumor removal using Kaplan-Meier plots of RFS have been published, but with slightly different results. Yousef et al.\textsuperscript{18} found that RFS was markedly lower in the vHL group than in the sporadic group, unlike our results. They described in the article that local recurrence can occur in vHL-associated lesions regardless of the degree of removal, as there was no significant difference in GTR rates between sporadic lesions and vHL-associated lesions. Garcés-Ambrossi et al.\textsuperscript{10} also revealed that GTR improved PFS. This trend is the same as the result of the present study but more marked in that previous report, and the reason for this is the small number of recurrence cases (3 of 15 cases).

In addition, we examined the association between RFS and GTR in each group, and the results indicated that the effect of GTR tended to be greater in the vHL group rather than in the sporadic group. These differences between the groups may be partly due to the high GTR rate, which maintains a low recurrence rate.

3. Differences in the Clinical Presentation and Radiological Characteristics Between the 2 Groups

The differences in clinical presentation and radiological characteristics between sporadic and vHL diseases are controversial. Previous reports suggested that patients with vHL-associated lesions are younger at onset, which is consistent with the present study.\textsuperscript{10,18} However, neurological symptoms are reported to be less severe than in patients with sporadic lesions\textsuperscript{18} whereas more likely to present with multiple symptoms in patients with vHL-associated lesions.\textsuperscript{18} Regarding the radiological characteristics of sHB, Yousef et al.\textsuperscript{18} reported no differences between the 2 groups. Yet, Takai et al.\textsuperscript{16} reported that lower spinal cord lesions were more frequently observed in patients with vHL disease than in those with sporadic disease with significant differences.

Although the radiological characteristics in the present study were not different between the 2 groups, there was more preoperative motor weakness and gait disturbance in the vHL group than in the sporadic group. Two hypotheses can explain these differences. One possibility is that preoperative motor dysfunction may have been significantly more frequent due to an overlying effect. Because the vHL group had a significantly more frequent history of brain tumor and spinal cord surgery than the sporadic group, it is highly likely that some patients had residual motor dysfunction due to previous treatment. Parker et al.\textsuperscript{20} reported that 60% and 83% of sHB patients with vHL disease presented with multiple sHBs and extraspinal lesions, respectively. Another hypothesis is that the same sHB may potentially have slightly different surgical indications in patients with sporadic disease versus those with vHL disease. Some reports indicated that asymptomatic lesions were removed when radiologically detected enlargement was present,\textsuperscript{16,21} whereas others reported surgery after the lesion became symptomatic.\textsuperscript{21} In an additional survey in this study about the surgical indications, 42.9% of the facilities indicated that they would extend the time to surgery for vHL cases more than for sporadic cases. This means that the time to surgery was intentionally postponed in 50.7% of the vHL cases in this study. Therefore, it is suggested that this may have influenced the difference in preoperative neurological dysfunction between the 2 groups.

4. Differences in the Perioperative Functional Status

In the present study, only the sporadic group showed significant functional improvement, both in the short- and long-term postoperatively. Although non-GTR in the vHL group was tended to be associated with recurrence, recurrence up to 6 months postoperatively was only observed in one patient, suggesting that other factors may be involved in this difference in functional improvement.

The first hypothesis is that an inferior preoperative functional status in patients with vHL disease leads to poor surgical outcomes. Among patients with spinal degenerative diseases, those with advanced myelopathy have poor surgical outcomes.\textsuperscript{22} The vHL group had a significantly more frequent history of CNS disease and tended to have inferior preoperative functional status than the sporadic group, which may have resulted in little functional improvement from surgery in some cases. It is also possible that additional functional impairment due to the appearance of another lesion specific to vHL may have been the cause of this difference. In vHL cases, 42% of cases presented new lesions during a mean follow-up of 60 months,\textsuperscript{20} and spinal cord lesions are more frequent than in sporadic cases.\textsuperscript{21} We additionally assessed the influence of past history of CNS tumor surgery and demonstrated that postoperative functional improvement was also shown on the vHL group without prior CNS tumor surgery like the sporadic group, indicating that patients with
vHL disease do not necessarily have poor postoperative functional improvement (Supplementary Fig. 2).

Based on this study’s results, the surgical treatment of sHB in vHL disease remains challenging compared to that in sporadic disease. Patients with vHL disease are at high risks for neurological deterioration because they require successive surgical treatments for the newly developed lesions in the CNS over their lifetime. Then, it is necessary to both increase the degree of removal to reduce recurrence and preserve functional status. In addition to more meticulous surgical techniques and optimal timing of surgery, GTR should be promoted using multimodal surgical support that have been developed in recent years, such as intraoperative neurophysiological monitoring, and indocyanine green (ICG) videoangiography or additional technique of temporary feeder occlusion under ICG videoangiography, particularly in vHL cases.

5. Limitations
This study has some limitations. First, this was a multicenter retrospective database study, and there are inevitable differences in the indications for surgery at each facility. Second, complete data on the appearance of other lesions are lacking. This is an essential endpoint in sHB, including VHL, when considering the long-term course of the disease. Third, there is no discussion of surgical strategy, such as when to remove the tumor or, in cases of multiple VHL, which tumor to remove first. Therefore, future studies on these points are warranted.

CONCLUSION
A high GTR rate may sufficiently decrease susceptibility to recurrence, especially in patients with sHB with VHL disease. In sporadic sHB, postoperative functional improvement can be expected, and the long-term functional prognosis is favorable. In VHL disease, short-term functional prognosis is expected to be adequate if there is no history of CNS tumor surgery, but thereafter the risk of functional deterioration increases with each surgery because of the tendency for new lesions to appear in the CNS. Therefore, the introduction of modern surgical assistance and optimal timing of surgery should be considered to achieve GTR to avoid local recurrence and preserve physical function.

NOTES
Supplementary Materials: Supplementary Figs. 1-2 can be found via https://doi.org/10.14245/ns.2346368.184.

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: TE, MM, KH; Data curation: YT, HT; Formal analysis: YT; Methodology: YT, HT, TE; Project administration: TE, MM, KH; Visualization: YT; Writing - original draft: YT; Writing - review & editing: HT, TE, MM, KH.

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ORCID
Yasuhiro Takeshima: 0000-0002-5438-6098
Hirokazu Takami: 0000-0001-9742-7462
Toshiki Endo: 0000-0002-5609-200X
Masaki Mizuno: 0000-0002-1761-344X
Kazutoshi Hida: 0000-0003-4789-8375

REFERENCES


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Supplementary Fig. 1. Morphological classification of the tumor on magnetic resonance images. Cystic (A), solid (B), mixed (C) types. Mixed type is defined as a solid tumor with cysts at the margins of the tumor. T2WI, T2-weighted image; GdT1, gadolinium-enhanced T1-weighted image.
Supplementary Fig. 2. Subanalysis of perioperative changes in functional status. (A) Sporadic cases without past history of CNS tumor surgery. (B) vHL cases without past history of CNS tumor surgery. (C) vHL cases with past history of CNS tumor surgery. The perioperative recovery trend seen in patients without prior CNS tumor surgery in both group is not seen in vHL group with prior CNS tumor surgery. CNS, central nervous system; vHL, von Hippel-Lindau; NS, not significant. Grade I, normal gait; grade II, mild gait disturbance not requiring support; grade III, gait with support; grade IV, assistance required; and grade V, wheelchair needed. *p < 0.05.
The Impact of Adjuvant Radiotherapy on Clinical Performance Status in Patients With Grade II Spinal Cord Astrocytoma – A Nationwide Analysis by the Neurospinal Society of Japan

Ryo Kanematsu¹, Masaki Mizuno², Tomoo Inoue³, Toshiyuki Takahashi¹, Toshiki Endo⁴, Seiji Shigekawa⁵, Jun Muto⁶, Daisuke Umebayashi⁶, Takafumi Mitsuhara⁷, Kazutoshi Hida⁹, Junya Hanakita¹; for the Investigators of Intramedullary Spinal Cord Tumors in the Neurospinal Society of Japan

¹Fujieda Heisei Memorial Hospital, Fujieda, Japan
²Department of Minimum-Invasive Neurospinal Surgery, Mie University, Tsu city, Japan
³Department of Neurosurgery, Saitama Red Cross Hospital, Saitama, Japan
⁴Division of Neurosurgery, Tohoku Medical and Pharmaceutical University, Sendai, Japan
⁵Department of Neurosurgery, Ehime University, Toon, Japan
⁶Department of Neurosurgery, Tohoku Medical and Pharmaceutical University, Sendai, Japan
⁷Division of Neurosurgery, Hiroshima University, Hiroshima, Japan
⁸Department of Neurosurgery, Kyoto Prefectural University of Medicine, Kyoto, Japan
⁹Department of Neurosurgery, Sapporo Azabu Neurosurgical Hospital, Sapporo, Japan

Objective: The impact of adjuvant radiotherapy on overall survival (OS) and progression-free survival (PFS) of patients with grade II spinal cord astrocytomas remains controversial. Additionally, the relationship between progression and clinical deterioration after radiotherapy has not been well investigated.

Methods: This study included 53 patients with grade II intramedullary spinal cord astrocytomas treated by either subtotal, partial resection or open biopsy. Their clinical performance status was assessed immediately before operation and 1, 6, 12, 24, and 60 months after surgery by Karnofsky Performance Scale (KPS). Patients with and without adjuvant radiotherapy were compared.

Results: The groups with and without radiation comprised 23 and 30 patients with a mean age of 50.3 ± 22.6 years (range, 2–88 years). The mean overall disease progression rate was 47.1% during a mean follow-up period of 48.4 ± 39.8 months (range, 2.5–144.5 months). In the radiation group, 11 patients (47.8%) presented with progressive disease, whereas 14 patients (46.7%) presented with progressive disease in the group without radiation. There were no significant differences in OS or PFS among patients with or without adjuvant radiotherapy. KPS in both groups, especially radiation group, gradually decreased after operation and deteriorated before the confirmation of disease progression.

Conclusion: Adjuvant radiotherapy did not show effectiveness regarding PFS or OS in patients with grade II spinal cord astrocytoma according to classical classification based on pathohistological findings.

Keywords: Intramedullary spinal cord tumor, Astrocytoma, Radiotherapy, Karnofsky Performance Scale
INTRODUCTION

Intramedullary spinal cord tumors are rare, accounting for 2%–4% of all central nervous system tumors; spinal cord astrocytoma is the most common spinal cord tumor in children (39%) and the second most common in adults (24%). The role of radiation therapy in the management of grade II spinal cord astrocytoma is controversial, as the standard therapeutic dose of 45 to 50 Gy with conventional fractionation of 1.8 to 2 Gy/day is well tolerated with low risk of toxicity, its influence in patient outcome is unknown. The aim of this study was to analyze progression free survival and clinical performance status in patients treated with and without adjuvant radiotherapy after incomplete resection of grade II spinal cord astrocytomas.

MATERIALS AND METHODS

1. Data Source

Data for this study was obtained from a multicenter cohort study authorized by the Neurological Society of Japan between 2009 and 2020. This database collects the clinical course and surgical outcomes of intramedullary spinal cord tumors from 58 neurosurgical centers across Japan.

2. Inclusion and Exclusion Criteria

In total, 168 patients with surgically treated intramedullary spinal cord astrocytomas were included. Of these patients, 56 patients with histologically confirmed grade II intramedullary spinal cord astrocytomas were identified and retrospectively reviewed. Although the updated 2021 World Health Organization (WHO) classification includes various diagnostic genes, molecules, pathways, and histological findings for diagnosis, this study was based on conventional histopathological grading. The extent of resection was defined as macroscopic gross total resection (100%), subtotal resection (> 90%), partial resection (< 90%), or open biopsy. In the present study, 3 patients with an attempt of gross total resection presented neurological decline related with the surgical treatment and were excluded from the analysis. Finally, 53 patients with grade II spinal cord astrocytomas with either subtotal, partial resection or open biopsy were enrolled.

3. Baseline Characteristics

Clinical characteristics including age, sex, Karnofsky Performance Scale (KPS), radiological data from magnetic resonance imaging (including tumor levels and lesion lengths), and pathological diagnoses (based on pathohistological diagnoses) were anonymously extracted from the database. Increase enhancement in axial and sagittal T1-weighted magnetic resonance imaging, or development of diffuse meningeal spread were considered to have disease progression. The patients’ clinical performance status following surgery with or without adjuvant radiotherapy was analyzed, comparing the subgroups with and without disease progression.

4. Functional and Performance Grades

The KPS enables the quantification of a patient’s overall state and quality of life. The score ranges from 0 to 100, with 100 indicating that the patient has normal physical abilities with no signs of disease, and 0 indicating that the patient is dead. The clinical functional status was assessed immediately before operation and 1, 6, 12, 24, and 60 months after surgery.

5. Statistical Analysis

The survival period, defined as the number of months from surgery to death, was censored at the last available follow-up or cutoff study date (December 31, 2020) for those who were still alive. Progression-free survival (PFS) was estimated using the Kaplan-Meier method with associated log-rank tests for the entire cohort and survival in subgroups classified based on the presence/absence of adjuvant radiotherapy and disease progression. Statistical analyses were performed using JMP statistical software ver. 13 (SAS Institute Inc., Cary, NC, USA). The chi-square test was used for continuous and binary values. For non-parametric tests, the Mann-Whitney U-test and Fisher exact probability test were used to compare subgroups. Significance of the obtained results was assessed at the 5% level.

6. Ethics

This study is a multicenter cohort study approved by the Neurospinal Society of Japan. The research protocol has been approved by the Institutional Review Board of Tohoku University Hospital (2021-1-130) and the participating institutions.

RESULTS

Patient demographics are described in Table 1. Patients included 32 men and 21 women with a mean age of 50.3 ± 22.6 years.
years (range, 2–88 years). The groups with and without radiation comprised 23 and 30 patients, respectively. The lesions were cervical (n = 13), cervicothoracic (n = 14), thoracic (n = 14), thoracolumbar (n = 3), and lumbosacral (n = 9). The mean overall disease progression rate (the number of progressions/the total of 53 patients) was 47.1% and mortality rate was 15.1% (8 of 53) during a mean follow-up period of 48.4 ± 39.8 months (range, 2.5–144.5 months). Seven out of 8 patients had death related with tumor burden and 1 patient died of a cause other than tumor. Overall survival (OS) and PFS were depicted with Kaplan-Meier curves (log rank, p = 0.092, p = 0.163) (Fig. 1). Tumors located in the cervical spine and with high MIB-1 index were more likely to receive post-operative radiation treatment (Table 2).

In the radiation group (n = 23), 3 patients (13%) underwent subtotal resection, 9 (39.2%) underwent partial resection, and 11 (47.8%) underwent open biopsy. These 23 patients underwent adjuvant radiotherapy 28 days (range, 15–91 days) after surgery. The radiation dose given to grade II spinal cord astrocytoma ranged between 45 and 50.4 Gy delivered in a conventional dose per fraction of 1.8–2.0 Gy. During the 36.8 months follow-up period, 11 patients (47.8%) showed clinical deterioration, exhibiting either local recurrence/progression (n = 6), intracranial dissemination (n = 1), or combined local progression and diffuse meningeal spread (n = 4). Treatments for local progression were reoperation (n = 1), temozolomide administration (n = 4), and palliative therapy (n = 1). Pathohistological findings of the reoperation for local progression revealed grade II glioblastoma, which suggested malignant transformation. The transition of KPS is shown in Fig. 2. KPS in subgroups without disease progression stayed flat, whereas KPS in the disease progression subgroup continued to decrease before adjuvant radiotherapy and was aggravated after the confirmation of progressive disease. In the radiation group, disease progression was more common in younger than older patients (Table 3).

In the group without radiation (n = 30), 5 patients (16.7%) underwent subtotal resection, 15 (50%) underwent partial resection, and 10 (33.3%) underwent open biopsy. In patients treated by only biopsy, close observation was made without any adjuvant treatment due to concern of radiation induced myelopathy and malignant transformation. During the 57.3 ± 39.8-month follow-up period, 14 patients (46.7%) showed clinical deterioration, exhibiting either local recurrence/progression (n = 12, 85.7%) or combined local recurrence/progression and dif-

### Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean ± SD (range)</td>
<td>50.3 ± 22.6 (2–88)</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>32:21</td>
</tr>
<tr>
<td>The length of lesion (mm), mean ± SD (range)</td>
<td>68.1 ± 43.9 (14–250)</td>
</tr>
<tr>
<td>Cervical</td>
<td>13</td>
</tr>
<tr>
<td>Cervicothoracic</td>
<td>14</td>
</tr>
<tr>
<td>Thoracic</td>
<td>14</td>
</tr>
<tr>
<td>Thoracolumbar</td>
<td>3</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>9</td>
</tr>
<tr>
<td>Degree of surgical resection</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>21</td>
</tr>
<tr>
<td>Partial resection</td>
<td>24</td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>8</td>
</tr>
<tr>
<td>Initial KPS (%), mean (range)</td>
<td>69.1 (20–90)</td>
</tr>
<tr>
<td>Disease progression rate (%)</td>
<td>47.1 (25/53)</td>
</tr>
<tr>
<td>MIB-1 index (%), mean (range)</td>
<td>4.3 (0.01–20)</td>
</tr>
</tbody>
</table>

SD, standard deviation; KPS, Karnofsky Performance Scale.

<table>
<thead>
<tr>
<th>Overall survival (day)</th>
<th>Probability of survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No radiation</td>
<td>100</td>
</tr>
<tr>
<td>Radiation</td>
<td>50</td>
</tr>
<tr>
<td>p = 0.092, log rank</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression free survival (day)</th>
<th>Probability of survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No radiation</td>
<td>100</td>
</tr>
<tr>
<td>Radiation</td>
<td>50</td>
</tr>
<tr>
<td>p = 0.163, log rank</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Overall survival and progression-free survival in 53 grade II spinal cord astrocytoma.
fuse meningeal spread (n = 2, 14.3%). Treatments for local recurrence/progression were reoperation (n = 5), radiotherapy after reoperation (n = 1), radiotherapy with/without temozolomide administration (n = 2), and palliative therapy (n = 4). The transition of KPS is shown in Fig. 2. KPS in the subgroup without disease progression stayed flat with a slight up and down,

Table 2. Comparison of 53 grade II spinal cord astrocytoma patients with or without adjuvant radiotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with adjuvant radiotherapy group (n = 23)</th>
<th>Patients without adjuvant radiotherapy group (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.9 (16–88)</td>
<td>50.7 (2–83)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>13:10</td>
<td>19:11</td>
<td>NS</td>
</tr>
<tr>
<td>The length of lesion (mm)</td>
<td>66.8 (8–250)</td>
<td>69.1 (14–170)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial KPS (%)</td>
<td>68.3 (40–90)</td>
<td>75.7 (50–90)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical/the total lesions</td>
<td>8/23 (34.8)</td>
<td>20/30 (66.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Degree of resection</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Biopsy</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Partial resection</td>
<td>9</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (34.8)</td>
<td>7 (23.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (4.3)</td>
<td>3 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1 (4.3)</td>
<td>5 (16.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer</td>
<td>3 (13)</td>
<td>2 (6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2 (8.7)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>MIB-1 index</td>
<td>6.7 (0.02–12)</td>
<td>1.9 (0.01–4.5)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Hazard ratio (log rank)

| Overall survival                |                                                   |                                                      |         |
| Median days                     | 1,103                                             | 1,720                                                |         |
| Death                           | 5 (21.7)                                          | 3 (10.0)                                             |         |
| Progression free survival       |                                                   |                                                      |         |
| Median days                     | 816                                               | 5,775                                                |         |
| Progression                     | 12 (52.2)                                         | 14 (46.7)                                            |         |

Values are presented as mean (range) or number (%).
KPS, Karnofsky Performance Scale; NS, not significant.

Fig. 2. The transition of Karnofsky Performance scale in adjuvant radiotherapy and no adjuvant radiotherapy group with or without disease progression. OP, operation; 6M, 6 months; 12M, 12 months; 24M, 24 months; 60M, 60 months.
whereas KPS in the disease progression subgroup decreased gradually just after operation and then deteriorated. There were no significant differences regarding age, lesion length, initial KPS, the percentage of cervical lesions, the extent of resection, or the MIB-1 index (Table 4).

**DISCUSSION**

Due to the rarity of spinal cord gliomas, no consensus has been reached in the literature regarding the role of adjuvant radiotherapy for grade II spinal cord astrocytoma.6-11 Díaz-Aguilar et al.12 report that younger age, gross total resection and absence of radiotherapy positively influenced survival factors in a series of 561 patients with low-grade spinal cord astrocytoma. A systematic review by Hamilton et al.13 found a negative correlation between radiation therapy and survival for low-grade spinal cord tumors (hazard ratio for OS, 5.20; p < 0.01). Lastly, Abdel-Wahab et al.14 report a multivariate analysis in 40 patients indicating that adjuvant radiotherapy enhanced disease progression. However, the extent of tumor resection has not been clearly shown in these studies, and the impact and therapeutic effect of radiotherapy have not been clarified.

Meticulous microsurgical technique and use of intraoperative neuromonitoring is the standard of care to maximize safe surgical resection in diffuse spinal cord astrocytomas, however, the lack of a separation plane and changes in sensory and motor evoked potential correlating with severe postoperative neurological dysfunction usually precludes a gross total resection of these lesions. This study investigated the impact of radiotherapy on clinical performance status by KPS, focusing on patients with either subtotal, partial resection or biopsy. The tolerance dose for the spinal cord has been reported to be 45–50 Gy with conventional fractionation schedules of 1.8–2 Gy/day, and the upper dose in the present study was under this level.15 The actual incidence of myelopathy with these conventionally fractionated doses is less than 0.2%–0.5% after 50 Gy and 1%–5% after 60 Gy.16 Additionally, patients who did not presented disease progression presented improvement in the KPS regardless of the radiation status. This observation can correlate with the decompressive effect of surgery as result of laminectomy and duraplasty during the partial resection or biopsy. Furthermore, regardless of adjuvant radiotherapy, KPS in both disease progression groups, especially radiation group, decreased gradually before the confirmation of disease progression.

The present study demonstrate that disease progression was more frequent in younger than older patients who received postoperative radiation therapy. This observation goes along with increase evidence younger age has been increasingly identified as a surrogate of aggressive behavior in adolescents and young adults (AYAs, age 15–39 years).17 It is considered that AYAs have polymorphisms or genomic properties that differ from older people with respect to cancer susceptibility and treatment. For example, melanomas with BRAF mutations are more prevalent in the AYA population and thus are more likely to respond to a BRAF inhibitor.18 Less favorably, triple negative breast cancer is more prevalent in patients under 40 years and is associated with increased mortality partly due to fewer treatment options.19 Similarly, spinal cord astrocytoma among AYAs may have unique genetic and epigenetic differences compared with older population.

Extent of resection is one of the most contentious and intriguing aspects of intramedullary spinal cord tumors, which had a

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**Table 3. Characteristics of 23 grade II spinal cord astrocytoma patients with adjuvant radiotherapy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No disease progression group (n = 12)</th>
<th>Disease progression group (n = 11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57.8 (16–88)</td>
<td>41.3 (18–75)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>The length of lesion (mm)</td>
<td>64.9 (34–151)</td>
<td>68.9 (15–250)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial KPS (%)</td>
<td>70 (40–90)</td>
<td>66.4 (40–90)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical/the total lesions</td>
<td>3/12 (25)</td>
<td>1/11 (9.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Extent of resection (biopsy/subtotal+partial resection)</td>
<td>4/8 (50)</td>
<td>7/4 (175)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MIB-1 index</td>
<td>5.9 (0.01–20)</td>
<td>7.4 (0.7–10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are presented as mean (range) or number (%).

KPS, Karnofsky Performance Scale; NS, not significant.

**Table 4. Characteristics of 30 grade II spinal cord astrocytoma patients without adjuvant radiotherapy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No disease progression group (n = 16)</th>
<th>Disease progression group (n = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.7 (6–72)</td>
<td>56.4 (2–83)</td>
<td>NS</td>
</tr>
<tr>
<td>The length of lesion (mm)</td>
<td>79 (14–170)</td>
<td>57.7 (33–90)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial KPS (%)</td>
<td>65 (20–90)</td>
<td>75.7 (50–90)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical/the total lesions</td>
<td>6/16 (37.5)</td>
<td>3/14 (21.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Extent of resection (biopsy/ partial+subtotal resection)</td>
<td>6/10 (60)</td>
<td>4/10 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>MIB-1 index</td>
<td>2.7 (0.01–10)</td>
<td>1.9 (0.01–4.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are presented as mean (range) or number (%).

KPS, Karnofsky Performance Scale; NS, not significant.
significantly greater factor in patients with grade II spinal cord astrocytoma with adjuvant radiotherapy in our study. A systematic review by Hamilton et al.\textsuperscript{13} showed patients undergoing GTR had a lower mortality rate at 2.5 and 10-year follow-up than patients with lesser resection volumes. Cytological reduction by greater extent of resection could have a positive effect on disease progression. Also, patients with adjuvant radiotherapy had higher MIB-1 index than those without adjuvant radiotherapy. In the patients with adjuvant radiotherapy, KPS in the disease progression subgroup continued to decrease. It may suggest that the tumor classified according to classical pathohistological diagnosis included more malignant properties. The updated 2021 WHO classification includes various diagnostic genes, molecules, pathways, and pathohistological findings for diagnosis.\textsuperscript{20} Dubbink et al.\textsuperscript{21} reported that out of 123 patients with anaplastic oligodendroglioma according to classical pathohistological classification, 55 patients exhibited intracranial glioblastoma according to the molecular classification. The genetic underpinnings of spinal cord tumors remain less well understood than those of their intracranial counterparts due to their rarity. This study suggested that conventional classical classification for spinal cord astrocytoma did not reflect disease progression and clinical outcome well.

In the present study, one patient showed pathohistological malignant transformation, which was confirmed in the specimen of the reoperation; however, the mechanisms underlying such transformations are still unknown. In the majority of published case reports regarding malignant transformation, patients had received previous radio- or chemotherapy.\textsuperscript{22,23} The incidence of malignant transformation in patients with intracranial low-grade glioma ranges between 23\% and 72\%.\textsuperscript{24,25} On the other hand, the incidence and the latency period of malignant transformation in patients with spinal cord low-grade glioma is unknown, therefore meticulous close observation is essential.

This study has several limitations. First, the indication of adjuvant radiotherapy varies by institution because the role is still debatable. This study is retrospective multi-institutional study and the indication of adjuvant radiotherapy may not be consistent, which could be one of the limitations. Second, this study was retrospective in nature, and the sample size was small and thus had limited statistical power. Despite these limitations, we believe that our study provides important information regarding the impact of adjuvant radiotherapy on the clinical performance status of patients with grade II intramedullary spinal cord astrocytoma.

**CONCLUSION**

Adjuvant radiotherapy did not show effectiveness regarding OS and PFS in patients with grade II spinal cord astrocytoma according to classical classification based on pathohistological findings.

**NOTES**

**Conflict of Interest:** The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: RK; Data curation: RK; Formal analysis: TI; Methodology: JH; Writing - original draft: RK; Writing - review & editing: MM, TT, TE, SS, JM, DU, TM, KH, JH.


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Adjuvant Radiotherapy for Grade II Spinal Cord Astrocytoma


ORCID
Ryo Kanematsu: 0000-0002-6390-2330
Masaki Mizuno: 0000-0002-1761-344X
Tomoo Inoue: 0000-0001-5131-4307
Toshiyuki Takahashi: 0000-0003-0289-4418
Toshiki Endo: 0000-0002-5609-200X
Seiji Shigekawa: 0009-0005-2884-1201
Jun Muto: 0000-0003-4620-2073
Takafumi Mitsuura: 0000-0003-0523-0107
Kazutoshi Hida: 0000-0003-4789-8375

REFERENCES

cer 2008;8:288-98.
Objective: The characteristics, imaging features, long-term surgical outcomes, and recurrence rates of primary spinal pilocytic astrocytomas (PAs) have not been clarified owing to their rarity and limited reports. Thus, this study aimed to analyze the clinical presentation, radiological features, pathological findings, and long-term outcomes of spinal PAs.

Methods: Eighteen patients with spinal PAs who were surgically treated between 2009 and 2020 at 58 institutions were included in this retrospective multicenter study. Patient data, including demographics, radiographic features, treatment modalities, and long-term outcomes, were evaluated.

Results: Among the 18 consecutive patients identified, 11 were women and 7 were men; the mean age at presentation was 31 years (3–73 years). Most PAs were located eccentrically, were solid or heterogeneous in appearance (cystic and solid), and had unclear margins. Gross total resection (GTR), subtotal resection (STR), partial resection (PR), and biopsy were performed in 28%, 33%, 33%, and 5% of cases, respectively. During a follow-up period of 65 ± 49 months, 4 patients developed a recurrence; however, the recurrence-free survival did not differ significantly between the GTR and non-GTR (STR, PR, and biopsy) groups.

Conclusion: Primary spinal PAs are rare and present as eccentric and intermixed cystic and solid intramedullary cervical tumors. The imaging features of spinal PAs are nonspecific, and a definitive diagnosis requires pathological support. Surgical resection with prevention of neurological deterioration can serve as the first-line treatment; however, the resection rate does not affect recurrence-free survival. Investigation of relevant molecular biomarkers is required to elucidate the regrowth risk and prognostic factors.

Keywords: Pilocytic astrocytoma, Spinal cord, Imaging features, Prognosis
INTRODUCTION

Pilocytic astrocytomas (PAs) are World Health Organization (WHO) grade I tumors that account for approximately 25% and 1.5% of all pediatric and adult brain tumors, respectively. They can occur anywhere in the neuraxis, with the cerebellum, cerebral hemispheres, optic tract, and hypothalamus and the brainstem being the most common locations. They are generally considered to be slow-growing, well-defined lesions that are surgically curable with gross total resection (GTR). Primary spinal PAs constitute a rare subset of these tumors, accounting for only 2% of all PAs and 21% of all intramedullary glial tumors in pediatric and young adult populations. They include secondary spinal PAs caused by the dissemination of intracranial PAs through the cerebrospinal fluid. Similar to other intramedullary spinal tumors, primary spinal PAs are managed using surgical resection; however, clear evidence that supports the need for postoperative adjuvant treatment is lacking. Accurate preoperative diagnosis of spinal PAs helps in the planning of clinical treatments; surgeons can determine the optimal extent of resection and postoperative adjuvant treatments. Due to the rarity of the condition, less than 100 cases have been reported so far. The common clinical data of such cases, such as demographics, natural history, optimal treatment, and prognosis, remain unclear.

Thus, the aim of this study was to analyze the clinical presentation, radiological features, and long-term outcomes of spinal PAs. Accordingly, we retrospectively analyzed the medical records and long-term follow-up data of 18 patients with spinal PAs in Japanese spinal tumor groups and reviewed the existing literature on the condition.

MATERIALS AND METHODS

1. Data Source

This study analyzed data obtained in a previous multicenter cohort study on patients treated between 2009 and 2020, which was authorized by the Neurospinal Society of Japan. This database collects data on the clinical courses and surgical outcomes of patients with intramedullary spinal cord tumors treated across 58 neurosurgical centers in Japan (Tables 1, 2).

2. Inclusion and Exclusion Criteria

Eighteen patients with intramedullary spinal cord PAs who were treated surgically and diagnosed pathologically were included in a previous multicenter cohort study. Although the updated 2021 WHO classification specifies various genes, molecules, pathways, and histological findings for diagnosis, patient diagnoses in this study were based on conventional histopathological grading. The extent of resection was classified as macroscopic GTR (100%), subtotal resection (STR; > 90%), partial resection (PR; < 90%), or an open biopsy.

3. Baseline Characteristics

The modified McCormick scale (MMCS) was used to assess the neurological function both perioperatively and during follow-up. We extracted the following data from the database; these data were anonymized: age; sex; duration of symptoms, presence of intracranial lesions; initial diagnosis; resection rate; follow-up term; term of recurrence; MMCS grades preoperatively, postoperatively, at the 12-month follow-up, and at the final follow-up; magnetic resonance imaging (MRI) data, including T1-weighted imaging (WI) findings, T2WI findings, gadolinium (Gd)-enhanced findings, lesion boundary and distribution, syringomyelia, lesion shape and appearance, vertical segment, and maximal length (mm) in the sagittal plane; pathological diagnoses; and histopathological diagnoses. Patients with tumor relapse due to local recurrence/progression, diffuse meningeal spread, or both were categorized into the disease progression subgroup; those without a tumor relapse were categorized into the no-disease progression subgroup. The patients’ postoperative clinical performance status, with or without adjuvant radiotherapy, was compared between the 2 subgroups.

4. Statistical Analysis

The survival period, defined as the number of months from surgery to death, was censored at the last available follow-up or the cutoff study date (December 31, 2020) for those who were still alive. The recurrence-free survival was estimated using the Kaplan-Meier method with associated log-rank tests for the entire cohort. Statistical analysis was performed using JMP ver. 14 (SAS Institute Inc., Cary, NC, USA). Binary variables were analyzed using the chi-square test. Continuous variables were compared between the subgroups using the Mann-Whitney U-test. A p-value of < 0.05 was considered significant. Significance level was set at 5%.

5. Ethics

This multicenter cohort study was approved by the Neurospinal Society of Japan. The research protocol was approved by the Institutional Review Boards of the Tohoku University Hospital (2021-1-130) and the participating institutions.
### Table 1. Demographic data of 18 patients with spinal pilocytic astrocytoma

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Duration (mo)</th>
<th>Location</th>
<th>Intracranial lesion</th>
<th>Initial diagnosis</th>
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BBD, bladder bowel disorder; FU, follow-up; GTR, gross total resection; PR, partial resection; MMCS, modified McCormick score; NA, not analysis; STR, subtotal resection.
We reviewed 2 largest number of spinal PA published by Zhang et al. and Jiang et al. and compared neurological changes and removal rates (Table 3).

RESULTS

1. Patients’ Characters

Eighteen patients (comprising 11 women and 7 men) were included in this study. The overall mean age was 31.7 ± 18.5 years (range, 3–73 years). At admission, neurological examination revealed the following: headache (n = 3 [17%]), back pain (n = 7 [39%]), extremity pain (n = 3 [17%]), extremity weakness (n = 13 [72%]), gait disturbance (n = 13 [72%]), and bladder and rectal disturbances (n = 5 [28%]). The symptoms lasted for varying durations, the mean duration was 7.5 ± 11.2 months (range, 0–38 months). The preoperative MMCS grades at admission were I, II, III, and IV in 3 (17%), 8 (44%), 5 (28%), and 2 patients (11%), respectively (Table 1).

2. MRI Findings

The average PA size was 66.1 ± 54.5 mm (range, 13–178 mm); the average vertebral level involved was 4.2 (range, 1–13). Of the 18 patients included, 8 (44%), 3 (17%), and 7 patients (10%)

Table 2. Radiographic data of 18 patients with spinal pilocytic astrocytoma

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<th>No.</th>
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<th>Boundary</th>
<th>Distribution</th>
<th>Syringomyelia</th>
<th>Shape</th>
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T1WI, T1-weighted image; T2WI, T2-weighted image.

Table 3. The comparison of neurological changes and removal rates among the 2 major previous literatures

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<th>Removal rate</th>
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<td>Improved (%)</td>
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<td>Jiang et al.17</td>
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GTR, gross total resection; STR, subtotal resection; PR, partial resection.

6. Literature Review

We reviewed 2 largest number of spinal PA published by Zhang et al., and Jiang et al. and compared neurological changes and removal rates (Table 3).17,27
had cervical, thoracic, and cervicothoracic junction tumors, respectively. During preoperative MRI, T1WI revealed low intensity and is intensity lesions in 42% and 58% of the patients, respectively. Conversely, T2WI revealed low intensity and high-intensity lesions in 17% and 83% of the patients, respectively. Gd-enhanced T1WI revealed heterogeneous, ring-shaped, and homogenous enhancements in 78%, 6%, and 6% of the patients, respectively; no enhancement was observed in 11% of the patients. The tumor locations were centric and eccentric in 33% and 67% of the patients, respectively; with the tumor borders being regular in 33% and irregular in 67%. The tumors were solid, cystic, and both in 50%, 11%, and 39% of the patients, respectively. Two spinal PAs (10%) showed evidence of hemorrhage. Additionally, 8 patients (44%) had a secondary syrinx: the cervical and thoracic regions were involved in 5 and 3 of these patients, respectively (Table 2).

3. Surgical and Follow-up Outcomes With Recurrence

All patients had PAs, and a total of 18 tumors were treated: GTR, STR, PR and biopsy were performed in 5 (28%), 6 (33%),...
6 (33%), and 1 patient (6%), respectively. The mean MIB-1 labeling index was 2.8%. In terms of perioperative complications, no cerebrospinal fluid leakage, postoperative hemorrhage, or infection was observed in the surgical area in any patient.

Postoperatively, the MMCS grade improved in 6 patients (33%), remained unchanged in 10 patients (56%), and worsened in 2 patients (11%). Four patients experienced postoperative neurological deterioration: this was transient and normalized to the baseline status in 2 patients (cases #3 and #6) but permanent in the other 2 patients (cases #14 and #16).

The average follow-up period was of 65.2 ± 49.2 months (range, 11–140 months). No deaths occurred, but 4 cases of re‐enlargement (22%) were observed. These 4 patients received additional treatments.

4. Cases of Recurrence or Regrowth

In case #5, MRI at admission revealed a high-intensity lesion on T2WI (Fig. 1A) and a heterogeneously enhanced, unclear, and eccentrically shaped lesion on Gd-enhanced T1WI (Fig. 1B: sagittal; Fig. 1C: axial). The patient underwent a biopsy (Fig. 1D) and received radiotherapy combined with temozolomide (TMZ) chemotherapy, which resulted in a neurologically stable preoperative and postoperative MMCS grade of I. Fourteen months after the initial therapy, MRI revealed tumor regrowth on T2WI (Fig. 1E) and T1WI with Gd enhancement (Fig. 1F). The patient received TMZ+avastin monthly, and the tumor size was controlled for 13 months as seen on T2WI (Fig. 1G) and T1WI with Gd enhancement (Fig. 1H).

In case #13, preoperative MRI revealed a cystic, eccentric tumor with an irregular shape and an unclear boundary at the C1–2 level on T1WI (Fig. 1I) and T2WI (Fig. 1J) and on axial (Fig. 1K) and sagittal (Fig. 1L) Gd-enhanced T1WI. The initial surgery involved only partial removal of the tumor; 8 months later, MRI revealed tumor regrowth on T2WI (Fig. 1M) and sagittal T1WI with Gd enhancement (Fig. 1N). The patient received 12 courses of TMZ, and a second PR was performed 26 months after the initial surgery. After the second surgery, the patient received carboplatin chemotherapy and radiotherapy. The overall survival was of 122 months. MRI revealed the shrunken tumor on T2WI (Fig. 1O) and on T1WI with Gd enhancement (Fig. 1P).

In case #17, the patient underwent PR, received 12 cycles of TMZ at the outpatient clinic, and exhibited recurrence 134 months after the initial surgery. In case #18, the patient underwent GTR and no additional therapy; however, they experienced a recurrence 60 months later, and thus, underwent addi-

Fig. 2. Kaplan-Meier curve of recurrence-free survival in the GTR and non-GTR groups. There are no significant differences between the GTR and non-GTR (STR, PR, and biopsy) groups (p = 0.94). GTR, gross total resection; STR, subtotal resection; PR, partial resection.

DISCUSSION

1. MRI Findings of Spinal PAs

Our study findings and literature review reveal that a preoperative imaging-based diagnosis of spinal PAs remains challenging. Following preoperative MRI, 11 out of 18 patients were radiologically diagnosed with astrocytomas (50%), ependymomas (22%), pilomyxoid astrocytomas (5%), and gliomas (11%). Astrocytomas and ependymomas are the most commonly misdiagnosed tumors. This misdiagnosis is attributed to the lack of distinctive imaging features; both spinal PAs and ependymomas present with secondary syringomyelia cavity formation and heterogeneous enhancement on imaging. In 4 cases in our series, the tumors mimicked ependymomas on MRI. However, spinal PAs usually show an eccentric growth pattern (67% in our case series), which is different from the characteristic centric growth pattern of ependymomas.29 Spinal PAs are rarely associated with intratumoral hemorrhage; it occurred in only 10% of our cases, as compared to the incidence of 0.5%17 and 12.5%24 reported previously. Conversely, the incidence of intratumoral hemorrhage in spinal ependymomas is high at 78%.28 Heterogeneous cyst formation, a common MRI feature of PAs report-
ed previously, was observed in approximately two-thirds (67%) of the PAs in our study.

There were no characteristic findings of PAs on MRI. These tumors appeared solid (present study: 50%; literature: 30%–44%), cystic (present study: 11%), and both solid and cystic (present study: 39%; literature: 47%–70%). The tumor borders were clear (present study: 28%; literature: 15%–60%) and unclear (present study: 72%; literature: 40%–85%). The distributions were centric (present study: 33%; literature: 38.5%) and eccentric (present study: 67%; literature: 61.5%). Secondary syrinx was found in 44% of our patients (literature: 37%–55%). Two spinal PAs in our study (10%) showed evidence of hemorrhage (literature: 17%). On preoperative MRI, T1WI revealed lesions of low intensity (incidence in present study: 42%; literature: 10%–25%), isointensity (present study: 58%; literature: 42%–15%–69%), and high intensity (literature: 10%). On preoperative MRI, T2WI revealed lesions of low intensity (present study: 25%; literature: not available), high intensity (present study: 75%; literature: 63%–85%), mixed intensity (literature: 5%), and isointensity (literature: 10%–19%). Gd-enhanced T1WI revealed heterogeneous enhancement (present study: 78%; literature: 36%–45%), no enhancement (present study: 11%; literature: 0%–14%), homogenous enhancement (present study: 6%; literature: 21%–25%), and ring-shaped enhancement (present study: 6%; literature: 30%–42%).

2. Clinical Outcomes and Recurrence

Our findings suggest that the benefits and drawbacks of GTR do not play a role in tumor recurrence. The tumor size (p = 0.30) and MIB-1 index (p = 0.36) were also not associated with recurrence. Interestingly, the MIB-1 index has been reported to be unrelated to prognosis. The MIB-1 index values in patients harboring with PA in our study were not significantly higher (mean, 2.7 ± 2.0) than those reported previously (≥ 4) in patients harboring with PAs of the brain. None of the 18 patients in our study died, indicating no cases of mortality; however, 4 cases of recurrence were observed. The average term of observation was 65.2 ± 49.2 months (range, 11–140 months). Although complete surgical resection is considered the first-line treatment for spinal PAs to prevent the worsening of neurological symptoms, 5 out of 18 patients underwent total resection (28%) in our study with maintained or improved MMCS grades, and 4 experienced a recurrence. In recurrent cases, 1 case was biopsy, 2 cases were PR, and 1 was GTR. The purpose of surgery is to confirm the pathological characteristics, establish a future treatment plan, and decrease the tumor mass. In this study, 6 and 6 patients underwent STR and PR, respectively. The removal rate was not related to border irregularity (p = 0.25), indicating that the tumor shape was not the only factor affecting the removal rate. Intraoperative neuromonitoring findings also played a role in determining the removal rate and postoperative neurological deficits. Some researchers consider cyst walls to represent tumor invasion, while others consider these walls to represent reactive changes; our study found that aggressive removal of the cyst walls was unnecessary, as the removal rate did not contribute to recurrence.

Our study also demonstrated that functional recovery after a surgery for PA was challenging: only 6 out of the 18 patients (33%) analyzed showed an improvement, whereas the remaining 10 (56%) and 2 patients (11%) exhibited no changes and permanent deterioration in the MMCS grade, respectively. However, surgical treatment prevented both immediate and permanent worsening of the MMCS grade postoperatively (Table 3).

Four patients (STR, 1; PR, 2; Biopsy, 1) experienced tumor progression and required additional treatment, including surgery, chemotherapy, and radiotherapy. Various treatments have been administered for PA recurrence. Despite incomplete resections and no adjuvant therapy, the tumor remained stable in 14 patients (78%) without growth during an average follow-up period of 65.2 months. While a few reports have described the use of chemotherapy for spinal PAs, the efficacy of chemotherapy and radiation therapy for spinal PAs remains unclear.

Therefore, in the future, it will be necessary to verify the efficacy of chemoradiation therapy by analyzing not only histological data, but also molecular data.

3. Literature Review

A considerable number of reports are available on PAs. We have compared our study findings with those from 2 previous studies with larger sample sizes. These studies were performed by Zhang et al. and Jiang et al.

The 3 studies are similar in terms of the patients’ demographics (including age and sex) and clinical characteristics (tumor location and number of tumor segments), but different in terms of the surgical outcomes. Table 3 summarizes the findings from these 3 studies. The removal rates in our study differ from those observed in the 2 previous studies, which revealed excellent removal rates. However, the recurrence rate is almost the same among the 3 studies. Conversely, Jiang et al. reported an excellent total removal rate of 81%, but a recurrence rate of 37.5%, which is almost twice as high as that noted in our study. This
indicates that the removal rate does not contribute to the recurrence rate. Because the rate of neurological worsening is also unchanged in the 3 studies, the basic surgical strategy remains the same: if the neurological findings do not worsen, maximal removal can be performed. The 2 previous studies were single centered in nature and obtained very good surgical outcomes; however, such good outcomes are difficult to obtain in a multicenter study with different surgeons, such as ours. Progression-free survival, by definition, should be calculated from the total number of cases; however, Jiang et al.,17 and Zhang et al.27 only considered recurrent cases. Therefore, it is not possible to directly compare our findings with the findings from their studies; such comparisons are possible if the progression-free survival in these previous studies is calculated correctly according to the aforementioned definition.

In conclusion, the removal rate does not contribute to the recurrence rate; if the neurological findings do not worsen, maximal removal can be performed (Table 3).

4. Limitations of This Study

Genetic examination of the tumors could not be performed due to the study’s multicentered, retrospective nature. Furthermore, this rarity of this tumor limits our sample size, even for a multicenter study. Further investigations into the molecular biomarkers of recurrence or prognosis are indispensable. Despite these limitations, we believe that the present study is one of the largest case series with a relatively long-term follow-up and detailed data. It provides important information regarding the treatment strategy for spinal PAs.

The limited sample size (n = 18) restricts the study’s statistical power and may compromise the reliability of its conclusions. The retrospective nature of the study could introduce potential biases, such as selection or information bias, which may affect the study’s validity. The wide age range of the included patients (3–73 years) may lead to confounding, as various age groups could present with different clinical manifestations or outcomes. The nonspecific imaging features of spinal PAs pose difficulties in establishing a definitive diagnosis, and may have resulted in misclassification of cases within the study.

CONCLUSION

Primary spinal PAs are rare, eccentric, and intermixed cystic and solid intramedullary cervical tumors. Surgical resection with prevention of neurological deterioration can be the first-line treatment, but the resection rate does not affect recurrence-free survival. The imaging features of spinal PAs are nonspecific, and a definitive diagnosis requires pathological support. Investigation of molecular biomarkers is required to elucidate the regrowth risk and prognostic factors. Future studies must investigate the significance of chemotherapy and radiotherapy in the treatment of PAs. Furthermore, the treatment of recurrent tumors should be established with the information of molecular biomarker.

NOTES

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Author Contribution: Conceptualization: JM, HM, SS, RK, TM, DU, MJ, Tle, Tl; Writing–Original Draft: JM; Writing–Review & Editing: HM, TE, YH.

ORCID
Jun Muto: 0000-0003-4620-2073
Hidetoshi Murata: 0000-0001-7356-979X
Seiji Shigekawa: 0009-0005-2884-1201
Daisuke Umebayashi: 0000-0001-8797-9546
Ryo Kanematsu: 0000-0002-6390-2330
Tomoo Inoue: 0000-0001-5131-4307
Toshiki Endo: 0000-0002-5609-200X
Yuichi Hirose: 0000-0002-1305-1830

REFERENCES
Characters and Outcomes of 18 Spinal Pilocytic Astrocytoma


Original Article

Predictors of Cerebrospinal Fluid Leak Following Dural Repair in Spinal Intradural Surgery

Lei Jiang1,*, Alexandru Budu1,*, Muhammad Shuaib Khan3, Edward Goacher4, Angelos Kolias3, Rikin Trivedi3, Jibin Francis3

1Department of Orthopaedic Surgery, Singapore General Hospital, Singapore
2Queen Elizabeth Hospital, Birmingham, UK
3Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
4Department of Neurosurgery, Hull University Teaching Hospitals NHS Trust, Hull, UK

Objective: We aim to compare the effectiveness of dural closure techniques in preventing cerebrospinal fluid (CSF) leaks following surgery for intradural lesions and seek to identify additional factors associated with CSF leaks. Surgical management of spinal intradural lesions involves durotomy which requires a robust repair to prevent postoperative CSF leakage. The ideal method of dural closure and the efficacy of sealants has not been established in literature.

Methods: We performed a retrospective analysis of all intradural spinal cases performed at a tertiary spine centre from 1 April 2015 to 29 January 2020 and collected data on patient bio-profile, dural repair technique, and CSF leak rates. Multivariate analysis was performed to identify predictors for postoperative CSF leak.

Results: A total of 169 cases were reported during the study period. There were 15 cases in which postoperative CSF leak was reported (8.87%). Multivariate analysis demonstrated that patient age (odds ratio [OR], 0.942; 95% confidence interval [CI], 0.891–0.996), surgical indication listed in the "others" category (OR, 44.608; 95% CI, 1.706–166.290) and dural closure with suture, sealant and patch (OR, 22.235; 95% CI, 2.578–191.798) were factors associated with CSF leak. Postoperative CSF leak was associated with the risk of surgical site infection with a likelihood ratio of 8.704 (χ² (1) = 14.633, p < 0.001).

Conclusion: Identifying predictors for CSF leaks can assist in the counselling of patients with regard to surgical risk and expected postoperative recovery.

Keywords: Intradural spinal tumors, Dural repair, Cerebrospinal fluid leak

INTRODUCTION

The surgical management of spinal intradural lesions involves opening of the dura1 which requires a robust repair to prevent postoperative cerebrospinal fluid (CSF) leakage. Despite best efforts, reported rates of CSF leakage range from 6.6%2 to 10%.3 Failure to achieve adequate dural closure could lead to potential complications of CSF fistulas,4 wound infection,5 nerve root entrapment6 and meningitis.7 To avoid these debilitating complications, watertight closure is advocated and is typically achieved with a meticulous dural suture. Biological materials have also been developed in recent decades to supplement dural closure primarily with the use of sealants such as fibrin which provides an adhesive effect from the formation of fibrin cross-linking polymers,8 allowing improved watertight closure in animal models.9 The clinical evidence for sealants is still debated, with a recent review8 recognizing the paucity of randomized control trials (RCTs) examining sealants in dural closure. Specific to intradural pathologies, retrospective studies have not demonstrated the superiority of fibrin sealants.10,11 Although RCTs have demonstrated the efficacy of autologous fibrin tissue12 and hydrogel sealants,13 a systematic review by Choi et al.14 suggested...
that sealants as an adjunct to primary closure did not reduce the rate of CSF leak.

Dural management is especially challenging in intradural lesions which vary in circumferential position and behavior. Resection of meningiomas, especially in recurrent cases, may lead to large dural defects which cannot be reliably closed primarily. To overcome the risk of CSF leak, dural patch techniques have evolved from epidural fat patches to biomaterials such as polyglactin acid sheets, collagen scaffolds and hemostatic pads. There is currently a lack of high-quality evidence demonstrating the efficacy of dural augmentation products. Of note, a retrospective study has shown higher rates of CSF leaks in cases treated with dural augmentation and no reliable comparison between the materials could be made.

Besides dural closure techniques, other factors could increase the risk of CSF leak in the management of intradural lesions. Sin et al. described that patients’ age and level of surgeon’s training were factors that predicted dural tear in patients undergoing lumbar surgery. In terms of surgeries requiring intended durotomy, however, predictive factors have yet to be identified in current literature. Filling this knowledge gap will help guide surgeons in the counselling of patients with regards to postoperative course and complications, in addition to aiding the preoperative preparation of dural augments and sealants.

Given this deficiency in literature, we aim to compare the effectiveness of dural closure techniques in preventing CSF leak following surgery for intradural lesions. Additionally, we seek to identify additional factors associated with CSF leak and evaluate their predictive ability, including patient bio-profile, the presence of a dural defect and the nature of the intradural lesion.

**MATERIALS AND METHODS**

We retrospectively analysed all intradural spinal cases performed at a tertiary spine centre from 1st of April 2015 to 29th January 2020 by a team of 3 fellowship-trained neurosurgeons. Operative notes, clinic notes, inpatient records, and imaging studies recorded in our electronic patient records were recorded in an anonymized dataset that did not include patient identifiers. The following selection criteria was applied: (1) surgical procedure must have included surgical opening of the spinal dura mater, (2) clear documentation of the dural closure technique applied and the material used.

The dural closure techniques were categorized into the following groups: (1) running stitch closure, (2) stitch closure plus application of dural sealant, (3) stich closure plus application of dural patch on top and dural sealant, (4) other closure techniques (e.g., application of dural clips, duraplasty techniques).

A dural defect was defined as a durotomy that could not be opposed primarily in a tension-free environment as assessed by the primary surgeon, usually due to dural adhesion to the tumour such as in meningiomas. These dural defects tend to result in a broader durotomy compared to a linear durotomy which could be primarily repaired. In these cases, the dural edges were sutured to the dural patch graft to maintain a tension-free closure. In cases without a dural defect, dural closure was performed using a 6-0 prolene running, nonlocking suture. The use of dural sealant, however, was not standardized and is based on surgeon choice. The dural sealant preferred in our unit during the duration of the study was Tissel (Baxter Healthcare Corp., Deerfield, IL, USA). The dural patches used were either TissuePatch-Dural (Tissuemed Surgical Technologies, Leeds, UK), Duraform (Depuy Synthes, Raynham, MA, USA) or Neuro-Patch (B Braun, Tuttingen, Germany). In instances where dural patch grafting was required or performed, DuraGuard (Baxter Healthcare Corp., Deerfield, IL, USA) was used. In all instances, after dural closure, a Valsalva manoeuvre was performed by the anaesthetic team to assess for absence of CSF egress, indicating the completeness of CSF closure.

A postoperative CSF leak was defined in this study as a CSF discharge from the operative wound or CSF collection which required prolonged bed rest, intervention during the same index admission or a subsequent readmission. In the cases where the nature of the fluid discharge was unclear, CSF was differentiated from serous exudate by the use of B-2 transferrin assay. Management of postoperative CSF leak was dependent on the surgeon’s preference but included at least 24 hours of bedrest. Time of onset of CSF leak was recorded as either: (1) within 48-hour postoperation, (2) after the initial 48-hour postoperation and until hospital discharge, (3) post hospital discharge. Postoperative instructions such as flat bed rest were analysed to see if they have any impact on the rate of CSF leak. Age, sex, and body mass index (BMI) data were also collected together with recorded comorbidities. The presence of surgical site infection was also noted, including both superficial and deep infections as defined by The National Institute for Health and Care Excellence (NICE) guidelines.

Data analysis was performed using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA). Chi-squared analyses were performed to evaluate the correlation between presence of postoperative CSF leak and categorical factors of sex, BMI category, type of intradural lesion and suture technique employed. For
multivariate analysis, we included the following variables: age, sex, BMI, type of intradural tumor, dural closure technique, the presence of a dural defect, whether a wound drain was placed and whether the patient was placed on bed rest following surgery. A logistic regression model was constructed to analyze the multivariate association between postoperative CSF leak and the abovementioned variables. Odds ratios and 95% confidence intervals were generated from logistic regression models. The Hosmer-Lemshow Goodness-of-Fit test was used to evaluate the lack of fit in the constructed model. Wald values of examined variables were evaluated and p-values of < 0.05 were considered statistically significant.

As the data used for the study was retrieved from an anonymized audit registry, informed consent was deemed exempt from requirement. Institutional Review Board approval was not required as the data was based on an anonymized audit registry.

**RESULTS**

A total of 169 cases were reported during the study period in a tertiary multisurgeon neurosurgical centre. No patients were excluded for unclear documentation of dural repair technique. All durotomies were created in the dorsal midline or dorsolateral overlying the intradural lesion. There were 15 cases in which postoperative CSF leak was reported (8.87%) in the following periods: 1 case (6.67%) of early (≤ 48 hours) CSF discharge which required suturing on the ward, 6 cases (40%) of CSF leakage during the same index admission (> 48 hours till discharge) and 8 cases (53.3%) of late presentation (after hospital discharge) with pseudo-meningoceles. The patients are dichotomized into groups which did not experience CSF leak (no leak) and those with CSF leak (leak) with their profile described in Table 1.

In terms of patient demographics comorbidity profile, sex was not associated postoperative CSF leak, but univariate analysis revealed that patients with CSF leak tend to be younger (53.7 ± 19.4 years vs. 41.7 ± 14.5 years, p = 0.020). Patients were categorized by their BMI with overweight defined as BMI of 25 kg/m² and above. The majority of patients with CSF leak (66.7%) did not have significant comorbidities nor were they smokers (86.7%). Neither smoking (p = 0.280) nor diabetes (p = 0.898) was associated with postoperative CSF leak.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 169)</th>
<th>No Leak (n = 154)</th>
<th>Leak (n = 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.352</td>
</tr>
<tr>
<td>Male</td>
<td>71</td>
<td>63 (88.7)</td>
<td>8 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>98</td>
<td>91 (92.9)</td>
<td>7 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52.7 ± 19.3</td>
<td>53.7 ± 19.4</td>
<td>41.7 ± 14.5</td>
<td>0.020*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td>0.208</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>69</td>
<td>65 (94.2)</td>
<td>4 (5.8)</td>
<td></td>
</tr>
<tr>
<td>≥ 25</td>
<td>86</td>
<td>76 (88.4)</td>
<td>10 (11.6)</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
<td></td>
<td>0.084</td>
</tr>
<tr>
<td>Meningioma</td>
<td>39</td>
<td>38 (97.4)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Schwannoma/neurofibroma</td>
<td>53</td>
<td>51 (96.2)</td>
<td>2 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>2</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Arachnoid cyst/web</td>
<td>3</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Intramedullary tumor</td>
<td>27</td>
<td>22 (81.5)</td>
<td>5 (18.5)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>45</td>
<td>38 (84.4)</td>
<td>7 (15.6)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Dural closure technique</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suture</td>
<td>73</td>
<td>67 (91.8)</td>
<td>6 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Suture with Sealant</td>
<td>41</td>
<td>40 (97.6)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Suture, sealant, and patch</td>
<td>40</td>
<td>32 (80)</td>
<td>8 (20)</td>
<td></td>
</tr>
<tr>
<td>Suture, sealant, and patch for dural defect</td>
<td>6</td>
<td>6 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). CSF, cerebrospinal fluid; BMI, body mass index. *p < 0.05, statistically significant differences.
The main pathologies treated were spinal cord schwannomas/neurofibromas (n = 53, 31.36%) followed by intradural meningiomas (n = 39, 23.08%) and intramedullary tumors (n = 27, 15.98%) as shown in Fig. 1. Rare intradural cases such as spinal cord teratomas, epidermoid or dermoid tumors, spinal cord herniation, open spinal cord biopsy were labelled as “others” (Fig. 1, Table 1). The proportion of patients in each indication who experienced CSF leak is also described in Table 1.

Dural closure technique is categorized into suture only, suture with sealant, suture with sealant and patch or others. Dural defects were reported in 56.4% of cases. The CSF leak rate based on technique is described in Table 1. Chi-square test of independence revealed that dural closure technique was associated with postoperative CSF leak, \( \chi^2(3, N = 160) = 8.4, p = 0.004 \). Dural closure technique was also associated with the reported presence of a dural defect, \( \chi^2(3, N = 160) = 16.9, p < 0.001 \).

Peri- and postoperative factors such as the effect of the presence of dural defects, prolonged bed rest and wound drains were evaluated and chi-square test of independence did not show a significant association between these factors and postoperative CSF leak. Forty-six point seven percent of patients with CSF leak and 51.8% of patients without CSF leak were allowed unrestricted ambulation and this proportion was not significantly different between the 2 groups (p = 0.704).

Multivariate analysis was performed using both patient profile factors and peri/postoperative factors as described above via logistic regression. The studied predictors and their respective odds ratios are summarized in Table 2. In summary, a younger patient age (OR, 0.942; 95% CI, 0.891–0.996), surgical indication listed in the “others” category (OR, 44.608; 95% CI, 1.706–166.290) and dural closure with suture, sealant, and patch (OR, 22.235; 95% CI, 2.578–191.798) were associated with postoperative CSF leak.

Surgical site infection was present in 4 of 15 (26.7%) of cases with CSF leak and 5 of 152 (3.3%) of cases without CSF leak. Postoperative CSF leak was associated with the risk of surgical site infection with chi-square test of independence demonstrating significance \( \chi^2(1, N = 167) = 14.633, p < 0.001 \) and a likelihood ratio of 8.704. The management of the postoperative CSF leak cases consisted of surgical re-exploration and repair (n = 4), wound stitch (n = 1) and conservative management via pressure dressing (n = 10). The re-exploration strategies consisted of ventriculo-peritoneal shunts (n = 2), thoraco-peritoneal shunt (n = 1) in patients with risk factors for increased intracranial pressure and lumbar drain insertion (n = 1).

**Table 2. Multivariate logistic regression model for developing postoperative CSF leak**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.942</td>
<td>0.891–0.996</td>
<td>0.034*</td>
</tr>
<tr>
<td>Sex</td>
<td>1.489</td>
<td>0.320–6.930</td>
<td>0.612</td>
</tr>
<tr>
<td>BMI</td>
<td>-</td>
<td>-</td>
<td>0.999</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwannoma/neurofibroma</td>
<td>6.348</td>
<td>0.187–21.564</td>
<td>0.304</td>
</tr>
<tr>
<td>Intramedullary tumor</td>
<td>15.616</td>
<td>0.480–50.792</td>
<td>0.122</td>
</tr>
<tr>
<td>Others</td>
<td>44.608</td>
<td>1.706–166.290</td>
<td>0.023*</td>
</tr>
<tr>
<td>Dural closure technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suture</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suture with sealant</td>
<td>-</td>
<td>-</td>
<td>0.998</td>
</tr>
<tr>
<td>Suture, sealant, and patch</td>
<td>22.235</td>
<td>2.578–191.798</td>
<td>0.014*</td>
</tr>
<tr>
<td>Suture, sealant, and patch for dural defect</td>
<td>-</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td>Dural defect</td>
<td>0.130</td>
<td>0.009–1.785</td>
<td>0.127</td>
</tr>
<tr>
<td>Bed rest</td>
<td>0.984</td>
<td>0.190–5.103</td>
<td>0.984</td>
</tr>
<tr>
<td>Wound drain</td>
<td>1.533</td>
<td>0.013–17.887</td>
<td>0.860</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; CI, confidence interval; BMI, body mass index.

*p < 0.05, statistically significant differences.

**DISCUSSION**

Our analysis revealed a CSF leak rate of 8.87%, comparable
to rates reported in previous studies and in a recent review. Postoperative CSF leak adversely affects patient recovery, with an increased likelihood of infection (likelihood ratio 8.704) and one-third of patients requiring operative reintervention. It is therefore useful to be able to identify risk factors that predispose to CSF leak and evaluate the efficacy of various dural closure techniques.

Patients with postoperative CSF leak were significantly younger than those without. We postulate that this could be related to the age predilection as well as behavior of the tumor. Spinal meningiomas typically have a benign course with low rates of morbidity, although they are less common in younger patients and more likely associated with aggressive histological subtypes in these age groups. Additionally, they vary in location with a higher prevalence of cervical tumors in younger patients, complicating their management. These factors contribute to a more aggressive clinical course in younger patients and the historical aggressiveness with dural invasion may explain the possible increase in dural complications. This differential behavior is similarly observed in intramedullary lesions which follow a more insidious course in younger populations and possibly presenting at a later, more advanced stage.

Intramedullary lesions were associated with a higher rate of CSF leak. Surgical resection of these lesions can be challenging due to the anatomical disruption of the spinal cord orientation and infiltrative lesions obscuring clear margins. Proper exposure with an extensive durotomy is necessary to plan the myelotomy. We hypothesize that increased CSF protein content from tumor and blood breakdown products, combined with the dissection required in these cases, can also disrupt CSF drainage and perivascular Virchow-Robin spaces, leading to local accumulation of CSF which adversely affects dural healing. This is further compounded by the disruption to the arachnoid plane, which may be preserved in some cases of extramedullary lesions such as certain meningiomas or schwannomas, leading to potential arachnoid adhesions. The surgery can be further complicated by the presence of hydrocephalus in some patients which increase the risk of CSF leak. Some of these difficulties have been recognized by Samartzis et al. and proper perioperative planning and identification is essential to the prevention of CSF leak in intramedullary lesions. Interestingly, the reported presence of a dural defect was not associated with CSF leak in our analysis which may be attributed to duroplasty techniques that decrease the local CSF pressure effects exerted on the dural closure.

Given the importance of a watertight seal following durotomy, we evaluated the efficacy of the various closure techniques. Although the use of sealants was associated with lower CSF leak rates, this association was not evident after multivariate analysis. Also, while patches were used more often in dural defect cases, they were not identified as interacting factors in multivariate analysis. The analysis revealed that cases in which a patch was used had higher odds of having a dural leak postoperatively. Despite the use of multivariate analysis, we acknowledge that this finding may be circumstantial in view of the retrospective nature of the study. A possible explanation could be that patches were used in cases where difficulties in securing a watertight dural closure were anticipated pre or perioperatively due to factors not captured in multivariate analysis. This result was also reflected in a series which found that the use of multiple dural substitutes led to increased CSF leak rates. An alternative explanation could be that patches may disrupt proper dural healing, as a study has demonstrated that collagen patches incite an initial inflammatory response that may disrupt anastomotic healing. Basic science studies investigating the healing of the dura after application of dural substitutes are lacking in this regard. We acknowledge that various methods of dural repair, such as inlay, onlay, or direct suture techniques, may affect the quality of dural repair, although the numbers in each subgroup did not permit multivariate analysis. In our centre, a combined inlay with onlay technique is commonly used with the inlay patch functioning to prevent CSF pressure effects on the dural closure by establishing a 1-way valve effect, and the onlay providing a buttress to the repair. In addition to dural closure techniques, intraoperative lumbar subarachnoid drainage has been investigated as an adjunct to decrease subcutaneous CSF accumulation postoperatively.

We acknowledge important limitations to the study. As there was a lack of consistent photographic data, we were unable to capture accurate information on the location, size and shape of durotomies which could influence the rate of CSF leak. Inherent to the uncommon nature of intradural tumors, especially postoperative CSF leaks, the relatively small numbers may decrease the robustness of a prediction model. Additionally, no prediction model can capture every significant variable and other factors such as the use of steroids, radiotherapy and patient fragility scores. Despite this, our analysed factors accounted for the majority of data variance and achieved a respectable classification rate for postoperative CSF leak. It is also important to note that the detection of postoperative CSF leak was dependent on early surgeon recognition and patient report, thus asymptomatic, occult cases of postoperative CSF leak are not captured in this analysis. Lastly, as the study did not prescribe a standard-

https://doi.org/10.14245/ns.2346432.216
ized protocol for the management of durotomies, the results are not controlled and may not be easily generalized to other practices managing a different profile of patients with durotomies.

CONCLUSION

Postoperative CSF leak following intradural tumor resection is associated with morbidity and can lead to re-operation and infection. Identifying predictors for CSF leak can assist in the counselling of patients with regards to surgical risk and expected postoperative recovery. Additionally, it may aid the surgeon in anticipating dural closure difficulties and preparation of augment.

NOTES

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Author Contribution: Conceptualization: AB, MSK, AK, RT, JF; Data curation: AB, MSK; Formal analysis: LJ, AB, MSK, EG; Methodology: MSK, JF; Project administration: JF; Writing - original draft: LJ; Writing - review & editing: LJ, EG, AK, RT, JF.

ORCID
Lei Jiang: 0000-0003-2727-0863
Alexandru Budu: 0000-0001-6783-6943
Edward Goacher: 0000-0002-2621-8388
Angelos Kolias: 0000-0003-3992-0587

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The Posterior Cranial Vertical Line: A Novel Radiographic Marker for Classifying Global Sagittal Alignment

Paul J. Park1,2, Fthimnir M. Hassan1, Xavier E. Ferrer1, Cole Morrissette1, Nathan J. Lee1, Meghan Cerpa1, Zeeshan M. Sardar1, Michael P. Kelly3, Stephane Bourret4, Kazuhiro Hasegawa5, Hee-Kit Wong6, Gabriel Liu6, Hwee Weng Dennis Hey6, Hend Riahi7, Jean-Charles Le Huec4, Lawrence G. Lenke1

1Department of Orthopedic Surgery, Columbia University Medical Center, The Och Spine Hospital at New York-Presbyterian, New York, NY, USA
2Department of Neurological Surgery, Weil Cornell Brain and Spine Center, New York, NY, USA
3Department of Orthopedic Surgery, Washington University, St. Louis, MO, USA
4Spine Unit 2, Surgical Research Lab, Bordeaux University Hospital, Bordeaux, France
5Niigata Spine Surgery Center, Niigata City, Japan
6Department of Orthopedic Surgery, National University Hospital (Singapore), Singapore
7Institut Kassab D’orthopédie, Ksar Said La Manouba, Tunis, Tunisia

Objective: To define a novel radiographic measurement, the posterior cranial vertical line (PCVL), in an asymptomatic adult population to better understand global sagittal alignment. Methods: We performed a multicenter retrospective review of prospectively collected radiographic data on asymptomatic volunteers aged 20–79. The PCVL is a vertical plumb line drawn from the posterior-most aspect of the occiput. The horizontal distances of the PCVL to the thoracic apex (TA), posterior sagittal vertical line (PSVL, posterosuperior endplate of S1), femoral head center, and tibial plafond were measured. Classification was either grade 1 (PCVL posterior to TA and PSVL), grade 2 (PCVL anterior to TA and posterior to PSVL), or grade 3 (PCVL anterior to TA and PSVL).

Results: Three hundred thirty-four asymptomatic patients were evaluated with a mean age of 41 years. Eighty-three percent of subjects were PCVL grade 1, 15% were grade 2, and 3% were grade 3. Increasing PCVL grade was associated with increased age (p < 0.001), C7–S1 sagittal vertical axis (SVA) (p < 0.001), C2–7 SVA (p < 0.001). Additionally, it was associated with decreased SS (p = 0.045), increased PT (p < 0.001), and increased knee flexion (p < 0.001).

Conclusion: The PCVL is a radiographic marker of global sagittal alignment that is simple to implement and interpret. Increasing PCVL grade was significantly associated with expected changes and compensatory mechanisms in the aging population. Most importantly, it incorporates cervical alignment parameters such as C2–7 SVA. The PCVL defines global sagittal alignment in adult volunteers and naturally distributes into 3 grades, with only 3% being grade 3 where the PCVL lies anterior to the TA and PSVL.

Keywords: Sagittal alignment, Spinal deformity, Scoliosis, Kyphosis, Asymptomatic

INTRODUCTION

Achieving an upright posture and appropriate spinal balance requires a dynamic alignment between the head, spine, pelvis and lower extremities. This is critical as malalignment in the sagittal plane has been correlated with poor functional status and patient outcomes. However, achieving proper alignment of all these structures during spinal deformity surgery can be challenging for a multitude of reasons, including the lack of a global measure for spinal sagittal alignment.
When examining the spine, establishing a “normal” set of comprehensive spinal measurements has been elusive given the vast variation within asymptomatic individuals. One fundamental aspect of an ergonomic posture that remains critical in all healthy individuals is the proper alignment of the spine with respect to the body’s center of mass. The gravity line (GL) remains an important measure of global spinal alignment in theory. The GL is obtained using a force plate on which the bipedal subject is standing. Traditionally, the C7 plumb line (C7PL) has been used as a radiographic proxy for the GL and as a means of estimating sagittal alignment. However, multiple studies have demonstrated there is discordance between these 2 measures, reducing the predictive value of the C7PL. Given the shortcomings of the C7PL and the inconvenience of establishing the true GL (i.e., via digital force plate), there exists a need for another measurement that can better approximate global sagittal alignment. By understanding the relative position of the head, spine, pelvis and lower extremities, surgeons will be better equipped to evaluate adult spinal deformity (ASD).

The purpose of this study is to define the posterior cranial vertical line (PCVL) as a potential marker for global spine alignment. The PCVL is a novel radiographic measurement which incorporates skull position as well as lower extremity position, which is frequently overlooked in other measurements. By comparison, the standard C7–S1 sagittal vertical axis (SVA) is a focal measurement of spinal balance from the C7 vertebral body down to the sacrum. Using the PCVL may provide a more complete picture of a patient’s global alignment and have important implications in preoperative planning and patient prognosis.

**MATERIALS AND METHODS**

Prospectively collected standing, full-length bi-planar radiographs were retrospectively reviewed for 334 asymptomatic adult volunteers ages 20–79 years old. Radiographs were obtained using imaging with 3-dimensional capabilities (EOS Imaging, Paris, France) with the patient in a relaxed position, with fingers resting on the clavicles—no further instructions were given in order to preserve physiologic stance. Patients were excluded if they had any history of back or neck pain requiring time off from work/school or affecting daily activity; history of prior hip or knee arthroplasty, lower extremity realignment surgery or any spine surgery; coronal deformity (Cobb angle > 10°); any degenerative or pathologic spinal conditions (requiring intervention); pregnancy; nonambulatory patients; or patients with history or neuromuscular disorder, inflammatory arthritis, or congenital anomalies. Age, sex, body mass index (BMI), Oswestry Disability Index (ODI), and Neck Disability Index (NDI) were collected for each patient included. This study was approved by the Institutional Review Board of Washington University in St. Louis (201812144) and all volunteers provided informed consent.

Patients were excluded if full-standing radiographs did not clearly visualize the posterior-most aspect of the skull, thoracic apex (TA), or the tibial plafond (TP). Cervical measurements obtained included C2–7 lordosis (measured from inferior endplate of C7 to inferior endplate of C7) and C2–7 SVA (distance from C2 midbody plumbline to posteroinferior corner of C7). Thoracic measurements obtained included T1 slope (angle formed by superior endplate T1 and a horizontal reference line), T4–12 kyphosis (measured from superior endplate of T4 to inferior endplate of T12), and apex of thoracic kyphosis (TA). Spino-pelvic measurements obtained included sacral slope, pelvic tilt, pelvic incidence (PI), L1–S1 lumbar lordosis (LL), PI–LL mismatch, and the C7–S1 SVA (distance from C7 midbody plumbline to posteroinferior corner of S1).

The PCVL was defined as a vertical plumb line from the posterior-most aspect of the occiput to the floor. The horizontal distances of the PCVL to the TA, posterior sagittal vertical line (PSVL; vertical line drawn superiorly from posteroinferior endplate of S1), the femoral head (FH) center, and center of the TP were measured. Each patient was then classified as either grade 1 (PCVL posterior to the TA and the PSVL), grade 2 (PCVL anterior to TA and posterior to the PSVL), or grade 3 (PCVL anterior to both the TA and the PSVL) (Fig. 1, Table 1). Grade 2 and 3 patients with a PCVL posterior to the center of the TP were given a “P” modifier; those with a PCVL anterior to the TP were given an “A” modifier (Table 1). All measurements were performed by a team of fellows and residents. A standardized protocol was created and written visual instructions were provided to every contributor. Individual measurements were reviewed throughout the cohort to assess interrater relatability using Cronbach alpha values, which exceeded 0.8 for all measures. Chi-square tests and analysis of variance were performed for bivariate analyses using SAS Studio Versions 3.4 (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

Our study included a total of 334 asymptomatic volunteers, 64% of whom were female. Average age was 41 ± 14 years and average BMI was 24.4 kg/m². The average ODI score was 2.7 ± 4.4.
When measuring the relative position of the PCVL to various reference points, negative values were used to indicate a relatively posterior PCVL position, while a positive value indicated a relatively anterior PCVL position. Average PCVL–PSVL distance was -7.4 cm and average PCVL–TA distance was -2.1 cm. Average PCVL–FH distance was -10.8 cm and average PCVL–TP distance was -5.4 cm. Eighty-three percent of subjects were grade 1, 15% were grade 2, and 2% were grade 3. Overall, 98%
of normal subjects were either grade 1 or grade 2.

Higher PCVL grade had a significant association with increasing age (p < 0.001). The mean age in grade 1 patients was 39.6 years, grade 2 was 45.6 years, and grade 3 was 63 years. Fig. 2 illustrates the age distribution of the asymptomatic cohort demonstrating an increase in age throughout the PCVL grades. Higher PCVL grade was also significantly associated with increasing greater T1 slope (p < 0.001), greater T4–12 kyphosis (p < 0.001), greater cervical lordosis (p = 0.006), greater pelvic tilt (p < 0.001), and increased knee flexion (p < 0.001) (Table 2). Conversely, higher PCVL grade was associated with decreased sacral slope (p = 0.045). Higher PCVL grade was associated with a larger C7–S1 SVA (p < 0.001) and C2–7 SVA (p < 0.001) (Table 2). Of note, PI remained similar between PCVL grades as expected. A strong positive correlation (coefficient ≥ 0.6) was seen with C2–7 SVA and greater T1 slope, while a moderate correlation (coefficient ≥ 0.4) was seen with C7–S1 SVA and T4–12 thoracic kyphosis. Similarly, a PCVL anterior to the TP was strongly correlated with greater C7–S1 SVA (p < 0.001), C2–7 SVA (p < 0.001), T1 slope (p < 0.001) (Table 2).

When the population was subdivided using the TP modifier (anterior vs. posterior position of the PCVL relative to TP), similar results were seen with the anterior modifier and increasing PCVL grade. An anterior modifier had significant association with age (p = 0.04) as well as increased C7–S1 SVA, increased C2–7 SVA, as well as increased T1 slope (p < 0.001) (Table 3).

**Table 2. The PCVL grade with demographic data and radiographic measurements**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCVL grade</th>
<th>Correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (N = 276)</td>
<td>2 (N = 48)</td>
<td>3 (N = 8)</td>
</tr>
<tr>
<td>Mean ± SD Range</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
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<tr>
<td>Age</td>
<td>39.6 ± 13.5</td>
<td>45.6 ± 14.9</td>
<td>63 ± 18.3</td>
</tr>
<tr>
<td>BMI</td>
<td>24.2 ± 5.2</td>
<td>25.2 ± 5.4</td>
<td>26.4 ± 5.7</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>-2.4 ± 5</td>
<td>-0.3 ± 4.6</td>
<td>4.7 ± 5.7</td>
</tr>
<tr>
<td>C2–7 lordosis</td>
<td>-1.3 ± 12.7</td>
<td>3.3 ± 10.3</td>
<td>8.9 ± 10.6</td>
</tr>
<tr>
<td>T4–12 kyphosis</td>
<td>34.9 ± 10.2</td>
<td>46.5 ± 11.7</td>
<td>49.8 ± 15</td>
</tr>
<tr>
<td>Sacral slope</td>
<td>39.7 ± 8.3</td>
<td>37.5 ± 9.5</td>
<td>33.4 ± 11.6</td>
</tr>
<tr>
<td>Pelvic incidence</td>
<td>51.9 ± 10.5</td>
<td>50.1 ± 11.7</td>
<td>57 ± 11.5</td>
</tr>
<tr>
<td>Pelvic tilt</td>
<td>12.3 ± 7.3</td>
<td>12.6 ± 6.8</td>
<td>23.6 ± 9.4</td>
</tr>
<tr>
<td>PI–LL</td>
<td>9.4 ± 7.5</td>
<td>10.5 ± 7.7</td>
<td>10.5 ± 8.4</td>
</tr>
<tr>
<td>L1–S1 LL</td>
<td>56.8 ± 11.8</td>
<td>57.9 ± 12.8</td>
<td>47 ± 13.3</td>
</tr>
<tr>
<td>C7–S1 SVA</td>
<td>-9.3 ± 24.5</td>
<td>5.7 ± 24.2</td>
<td>67.9 ± 32.3</td>
</tr>
<tr>
<td>C2–7 SVA</td>
<td>17.2 ± 8.6</td>
<td>30.4 ± 8.9</td>
<td>30.4 ± 8.9</td>
</tr>
<tr>
<td>T1 slope</td>
<td>21.4 ± 6.9</td>
<td>30.6 ± 6.4</td>
<td>38.8 ± 7.2</td>
</tr>
<tr>
<td>ODI score</td>
<td>2.5 ± 4.3</td>
<td>3.5 ± 4.9</td>
<td>3.8 ± 4.9</td>
</tr>
</tbody>
</table>

PCVL, posterior cranial vertical line; SD, standard deviation; BMI, body mass index; PI–LL, pelvic incidence minus lumbar lordosis; SVA, sagittal vertical axis; ODI, Oswestry Disability Index.

Grade 1: The PCVL lies posterior to the thoracic apex (TA) and posterior sagittal vertical line (PSVL). Grade 2: The PCVL lies posterior anterior to the TA and posterior to the PSVL. Grade 3: The PCVL lies anterior to both the TA and PSVL.
In addition, there is...
slope. Regarding the skull and lower extremity position, the higher PCVL grade was significantly associated with expected compensatory increasing C2–7 lordosis, greater C2–7 SVA, as well as with increased knee flexion. In fact, C2–7 SVA and T1 slope both had a strong correlation (coefficient ≥ 0.6) with increasing PCVL grade. Based on our results, we hypothesize that the PCVL grade is an accurate reflection of global positive sagittal alignment, and as seen with prior sagittal measures that a higher PCVL grade may be associated with higher risk of PJK following a fusion procedure. The next step in this study would be to measure the PCVL in ASD patients preoperatively and postoperatively while tracking patient-reported outcome measures as well as radiographic evidence of PJK postoperatively.

When interpreting the results of this study, it is important to consider its limitations. First, the generalizability of the asymptomatic volunteers used in this study and whether they represent a true normal distribution of humanity upon which to base a new classification system may be brought into question. However, this cohort of asymptomatic volunteers is one of the largest collection of volunteers with full-standing radiographs across a wide variety of ages and ethnic backgrounds which we believe is a powerful tool in understanding a normative population. Secondly, the use of the PCVL requires radiographs to be obtained via imaging with 3-dimensional capabilities (EOS Imaging) which may not be available to every institution. Nonetheless, we believe that full-standing radiographs will be the new gold standard moving forward. Thus, this measure is crucial to further characterizing sagittal alignment with additional information provided by both the position of the skull as well as the lower extremities. Thirdly, the conducted study focuses on establishing a classification to patients with no spinal pathologies which may question if the proposed measurements correlate with the disease process. It is important to note that the purpose of this study is to establish a baseline distribution in the asymptomatic population in order to first characterize the measurement. Thus, the aforementioned relationship will be assessed in a subsequent study on its application in the ASD population.

CONCLUSION

We present the PCVL as a novel singular sagittal alignment marker that may play a helpful role in understanding global sagittal alignment. The PCVL is easy to implement and allows for immediate visualization of skull position relative to the thoracic spine, sacrum, as well as the TPs that is simple to interpret. Our population showed that a majority of asymptomatic volunteers were grade 1 (83%), while 17% of patients were grade 2 or 3 with a PCVL anterior to the TA. We propose here a simple grading system that may have the potential to aid in preoperative planning to correct sagittal malalignment, as well as assess patients postoperatively over time.

NOTES

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Author Contribution: Conceptualization: PJP, ZMS, MPK, SB, KH, HKW, HWDH, HR, JCLH, LGL; Formal Analysis: PJP, FMH, MC; Investigation: LGL; Methodology: PJP, XEF, FMH, CM, NJL; Project Administration: FMH; Writing – Original Draft: PJP, XEF, FMH, CM, NJL, MC; Writing – Review & Editing: PJP, FMH, ZMS, MPK, SB, KH, HKW, HWDH, HR, JCLH, LGL.

ORCID
Fthimnir M. Hassan: 0000-0003-3928-8972
Cole Morissette: 0000-0001-5667-5056
Meghan Cerpa: 0000-0002-5931-7067
Zeeshan M. Sardar: 0000-0002-8417-3798
Lawrence G. Lenke: 0000-0002-5595-4958

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PCVL: Novel Marker for Global Sagittal Alignment
Park PJ, et al.


Commentary on “The Posterior Cranial Vertical Line: A Novel Radiographic Marker for Classifying Global Sagittal Alignment”

Samuel K. Cho
Department of Orthopaedics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

The radiographic study titled, “The Posterior Cranial Vertical Line: A Novel Radiographic Marker for Classifying Global Sagittal Alignment,” proposes a “novel” radiographic measurement, namely PCVL, a vertical line drawn from the back of the skull, to calculate the relative distance between it and selected points below the head of the patient. With the advent of full-body radiography, the authors were able to appreciate the global alignment of asymptomatic persons and further their understanding of the interplay between different regions of the body relative to the head. I congratulate the authors as PCVL offers a simple way to quickly assess global sagittal alignment. Other investigators also have used this full-body scan technology to assess “head-to-toe” alignment, and as the authors have alluded to in the body of their work, came up with such concepts as cranial sagittal vertical axis (crSVA). Looking ahead, it is important to further our understanding by analyzing how each region of the spine contributes to the overall alignment. The ever important spinopelvic relationship and the more recent hip-spine relationship must be accounted for. Moreover, the full-body scan allows for measurement of each motion segment in the spine as, for example, lower lumbar segments contribute more to achieve lordosis than upper lumbar segments. The cumbersome task of measuring various radiographic parameters will soon be automated by artificial intelligence and machine learning technologies.

• Conflict of Interest: The author has nothing to disclose.

REFERENCES

**Selection of Optimal Lower Instrumented Vertebra for Adolescent Idiopathic Scoliosis Surgery**

Seung-Ho Seo¹, Seung-Jae Hyun¹, Jae-Koo Lee¹, Yong Jae Cho², Dae Jean Jo³, Jin Hoon Park⁴, Ki-Jeong Kim¹; On Behalf of the Korean Spinal Deformity Society

¹Department of Neurosurgery, Spine Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
²Department of Neurosurgery, Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine, Seoul, Korea
³Department of Neurosurgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, Korea
⁴Department of Neurological Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Adolescent idiopathic scoliosis (AIS) affects approximately 2% of adolescents across all ethnicities. The objectives of surgery for AIS are to halt curve progression, correct the deformity in 3 dimensions, and preserve as many mobile spinal segments as possible, avoiding junctional complications. Despite ongoing development in algorithms and classification systems for the surgical treatment of AIS, there is still considerable debate about selecting the appropriate fusion level. In this study, we review the literature on fusion selection and present current concepts regarding the lower instrumented vertebra in the selection of the fusion level for AIS surgery.

**Keywords:** Adolescent idiopathic scoliosis, Fusion level selection, Lower instrumented vertebra, Adding-on phenomenon

**INTRODUCTION**

Adolescent idiopathic scoliosis (AIS) affects 1%–3% of children in the at-risk population of those aged 10–16 years.¹ Surgical intervention for AIS is usually recommended for patients whose curves progress despite nonoperative management.²,³ The main objectives of the surgical treatment of AIS are to achieve coronal and sagittal balance, preserve motion segments, and avoid complications such as coronal decompensation, curve progression, junctional kyphosis, the adding-on (AO) phenomenon, and revision surgery.⁴-⁷ The selection of the fusion level is the single most important factor influencing the result of AIS surgery.⁴ Inappropriately selecting the extent of fusion can result in undercorrection or overcorrection of the main and compensatory curves, which may lead to a failure to stabilize the index curve.⁹,¹¹ Moreover, it may exacerbate unfused curves and cause trunk imbalance and decompensation.⁸,¹²

There has been considerable debate about the appropriate fusion-level selection for AIS. Selecting the appropriate lower instrumented vertebra (LIV) is essential for avoiding distal junctional problems such as distal junctional kyphosis (DJK) and AO.¹³ Before the development of the Harrington rod in the late 1950s, based on the reports of Hibbs et al.,¹⁴,¹⁵ the lower end vertebra (LEV) with neutral rotation was recommended as the ideal LIV to prevent AO. Starting with these reports, various LIV selection methods have been studied. In this review, we discuss how LIV selection has developed historically and describe up-to-date concepts regarding optimal LIV selection in AIS surgery.
HISTORY OF CRITERIA FOR THE LOWER INSTRUMENTED VERTEBRA

The traditional fusion level, recommended by Harrington et al.\textsuperscript{26,27} and called the Harrington Stable Zone, was to fuse 1 vertebra above and 2 below the endpoints of the Cobb measurement, with instrumentation in the stable zone based on bending, traction, and intraoperative radiographs. The first treatment-based AIS classification system was developed in 1983 by King et al.\textsuperscript{8,19-23} This system, based on the extensive experience of Dr. John Moe in the surgical treatment of AIS patients with Harrington rod instrumentation, divides curves into 5 types and gives guidelines and recommendations for which levels should be instrumented according to these types in order to preserve as much motion as possible.\textsuperscript{18} However, this system is limited because it is only based on the coronal plane, lacks a defined isolated thoracolumbar curve type, and has relatively poor to fair inter- and intraobserver reliability.\textsuperscript{19}

To overcome the limitations of King-Moe classification, Lenke et al.\textsuperscript{19} introduced a classification system redefining how arthrodesis levels are selected. The classification combines 6 coronal curve types (1 through 6), with 3 lumbar modifiers (A, B, or C) and 3 sagittal thoracic modifiers (minus, normal, or plus). It requires not only standing coronal and lateral full spine radiographs, but also supine side-bending films. The spinal column regions evaluated in this classification are proximal thoracic, main thoracic, and thoracolumbar (TL/L). The authors recommended that the major curve, namely the curve with the largest Cobb angle, should always be included in the fusion extent. If the curve is regarded as nonstructural (corrects to < 25° as measured on side-bending radiographs and/or with kyphosis of < 20° between T2–5 and T10–L2), it does not have to be included in the fusion.

However, even with a better classification of AIS, the selection of fusion levels remains highly variable and is a hot topic in spinal deformity research.\textsuperscript{8,19-23} The selection of the LIV has been a matter of debate, and the optimal positioning is often difficult to identify or predict.\textsuperscript{20} To date, numerous studies have been conducted to identify the optimal LIV for AIS surgery. Suk et al.\textsuperscript{24} have suggested that the LIV should be selected based on the relative position of the neutral vertebra (NV). They recommended selecting the NV when it is either the same as or 1 level distal to the LEV of the main curve, and NV-1 if more than 2 levels separate the LEV from the NV. Nonetheless, due to its low inter- and intraobserver reliability, the application of the NV for selecting the optimal LIV shows limitations.\textsuperscript{25} Parisini et al.\textsuperscript{26} investigated the rotation of the lumbar vertebra just below the LEV as an important factor, like the position of the stable vertebra (SV), for selecting fusion levels in single thoracic curves in which the lumbar compensatory curve did not cross the midline. If the rotation of the first vertebra just below the LEV is in the same direction as the thoracic curve, and if the SV and LEV show a difference of more than 2 levels, then L2 or L3 is recommended as the LIV. However, if the rotation of the first vertebra just below the LEV is in the opposite direction, and if the SV and LEV show a difference of no more than 2 levels, then the LIV can be selected 2 or 3 levels below the SV. Wang et al.\textsuperscript{27} reported that the selection of the LIV correlated strongly to the presence of distal AO in Lenke 1A curves and stated that the best outcomes resulted from choosing as the LIV the first vertebra in the cephalad direction from the sacrum whose deviation from the central sacral vertebral line (CSVL) was more than 10 mm. Their reasoning was that this method might not only prevent distal AO, but also preserve more lumbar motion and growth potential. Sarlak and colleagues argued that the tilt of L3 and L4 in the coronal plane may play a significant role in determining the distal fusion level in Lenke 1A curves.\textsuperscript{2,28} They recommended that the distal fusion level should be extended to at least LEV-1 in Lenke 1A curves with L3 as NV, while it might be necessary to go down to the LEV with L3 vertebral tilt.\textsuperscript{28} However, choosing the appropriate LIV for major thoracic curves with lumbar type C is still debatable. Takahashi et al.\textsuperscript{1} focused on choosing fusion levels for selective thoracic fusion of AIS with specific Lenke types.\textsuperscript{7} The authors identified 3 curve patterns according to the relative positions of the SV and LEV in Lenke 1B, 1C, or 3C curves. They recommended choosing the LIV 1 level distal to the SV/LEV when the SV and LEV are the same, in order to achieve the greatest correction of thoracic and lumbar curves as well as trunk shift, and choosing the LIV as either the SV or at least 1 level distal to it if the SV is below the LEV.

Recent studies have investigated the last touched vertebra (LTV) to assist in determining the LIV.\textsuperscript{20,29} The LTV is the most cephalad TL/L vertebra (T12–L5) of the lowest structural curve that is touched by CSVL. Matsumoto et al.\textsuperscript{29} investigated the occurrence of postoperative AO and related factors in Lenke 1A curves. They suggested that the LIV should be extended to or beyond the LTV to avoid the development of postoperative AO. Lenke et al.\textsuperscript{30} reported that selecting the LTV as the LIV for Lenke 1A curves produced acceptable radiographic results at a minimum 5-year follow-up. Fischer et al.,\textsuperscript{13} who evaluated the optimal LIV on the basis of rotation or the CSVL, proposed using either the LTV or a vertebra within 2 levels proximal to the NV as the LIV.
<table>
<thead>
<tr>
<th>Study</th>
<th>Curve type</th>
<th>Total No. of patients</th>
<th>Mean age (yr)</th>
<th>Mean follow-up (yr)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suk et al.</td>
<td>King type 3, 4</td>
<td>42</td>
<td>15.5</td>
<td>4.2</td>
<td>When preoperative NV and EV show no more than 2-level gap differences, fusion down to NV. When the gap is more than two levels, fusion down to NV-1</td>
</tr>
<tr>
<td>Parisini et al.</td>
<td>Lenke type 1A</td>
<td>31</td>
<td>16.3</td>
<td>Min. 2</td>
<td>If the rotation of just below the thoracic LEV in the same direction as the thoracic curve, and SV and EV show &gt; 2 level differences, fusion should extended to L2 or L3. Otherwise, SV-2 or SV-3 would be distal fusion level</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Lenke type 1A</td>
<td>45</td>
<td>-</td>
<td>3.6</td>
<td>Choosing the first vertebra in cephalad direction from sacrum whose deviation from CSVL is more than 10 mm as the LIV provide the best outcome</td>
</tr>
<tr>
<td>Sarlak et al.</td>
<td>Lenke type 1A</td>
<td>36</td>
<td>15.8</td>
<td>4.3</td>
<td>Distal fusion level should be extended to LEV-1 in case of neutral L3 vertebra and to LEV in case of L3 vertebral tilt</td>
</tr>
<tr>
<td>Takahashi et al.</td>
<td>Lenke type 1B,</td>
<td>172</td>
<td>14</td>
<td>2</td>
<td>If the SV was below the EV, the LIV should be chosen at least one level distal to the SV. If the SV and the EV are same, the LIV one level below the SV/EV was recommended</td>
</tr>
<tr>
<td>Cho et al.</td>
<td>Lenke type 1A</td>
<td>195</td>
<td>-</td>
<td>Min. 2</td>
<td>Selecting the LIV for Lenke type 1A curves should depend on the direction of the L4 tilt</td>
</tr>
<tr>
<td>Matsumoto et al.</td>
<td>Lenke type 1A</td>
<td>112</td>
<td>16.1</td>
<td>3.6</td>
<td>Fusion extended at least to the LTV to avoid postoperative AO</td>
</tr>
<tr>
<td>Lenke et al.</td>
<td>Lenke type 1A</td>
<td>65</td>
<td>-</td>
<td>5</td>
<td>Selecting the LTV as the LIV in the Lenke 1A main thoracic pattern, prevented an increase in final CSVL-LIV distance without any AO or angulation/tilt at a minimum 5-year follow-up, and resulted in a significantly better LIV position than when fusing to the LTV-1 level</td>
</tr>
<tr>
<td>Ding et al.</td>
<td>-</td>
<td>60</td>
<td>15.4</td>
<td>Min. 2</td>
<td>There were no significance differences in the clinical scores between the L3 and the L4 group</td>
</tr>
<tr>
<td>Sun et al.</td>
<td>Lenke 5</td>
<td>37</td>
<td>14.9</td>
<td>3.5</td>
<td>No benefit for fusing to LEV+1 in moderate TL/L idiopathic scoliosis patients than fusing to LEV. TL/L Cobb angle more than 60°, the distal fusion level was probably needs to be LEV+1</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Lenke 5</td>
<td>66</td>
<td>15.2</td>
<td>Min. 2</td>
<td>Fused to L3 showed favorable radiographic outcomes when L3 crosses the midsacral line with rotation of less than grade II in bending film. Otherwise, fusion has to be extended to L4</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>Lenke 3C, 5, 6</td>
<td>229</td>
<td>15.6</td>
<td>3.7</td>
<td>Fused to L3 may be sufficient if LEV ≥ L3 and LTV ≥ L4</td>
</tr>
<tr>
<td>Chang et al.</td>
<td>Major TL/L curves</td>
<td>64</td>
<td>15.0</td>
<td>Min. 2</td>
<td>If the curve is flexible (L3 crosses CSVL with a rotation &lt; grade II), LIV should be selected at L3 (LEV)</td>
</tr>
<tr>
<td>Fischer et al.</td>
<td>Lenke type 1, 2</td>
<td>544</td>
<td>14.7</td>
<td>4.1</td>
<td>LTV or within 2 level proximal to the NV be used as the choice of the LIV</td>
</tr>
<tr>
<td>Shen et al.</td>
<td>Lenke type 1A</td>
<td>55</td>
<td>14.2</td>
<td>Min. 2</td>
<td>LIV choosing both SV and LSTV can acquire satisfied correction</td>
</tr>
<tr>
<td>Qin et al.</td>
<td>Lenke type 2A</td>
<td>101</td>
<td>14.9</td>
<td>Min. 2</td>
<td>Extend the fusion level to LSTV in 2A-R (L4 tilt to right) curve and to 1 level distal from LSTV in 2A-L (L4 tilt to left) curve</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Lenke type 1, 2</td>
<td>57</td>
<td>15.1</td>
<td>2.2</td>
<td>The LTV on preoperative supine radiographs is acceptable as the LIV in AIS surgery to maximize motion segments</td>
</tr>
<tr>
<td>Sarwahi et al.</td>
<td>Lenke type 1, 2</td>
<td>148</td>
<td>14.8</td>
<td>Min. 2</td>
<td>Choosing LIV as LTV with minimal rotation on prone radiograph can reduce fusion levels and have comparable radiographic outcomes without AO</td>
</tr>
</tbody>
</table>

LIV, lower instrumented vertebra; AIS, Adolescent idiopathic scoliosis; NV, neutral vertebra; EV, end vertebra; LEV, lower end vertebra; SV, stable vertebra; Min., minimum; LSTV, last substantially touched vertebra; CSVL, center sacral vertical line; LTV, last touched vertebra; AO, adding-on phenomenon; TL/L, thoracolumbar/lumbar.
However, in clinical practice, if the CSVL touches the LTV slightly, choosing the proper LIV can be challenging. Qin et al.\(^{31}\) proposed the concept of the last substantially touched vertebra (LSTV), defined as the vertebra nearest where the CSVL either intersects the pedicle outline or is medial to the pedicle outline. Shen and colleagues argued that both the SV and LSTV could be relevant for LIV and showed favorable outcomes in the management of Lenke 1A curves.\(^{32}\) Cho et al.\(^{39}\) reported that Lenke 1A-R curves (L4 vertebral tilt to the right) were 2.2 times more likely to experience AO than 1A-L (L4 vertebral tilt to the left) curves and recommended selecting the LSTV as the LIV for Lenke 1A-R. Qin et al.\(^{31}\) asserted that Lenke type 2 curves could be categorized analogously into 2A-R (L4 vertebral tilt to the right) and 2A-L (L4 vertebral tilt to the left). They proposed that to avoid distal AO, the LIV should be extended to LSTV (usually located upper or mid lumbar area) for 2A-R, and to LSTV+1 (usually located in the TL junction area) for 2A-L.

For AIS patients with a major TL/L curve, the spine surgeon’s goal is to apply a shorter fusion strategy that preserves distal motion segments maximally while minimizing the risks of lower back pain and long-term disc degeneration in the lower fusion segment. According to earlier investigations, no clinical or radiological difference was observed in relation to the distal fusion level (L3 vs. L4, LEV vs. LEV+1).\(^{34,35}\) However, recent long-term follow-up studies comparing L3 LIV to L4 LIV demonstrated that the latter led to worse experiences of back pain than the former.\(^{36,37}\) Additionally, a ≥ 40-year follow-up study revealed that patients with spines fused to L4 were more likely to undergo an additional surgical procedure than those fused to L3.\(^{38}\)

Therefore, in order to achieve a better long-term prognosis, it is still believed that the preservation of one additional distal segment may be necessary. In 2014, Kim et al.\(^{39}\) who analyzed 66 patients with TL/L AIS, concluded that L3 could serve as the LIV when preoperative L3 crosses the midsacral line with less than grade II rotation on bending-posture radiographs, although other patients fused to L4 also showed favorable outcomes. Chang et al.\(^{40}\) distinguished the LIV selection of TL/L AIS depending on the flexibility of the TL curve in a subsequent study. The LIV should be set to L3 (LEV) if the curve is flexible (L3 crosses the CSVL with rotation of grade II), whereas LIV should be set to L4 (LEV+1) if the curve is rigid (L3 does not cross the CSVL or the rotation exceeds grade II). Lee et al.\(^{41}\) argued that the LTV is a significant element in determining the appropriate correction rate and development of adjacent disc wedging. They suggested that if LEV ≥ L3 and LTV ≥ L4, distal fusion at L3 could be feasible for preserving the lumbar motion segments. Therefore, caution is required when choosing the distal fusion level if LEV ≤ L4 and LTV = L5. The results of studies on LIV selection in AIS are summarized in Table 1.

### RECENT TRENDS IN LOWER INSTRUMENTED VERTEBRA SELECTION USING POSITIONAL RADIOGRAPHS

Because there are several methods for selecting the optimal LIV, no consensus has been reached. However, spinal fusion should affect as short a segment as possible to preserve distal mobility. Several recent studies have been conducted on LIV selection using positional radiographs.

Kim et al.\(^{42}\) pointed out that the LTV on a preoperative supine radiograph can be an optimal LIV in most types of AIS surgery to maximize mobility. Radiographs are easy to take while a patient is supine, which resembles the intraoperative posture, because spinal curves are reduced to a more relaxed state without a meaningful impact from gravity and the patient’s body weight. The study included consecutive patients who underwent corrective surgery for AIS. The Scoliosis Research Society (SRS)-22 questionnaire and postoperative serial standing radiographs were utilized to evaluate clinical and radiographic outcomes. The patients were classified into 4 groups according to the relationship of the locations of the LIV, LTV, and LSTV on upright radiographs and the LTV on supine radiographs. In group 1, the upright LTV and supine LTV were the same. Group 1 was subdivided into group 1A and group 1B according to whether the LTV and LSTV differed or were the same, respectively. In group 2, the upright LTV was selected as the LIV, whereas in group 3, the supine LTV was selected. The demographic data showed that there were no significant differences among groups in terms of age, sex, body mass index, preoperative Cobb angle, or Lenke classification. The surgical data showed no significant differences among groups in terms of operative time or estimated blood loss. The clinical outcomes evaluated by the SRS-22 questionnaire showed no significant differences among groups in pain, self-image, mental health, function, or satisfaction scores. Furthermore, poor radiographic outcomes (such as AO, DJK, and proximal junctional kyphosis) were not significantly different at follow-up intervals for each group. The authors concluded that selecting the supine LTV in AIS correction surgery could offer an optimal LIV for most Lenke curves, while maximally preserving motion segments and being simple to apply (Fig. 1).

Similarly, Sarwahi et al.\(^{43}\) investigated whether conducting fusion to the touched vertebra on prone radiographs with mini-
mal rotation (grade 0 or I) would allow shorter fusion with optimal correction. In the study, patients with minimal rotation in their LTV were selected using prone or standing radiographs. Patients who were fused to a rotated LTV on standing or prone radiographs were categorized as touched vertebra rotated (TVR), while those in the non-TV (NTV) group had the LIV fused proximal to the LTV. The risk of AO was determined based on ≥ 5° of disk wedging. The study compared patients in 2 groups: group A consisted of patients fused to minimally rotated LTV (selected from prone and standing radiographs), and group B included TVR and NTV patients. The study also conducted subanalyses comparing levels saved in TVP (LTV on prone radiographs) and TVS (LTV on standing radiographs) patients, as well as subanalyses for different scoliosis classifications. In addition, radiographs of nonoperative adolescents with scoliosis were analyzed as controls. The results showed a significantly greater number of patients in group B with final disk wedging and LIV translation. Utilizing prone radiographs in TVP patients saved an average of 1 level, while TVS patients saved 1.2 levels. Furthermore, TVP patients had similar radiographic outcomes compared to controls in terms of LIV tilt, disk wedging, and coronal balance. They concluded that choosing a minimally rotated LTV on prone radiographs can preserve levels without sacrificing radiographic outcomes.

Applying positional radiographs to LIV selection could lead to more favorable results when considering other factors supported by research on selecting the LIV. For instance, Lenke 1A-R curves were found to be more susceptible to AO than 1A-L curves. To prevent AO in 1A-R curves, LSTV or LTV+1 has been recommended as the optimal LIV. If LTV is set using a supine
Fig. 3. A representative case of considering LIV deviation from the CSVL. (A) Preoperative radiographs of a 14-year-old female patient diagnosed with a Lenke 1AN curve. (B) L3 was touched by the CSVL on an upright radiograph, but the supine LTV was L2 on a supine plain radiograph. (C) On an upright radiograph, the L3 deviation from CSVL was less than 1 cm and the L2 deviation was greater than 2 cm, but on a supine radiograph, the L2 deviation from CSVL was less than 2 cm. (D) L2 was chosen as the LIV because the LIV deviation from CSVL did not exceed 2 cm on supine radiographs. At the 1-year follow-up, no AO phenomenon or DJK was observed. LIV, lower instrumented vertebra; CSVL, central sacral vertical line; LTV, last touched vertebra; AO, adding-on; DJK, distal junctional kyphosis.

Fig. 4. A representative case where sacral slanting was continued. (A) Preoperative radiographs of a 16-year-old female patient diagnosed with a Lenke 4CN curve and left-sided sacral slanting. (B) Supine LTV was L4 on a supine plain radiograph. (C) L3 was chosen as the LIV, considering left-sided sacral slanting. As a result, clinical outcomes were excellent at the 4-year follow-up. LTV, last touched vertebra; LIV, lower instrumented vertebra.
radiograph, the lumbar motion segment can be preserved while considering Lenke 1A-R curves (Fig. 2). LIV deviation > 2 cm from CSVL was an independent predictive factor for the prevalence of distal AO or DJK. Consequently, the LIV deviation from CSVL should not exceed 2 cm. When applying positional radiographs in LIV selection, it is possible to select the LIV at a more proximal position when the LIV deviation from the CSVL is less than 2 cm (Fig. 3). Because sacral slanting is frequently observed in patients with AIS, it is a critical consideration in selecting the distal fusion level when corrective surgery is planned.

For patients with L4-L (L4 vertebral tilt to the left) and left-sided sacral slanting, stopping fusion at L3 could be sufficient to maintain the correction and preserve more of the lumbar motion segment to balance the residual distal curve, which would reduce the risk of decompensation. Exceptionally, in such an instance, even if the LTV is distal to L3 on supine radiographs, favorable outcomes could be obtained by selecting L3 as the LIV (Fig. 4).

CONCLUSION

The selection of the fusion level in AIS surgery has been at the forefront of spine deformity research. One of the most important long-term goals of corrective surgery is to minimize the fusion extent in order to preserve motion segments while achieving a well-balanced spine and limiting disease progression. The selection of the LIV plays an essential role in AIS correction surgery because inappropriate selection may lead to various complications, such as AO or DJK. Although the selection method has not been standardized, recent studies have shown that basing LIV selection on positional radiographs is promising. Applying positional radiographs (standing, supine, and prone) to LIV selection is expected to be of great help to spine surgeons, since it is a simple, universal, and easy-to-apply method to preserve motion segments to the maximal extent possible. Also, there has been increasing research interest in utilizing three-dimensional analysis for LIV selection in AIS surgery recently. Continued research efforts about the application of three-dimensional analysis in LIV selection will contribute to improving the accuracy and efficacy of fusion level determination, ultimately leading to enhanced surgical outcomes and better long-term stability for patients with AIS.

In summary, future criteria for optimal LIV selection should consider curve flexibility and positional status in order to provide an appropriate surgical strategy for preventing postsurgical AO or distal decompensation.


Commentary on “Selection of Optimal Lower Instrumented Vertebra for Adolescent Idiopathic Scoliosis Surgery”

Moritz C. Deml
Department of Orthopedic and Trauma Surgery, Inselspital, University Hospital Bern, University Bern, Bern, Switzerland

Besides being the most common form of scoliosis, adolescent idiopathic scoliosis (AIS) is a complex three-dimensional deformity, necessitating surgical intervention in cases of severe curvature progression.1 Selecting the optimal segments to fuse, especially the most proximal and lowest instrumented vertebra (LIV) for the surgical treatment of AIS is a critical decision that requires careful consideration of several factors. The choice of LIV plays a pivotal role in achieving successful surgical outcomes, a good sagittal and coronal balance of the spine and therefore minimizes the potential risks like adding on (AO), and proximal and distal junctional kyphosis (DJK). On the other hand, the length of the stabilization should be performed as short as possible to preserve motion segments, granting for a high quality of life after surgery.2

Different concepts were recommended such as Harringtons’ stable zone, the stable vertebra and neutral vertebra theory, disc reversal on bending radiographs, last touched vertebra (LTV) and substantial touched vertebra.2-7 However, the selection of the correct LIV in AIS is still discussed controversially and AO as well as DJK are reported with up to 14% occurrence after surgery, dependent on the curve pattern and the lengths of the stabilization.5,8

Seo et al.9 summarize the historical recommendations of the LIV selection in AIS and review the actual literature with adopted selection methods of the LIV dependent on the different curve patterns. They included 18 mainly retrospective studies from 2003–2022 in their nonsystematic review. The historical overview in the first part emphasizes the problem of the different strategies of selecting the “correct” LIV and the reason, why this problem is still unsolved. They give also a detailed overview of the actual literature and enlighten the potential benefit of preoperative LIV assessment with additional positional radiographs. Just recently, Kim et al.10 published their retrospective clinical and radiographic outcome of 57 patients with 2.2 years follow-up comparing the LIV selection dependent on the LTV on supine and upright anteroposterior radiographs of the whole spine. They concluded that the LTV on supine radiographs can be the optimal LIV in AIS patients. Seo et al.9 point out, that also the type of curve to address has an essential role on the LIV selection. For example, Lenke 1A-R curves were found to be more susceptible to AO than 1A-L curves.11 Therefore, to prevent AO in Lenke 1A-R curves, LTV+1 has been recommended as the optimal LIV in 1A-R curves. Other important factors to be taken into account are...
the LIV rotation, the deviation of the LIV of less than 2 cm from the central sacral vertebral line and the necessity to consider sacral slanting when stabilizing to L3 or L4. In summary, the review of Seo et al. gives a detailed overview of the actual literature and enlightens the benefit of positional radiographs in LIV selection in AIS. Positional radiographs seem to be a reliable tool to gain high quality, reproducible clinical, and radiographic surgical outcomes for AIS patients.

As surgeons, we currently determine the decision of the length of fusion in AIS according to the different curve patterns according to Lenke et al., the curves’ flexibility, kyphotic segments, the rotation of the end-vertebra, the lateral deviation of the LTV, and sacral slanting. The focus in general is on anterior posterior imaging. In the future, a standardized decision should also consider more the sagittal profile, pelvic parameters, and possible transition anomalies of the thoracolumbar and lumbosacral junctions, and the individual maturity. Further 3-dimensional curve evaluation and big-data analyzes may lead to even improved patients specific decision-making with better clinical and radiographic outcomes and less postoperative complications. Until then the surgeon’s experience and expertise play a pivotal role in LIV selection. Experienced surgeons are better equipped to make informed decisions regarding LIV selection based on the patient’s unique anatomy and clinical presentation. Lastly, discussing the surgical plan, potential risks and expected outcomes with the patient and her or his family is crucial. Patients’ goals, activities, and aspirations should be factored into the decision-making process.

• **Conflict of Interest:** The author has nothing to disclose.

**REFERENCES**


Surgical Outcomes of Symptomatic Intramedullary Spinal Cord Cavernous Malformations: Analysis of Consecutive Cases in a Single Center

Zheng Cai¹,²,†, Xinjie Hong¹, Wei Dai¹, Zhengwei Zhang¹, Qiang Liang¹, Xuehua Ding¹, Wei Sun¹

¹Department of Neurosurgery, Shanghai Institute of Neurosurgery, Changzheng Hospital, Second Military Medical University, Shanghai, China

Objective: Intramedullary spinal cavernous malformations (ISCMs) are rare vascular lesions of the spinal cord with unclear natural history and controversy over treatment. This study aimed to report a series of symptomatic ISCMs underwent microsurgical management to illustrate the natural history, clinical presentation, and surgical outcomes and to evaluate factors associated with hemorrhage events and neurological prognosis.

Methods: This single-center retrospective study included 29 consecutive patients with whose demographic, symptomology, imaging, neurological, and surgical data were collected. The risk for hemorrhage events and factors affecting surgical outcomes were retrospectively analyzed.

Results: There were 12 female (41.4%) and 17 male patients (58.6%), with an average age of 45.2 years (range, 17–69 years). The mean size of the lesion was 9.7 mm (range, 3–20 mm). Most patients had a bowel or/and bladder dysfunction symptom (n = 11, 37.9%), followed by sensory deficits (n = 5, 17.2%), gait disturbance (n = 5, 17.2%), pain (n = 4, 13.8%), and weakness (n = 4, 13.8%), most (n = 15, 51.7%) with a chronic onset. All patients received total resection without rehemorrhages after surgical resection in follow-up. Sixty-five point five percent patients (n = 19) improved, 13.8% (n = 4) remained stable, 20.7% (n = 6) got worsen. The overall annual hemorrhage risk was 2.1% per patient-year. A total of 27 hemorrhages occurred in the 18 patients, of which rehemorrhage rate increased to 50.0% (n = 9) with a previous history of hemorrhage. Patients with smaller lesion sizes were more likely to have hemorrhage or rehemorrhage events (p = 0.008). Recurrent hemorrhage of the lesions was a risk factor for neurological outcomes (p = 0.016).

Conclusion: The risk of rehemorrhage was significantly increased in symptomatic ISCM patients with a previous history of hemorrhage. Rehemorrhage was a risk factor for neurological outcomes. Patients can benefit from microsurgical treatment to avoid rehemorrhage and further neurological deterioration.

Keywords: Cavernous malformations, Spinal cord cavernous malformations, Spinal cord malformations, Intramedullary tumors

INTRODUCTION

Cavernous malformations (CMs) are rare vascular malformations with an incidence of about 0.4%–0.6% when occurring within the central nervous system.¹² Most of these benign lesions are usually intracranially located, particularly in the supratentorial compartment. Compared with their intracranial counterparts, only 3%–5% are in the spinal cord, with intramed-
ullary spinal cavernous malformations (ISCMs) accounting for approximately 5%–12% of all spinal cord vascular disease. With a considerably increased risk of hemorrhage or rehemorrhage events in CMs of the spinal cord compared to cerebral CMs, it is often associated with severe neurological deficits such as tetraplegia.

With the widespread use of magnetic resonance imaging (MRI), the detection rate of ISCMs has been rising. Some ISCMs were found incidentally without symptoms, while others with chronic presentation or even acute onset of neurological deterioration. The natural course of ISCMs remains unclear, and the choice of conservative and surgical management remains controversial.

In the present study, we reported a consecutive case of 29 ISCMs patients in a single center, which was purely comprised of symptomatic patients who underwent microsurgical treatment. We reviewed and analyzed the clinical characteristics and surgical outcomes particularly focused on the risk for hemorrhage events and factors associated with neurological prognosis.

MATERIALS AND METHODS

1. Study Population

Twenty-nine consecutive patients with symptomatic ISCMs underwent surgical resection in the Neurosurgery department of Changzheng Hospital, Shanghai Institute of Neurosurgery, Shanghai, China, from June 2014 to May 2021 were retrospectively analyzed. The exclusion criteria included patients with previous microsurgical treatment, multiple lesions, unclear pathological diagnosis, and ages less than 16 years old. The patient’s medical records were reviewed for clinical symptoms, neuroimaging characteristics, intraoperative reports, surgical outcomes, pathology reports, and neurological progress. The study was approved by the Ethics Committee of Changzheng Hospital (No. 2022NS017), affiliated with Second Military Medical University (Shanghai, China), and written informed consent was obtained from each patient.

2. Data and Outcome Definition

Patient clinical data such as age, sex, clinical symptoms, location and lesion size, prior history of ISCM-related hemorrhage, postoperative status, etc., were properly collected. Patients’ pre- and postoperative neurological status was classified according to the modified McCormick scale (MMcS) (Table 1). Clinical course before the presentation was classified into 3 types as described by Choi et al.: acute onset of symptoms with the rapid decline (type A), slow progression of neurological degeneration (type C), or acute neurological deficit because of sequelae from multiple previous hemorrhagic events (type M). MRI was performed preoperatively in all patients. The lesion size was defined as the maximum metric value to eliminate hemorrhage on the MRI inspection image. The annual retrospective hemorrhage rate was calculated using formula: hemorrhage rate = the number of hemorrhagic events/summation of patient age in years. A hemorrhage event was described as symptomatic with radiographic evidence of overt hemorrhage. Intramedullary hemorrhage was defined as centrally and eccentrically located linear or flame-shaped nonedematous signal abnormality extending longitudinally away from SCMs, distinct from lesion rim.

The pathological diagnosis was confirmed postoperatively by 2 experienced pathologists independently. The ISCM-related hemorrhage was defined as an exacerbation of neurological deficits, MRI confirmation, and intraoperative findings. The extent of resection was defined as gross total resection (GTR), subtotal resection (STR), or partial resection.

3. Surgical Procedure and Follow-up

All patients of the present symptomatic ISCMs group received microsurgical treatment mainly by 2 experienced neurosurgeons. Patients were placed in a prone position, with an additional 3-point Mayfield (Codman, Inc., Raynham, MA, USA) or Maquet (MA-QUET, Rastatt, Baden-Wuerttemberg, Germany) head holder used for cervical lesions. The conventional posterior approach was used in all the patients via laminectomy or laminoplasty of the appropriate spinal level. One more laminectomy level above or below was performed if the lesion located laterally or ventrally to obtain adequate surgical operation space. The intraoperative monitoring was performed to minimize the risk of injury. After the dura opening was made along the long axis of the thecal sac, a posterior myelotomy was preferably used for lesions in the midline (Fig. 1B–D). A posterolateral sulcus myelotomy, being equivalent to the dorsal root entry zone myelotomy, was used when the lesions were located laterally (Fig. 2C–E).

Table 1. Modified McCormick scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Intact neurologically, normal ambulation, minimal dysesthesia</td>
</tr>
<tr>
<td>II</td>
<td>Mild motor or sensory deficit, functional independence</td>
</tr>
<tr>
<td>III</td>
<td>Moderate deficit, limitation of function, independent w/external aid</td>
</tr>
<tr>
<td>IV</td>
<td>Severe motor or sensory deficit, limited function, dependent</td>
</tr>
<tr>
<td>V</td>
<td>Paraplegia or quadriplegia, even with flickering movement</td>
</tr>
</tbody>
</table>

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1–2 illustrate 2 representative examples of different spinal cord myelotomy approaches. The typical changes associated with the lesion in intraoperative findings were discoloration or hemosiderin deposition, partially accompanied by fresh hemorrhage. The lesion was removed en bloc along the gliotic plane surrounding the malformation.

After resection, the tumor bed was explored carefully to exclude residual vascular malformations, followed by layer-to-layer and water-tight suturing of the dura. All patients were routinely followed at outpatient clinics at 3, 6, and 12 months and subsequently assessed every year by outpatient visits or by telephone. MRI was regularly performed in the first 3 years after discharge, and then every 3 years. The long-term surgical outcome was based on follow-up from the time of surgery to the most recent medical information. The mean follow-up period was 4.8 years (1.6 years to 8.8 years). The outcome data included the patient’s current neurological status compared with their preoperative clinical presentation results.

4. Statistical Analysis

Descriptive statistics were performed to assess baseline patients’ demographic and clinical characteristics. Continuous variables were compared using the Kruskal-Wallis correlation test, while categorical variables were compared using the chi-square test or Fisher exact test. A p-value of < 0.05 signified a statistically significant difference. Statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline Characteristics and Clinical Presentation

A total of 29 patients (17 males, 58.6%) met inclusion criteria (Fig. 3). The mean age of the patients was 45.2 ± 14.3 years (range, 17–69 years). The majority of lesions were located in the thoracic spinal cord (n = 15, 51.7%), followed by the cervical (n = 12, 41.4%) and cervicomedullary junction (n = 2, 6.9%). The mean size of the lesions was 9.7 mm (range, 3–20 mm). Most patients
suffered a bowel or/and bladder dysfunction symptom (n = 11, 37.9%), followed by sensory deficits (n = 5, 17.2%), gait disturbance (n = 5, 17.2%), pain (n = 4, 13.8%), and weakness (n = 4, 13.8%). Seven patients (24.1%) had severe neurological deficits with grade IV/V on the MMcS. According to the classification of patients' clinical presentation, 12 cases (41.4%) were classified as type A, 15 cases (51.7%) as type C, and 2 cases (6.9%) as type M. Detailed description of baseline characteristics and clinical presentation were illustrated in Tables 2–3.

2. The Risk Associated With Hemorrhage Events

A total of 27 hemorrhagic episodes were observed in 1,310 patient-years. The calculated annual retrospective hemorrhage rate for symptomatic ISCMs was 2.1% per patient/year. A total of 27 hemorrhages occurred in the 18 patients, with 50.0% (n = 9) of patients experienced rehemorrhage events before the initial clinical visit to our hospital. A significantly higher proportion of patients in the hemorrhage group had smaller lesion size (p = 0.008). In addition, hemorrhage can also be suggested by the patient's acute onset (p = 0.036) and higher MMcS on presentation (p = 0.003). Thirty-one percent cases (n = 9) had rehemorrhage events before the treatment. No statistically significant differences were found between the 2 groups regarding age, sex, location, symptom types, and duration before the presentation (Table 4).

3. Surgical Outcomes and Prognostic Factors

All patients received total resection of the lesions without subsequent bleeding or rehemorrhages during follow-up. According to the MMcS measured at the last postoperative follow-up,
Table 2. Demographic and clinical features of patients included in this series

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)/ sex</th>
<th>Lesion</th>
<th>Location</th>
<th>Size (mm)</th>
<th>Symptom Type</th>
<th>Clinical course</th>
<th>Duration (mo)</th>
<th>McCormick grade</th>
<th>Hemorrhage</th>
<th>Recurrent hemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62/M</td>
<td>Thoracic</td>
<td>8</td>
<td>Gait disturbance</td>
<td>A</td>
<td>60</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>19/M</td>
<td>Thoracic</td>
<td>9</td>
<td>Bladder dysfunction</td>
<td>A</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>38/F</td>
<td>Cervical</td>
<td>20</td>
<td>Right upper limb paresthesia</td>
<td>C</td>
<td>0.4</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>23/F</td>
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<td>61/M</td>
<td>Cervical</td>
<td>9</td>
<td>Bladder dysfunction</td>
<td>C</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

-, no; +, yes.

19 patients improved, 4 patients remained stable, and 6 patients worsen compared with preoperative status. The 6 patients who decline mainly suffered numbness and pain. The patients were divided into improved and not-improved groups according to neurological outcomes. Patient age, sex, tumor size, tumor location, symptom types, symptom duration, clinical course before
with a more prolonged course ($p = 0.015$) and the chronic onset of disease ($p = 0.003$). We also found that patients with lower preoperative MMcS had better outcomes ($p = 0.035$). Overall neurological results were not significantly correlated with the initial hemorrhage before surgical treatment ($p = 0.530$), but those were worse in patients with a history of recurrent hemorrhages ($p = 0.016$). Detailed statistical data are presented in Table 5.

**DISCUSSION**

**1. Demographics**

CMs occur mostly intracranially and rarely in the spinal cord. With the increased availability of MRI, the detection rate of ISCMs has increased. However, the true incidence of ISCMs remains unclear. Jellinger\(^{15}\) has suggested that ISCMs represent 5%–12% of all spinal vascular diseases. Liang et al.\(^{16}\) have estimated that the incidence of ISCMs represented 8.7% of spinal vascular diseases. Our calculated incidence of ISCMs is 10.5% of spinal vascular diseases, similar to previously published rates. Appiah et al.\(^{17}\) included 157 patients for analysis and showed that 51% of the lesions were in the epidural, 34% in the intramedullary, and 15% in the perimedullary. Histologically, they consist of endothelial-lined vascular spaces of varying sizes embedded in a connective tissue matrix, lacking apparent arteries for blood supplement and draining veins. Multiple small vessels can be seen entering the lesion, and there are often small foci of hemorrhage within or around it\(^{18}\) (Fig. 2G). A female prevalence in the population with ISCMs has been reported, with a female-to-male ratio of approximately 2:1.\(^{19,20}\) Interestingly, the ratio in our study was 1:1.4. When it comes to the distribution of lesions in the spinal cord, the cervical and thoracic cord occurred in comparable proportions in this series (48.3% vs. 51.7%). This result is identical to the findings of a large meta-analysis conducted by Badhiwala et al.,\(^4\) which included 631 patients. It has also been shown that lesions are more likely to arise in the thoracic. The mean age of onset in this series was 45.2 years (range, 17–69 years), which was concordant with previous literature.\(^{17,18}\) Most patients in our series tended to present with chronic progressive myelopathy (type C). Chronic progressive symptoms are thought to occur due to microhemorrhage of intraleision, microcirculatory changes, and partial thrombosis.\(^{20}\) In other patients, there was a rapid deterioration of neurological function (type A) due to acute hemorrhage within the ISCMs.

### Table 3. Baseline patient characteristics (n = 29)

<table>
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<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
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<tr>
<td>Age at presentation (yr)</td>
<td>45.2 ± 14.3 (17–69)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>Male</td>
<td>17 (58.6)</td>
</tr>
<tr>
<td>Location</td>
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</tr>
<tr>
<td>Cervical</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Cervicomedullary junction</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Size (mm)</td>
<td>9.7 ± 4.2 (3–20)</td>
</tr>
<tr>
<td>Symptom type</td>
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</tr>
<tr>
<td>Pain</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Weakness</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Sensory deficits</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Bowel/bladder dysfunction</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Symptom duration (mo)</td>
<td>23.8 ± 42.3 (0.3–180)</td>
</tr>
<tr>
<td>Clinical course prior to presentation</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>C</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>M</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>MMcS on presentation</td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>3 (10.3)</td>
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<td>4 (13.8)</td>
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<td>Yes</td>
<td>18 (62.1)</td>
</tr>
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<td>Long-term outcome</td>
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</tr>
<tr>
<td>Unchanged</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Worsen</td>
<td>6 (20.7)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation (range) or number (%). MMcS, modified McCormick scale.
2. Hemorrhage Events

It is well known that hemorrhage was an essential factor in the progression of patients suffering from ISCMs. The annual hemorrhage rate for the present group of patients was calculated to be approximately 2.1%. This was consistent with the rate of 1.4%–6.8% previously reported in the literature. \(^{21,22}\) Some researchers have conducted follow-up studies of ISCMs patients in the conservative group and found an annual hemorrhage rate of about 3.9%–5.5%. This figure may better reflect the actual situation. \(^{21,23}\) Our study showed that the lesions in the thoracic group had a higher risk of hemorrhage than the cervical group. This may be due to the smaller space in the thoracic spinal canal, resulting in a poorer tolerance of the patient. While in the cervical group, the patients ignore some of the older hemorrhagic events that may be smaller and cause less severe symptoms because of recall bias. In addition, we observed a higher incidence of hemorrhage in smaller lesions, which contradicts Tong's results. \(^8\) However, the study of Goyal et al. \(^7\) did not demonstrate a clear relationship between hemorrhage events and lesion size in ISCMs, but did find a significantly greater risk of hemorrhage in lesions larger than 1 cm. Consequently, larger amounts of case data are needed to elucidate this issue. There was no significant correlation between the initial presence or absence of hemorrhage and the outcomes of the patient; however, it is noteworthy that patients with a history of recurrent hemorrhage had significantly worse results. While a subset of patients may remain neurologically and clinically stable after initial presentation, a small prospective study suggests a very

<table>
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<tr>
<th>Variable</th>
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<th>Hemorrhage (n = 18)</th>
<th>Total (n = 29)</th>
<th>p-value</th>
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<td>12 (41.4)</td>
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<td>11 (61.1)</td>
<td>17 (58.6)</td>
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</tr>
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<td>5 (17.2)</td>
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Values are presented as mean ± standard deviation or number (%).

MMcS, modified McCormick scale.
Table 5. Comparison of factors affecting patient outcomes

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<th>Improved (n = 19)</th>
<th>Not-improved (n = 10)</th>
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<th>p-value</th>
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Values are presented as mean ± standard deviation or number (%).
MMcS, modified McCormick scale.

high annual rehemorrhage rate after that. Additionally, several patients in this series experienced acute hemorrhage resulting in a dramatic decline in neurological function that did not return to their prehemorrhagic state even after surgery, so we believe that in cases with a high risk of hemorrhage, such as lesions located in the thoracic spine and history of prior hemorrhage, surgical treatment should be considered to benefit the patient and avoid subsequent rehemorrhage resulting in severe neurological deficits.

3. Surgical Outcomes
GTR can be accomplished safely and is an available option for the treatment of ISCMs. Although a transient deterioration may occur after surgery, most improved postoperatively after 3 to 6 months. Outcomes of patients were attributed to a variety of factors. In an extensive pooled analysis, Badhiwala et
al. found that lesions > 10 mm, duration of disease < 3 months, via hemilaminectomy, and GTR, were factors associated with improved neurological function in patients after surgery. Zhang et al. found that patients with lesions located in the cervical cord had better outcomes because of earlier defect detection and better intraoperative visualization. Our study showed that patient outcomes were not correlated with lesion location and size. Meanwhile, we found that initial hemorrhage was not a risk factor for results, even though the patients may suffer an acute neurological deterioration before surgical treatment. Zhang et al. emphasized the importance of conservative treatment for asymptomatic or less symptomatic patients. This result should be viewed with caution because based on previous literature and the results of this study, satisfactory outcomes can be achieved with surgical treatment of this disease when the surgical strategy is carefully planned. Badhiwala et al. counted a total of 631 patients in 40 publications, and a total of 567 patients were treated surgically, of which 264 (51.5%) improved, 194 (37.8%) remained unchanged, and 55 (10.7%) worsened. For 64 patients in the conservative treatment group, only 16 (30.2%) had im-

Fig. 4. Hemorrhage events of intramedullary spinal cavernous malformation in the cervical spinal cord. The patient was admitted to the hospital with a sudden onset of limb hemiparesis. (A-C) Magnetic resonance imaging (MRI) revealed an intramedullary occupancy of the C2 cervical intramedullary spinal cord, with noticeable hemorrhagic changes and large edema in the right cervical medulla. After 2 weeks of conservative treatment with dehydration and hormones, most of the hemiplegic symptoms improved, then the limb movement function was fully restored at 3 months. (D, E) The repeat MRI showed that most hematoma and edema were absorbed, and the tumor border was formed. With an elective procedure, the tumor was well visualized and resected. (F, G) A hemosiderin-stained cavity can be observed. Three months after the operation, the MRI cavernous hemangioma was completely removed, and the patient recovered well and could work normally. (H, I) MRI 3 months later showed a GTR of the lesion, and the patient recovered well and can normally work.
proved neurological function, 31 (58.5%) remained unchanged, while 17 (11.3%) experienced a neurological decline. Compared with conservative, resection was significantly associated with favorable neurological outcomes (odds ratio, 2.97; 95% confidence interval, 1.46–5.33; p = 0.002). Therefore, this data should not be overinterpreted as evidence favoring conservative management. Our standard protocol is to perform surgical resections for patients with symptomatic ISCMs, especially those with a history of recurrent hemorrhages.

4. Surgery Timing
As a kind of vascular disease, when the surgical decision is made for symptomatic ISCM patients, the perfect timing of surgical management should also be considered.

Some authors have argued that early surgical intervention is recommended for a better surgical outcome. Other authors, however, hold a different view. Zevgaridis et al. argued that if surgery is to be performed for cavernomas in critical areas, 4 ± 6 weeks after a hemorrhage seems to be the optimal point in time. A glial scar has developed, and the hematoma is in resolution and can be used to the surgeon’s advantage. Following the decompression of the hematoma, there is sufficient space to excise the malformation. Kondziella et al. also argued that if a decision in favor of surgical excision is made, subacute intervention after 4–6 weeks seems optimal when the hematoma is in resolution and a glial scar develops. Zhang et al. reported 18 cases of pediatric ISCMs treated outcomes. 3 of the patients (16.7%) underwent emergence surgery immediately after hospitalization, and 2 patients (11.1%) underwent surgery 7 days after the recent episodes of hemorrhage, these lesions were found to adhere tightly to the spinal cord without an obvious gliotic plane, and the resection process was technically challenging. Two of them underwent STR since total resection was deemed unsafe. In a patient with an acute hematoma onset, the hemorrhagic stimulation and subsequent extensive edema were often the main causes of neurological deterioration, rather than the lesion itself. For such patients, we also advocate that conservative treatment should be given for 4–6 weeks before surgery, pending the absorption of the hematoma and edema, and that neurological function can generally be largely restored. After most of the hematoma and edema were absorbed, a clear operating boundary was formed, conducive to surgical separation and reducing the risk of secondary injury and residual lesions (Fig. 4).

5. Limitations
Despite the present report focusing on the point of the symptomatic ISCMs with a relatively large number of consecutive cases, the study cohorts are still limited due to the rarity of the lesions. We assessed the data from a single center, which can lead to well-known information and selection biases. More case series with large cohorts are still needed, and a prospective multicenter randomized study or a registry for patients with ISCMs is highly recommended. Despite these limitations, our study still provided comprehensive information on this rare entity to aid treatment strategy-making.

CONCLUSION
Rehemorrhage is a risk factor for neurological outcomes of symptomatic ISCM patients. With strictly preoperative assessment and carefully intraoperative technique, patients can benefit from microsurgical treatment to avoid rehemorrhage and further neurological deterioration.

NOTES
Conflicts of Interest: No potential conflict of interest relevant to this article was reported.
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Author Contribution: Conceptualization: XD, WS; Formal Analysis: XH, WD; Investigation: XH, ZZ, QL; Methodology: ZC; Project Administration: WS; Writing – Original Draft: ZC, WS; Writing – Review & Editing: ZC, WS, XD.

REFERENCES
Spinal cord cavernous malformations (SCCM) are relatively rare entities comprising 5%–12% of all spinal cord vascular lesions, affecting mostly the cervical and thoracic segments. It is estimated that 12% of patients affected by this condition will have positive family history of SCCM and up to 16.5% will have associated intracranial cavernomas. Diagnosis is usually made at the midages and data on sex predilection is divergent, although gathered evidenced supports the existence of an equilibrium. They may be asymptomatic or present as variable degrees of myelopathy. Chronic progressive symptoms seem to originate from microhemorrhage, microcirculatory variations, and partial thrombosis, whereas acute presentations are often related to frank hemorrhage.

Surgery is the mainstay treatment for symptomatic cases, although the appropriate timing and patient selection is subject of debate. In this elegant study, Cai et al. describe their experience on microsurgical treatment of symptomatic SCCM. Clinical presentation, surgical outcomes, and factors related to spontaneous hemorrhage and neurological outcomes were assessed. The neurological outcome was measured using the modified McCormick scale (MMCS). Surgeries were performed by 2 experienced surgeons using a posterior approach with either laminectomy or laminoplasty. Microsurgical technique was used in all cases and the myelotomy was performed in the midline or along the posterior lateral sulcus, depending on SCCM position inside the parenchyma.

The present study analyses the outcome in 29 consecutive patients (12 females and 17 males) treated in a single center from June 2014 to May 2021. The current cohort is similar in many aspects to prior studies, however, they differ in a male predominance (1:4:1 ratio) and an increased prevalence of bladder/bowel dysfunction over motor/sensory dysfunction. Seven patients (24.1%) presented severe preoperative deficits (MMCS IV/V). It is important to highlight that the MMCS focuses on motor and sensory functions, while a large proportion of individuals in this series had symptoms related to visceral dysfunction. Although not being the purpose of this study, a better description of the outcome in terms of sphincter continence and pain scores would be interesting as SCCM are rare and reports in the literature are limited.

In their series, all patients had a gross total resection, with some experiencing a transient...
neurological decline after surgery. By the last follow-up, 19 patients (65.5%) had an objective improvement of neurological function and 6 cases (20.7%) declined in performance. Unfavorable outcomes occurred in patients with recurrent hemorrhages, whereas older age and lower preoperative MMCS scores correlated with better functional results.³ Interestingly, chronic presentation and longer duration of symptoms were consistent with better outcome, conflicting with the conclusion of a recent systematic review that reported duration of symptoms less than 3 months prior to surgery to lead a better functional status.⁵ Arguments favoring early intervention include that chronic damage to the perilesional neural tissue produces gliosis that can interfere with microsurgical dissection, increasing the chances of postoperative neurological deficits and early surgery is recommended after an acute hemorrhage, when the blood has created a dissection plane and adherences were not formed.⁴ Nevertheless, the current study demonstrate that functional improvement can be achieved when appropriate and careful microdissection is performed by an experienced surgeon, even in complex cases of SCCM presenting along a chronic timeline.

The annual hemorrhage rate found in this study was 2.1%. Eighteen cases (62.0%) had symptoms related to acute hemorrhage, with half of these patients presenting recurrent events. Smaller lesions had higher risk of bleeding and acute presentations had worse preoperative MMCS.³ Thoracic location and recurrent bleeding were found to predict poor outcome and the authors advocate early surgical intervention in such cases.

In conclusion, this study brings valuable information as it shows that surgery may have better results in patients with chronic presentation and provide evidence that thoracic location and recurrent hemorrhage associate with poorer functional outcome. The discrepancies in demographical and clinical presentation to previous reports suggest the occurrence of heterogeneity in this population. Identifying subsets of patients who are more likely to benefit from early surgery is of great importance in clinical practice. The contrary is also relevant, as surgical risks may overcome benefits in patients at low risk of bleeding, especially when the SCCM is deep seated not in contact with the dorsal pial surface.

- **Conflict of Interest:** The authors have nothing to disclose.

**REFERENCES**

Simultaneous Single-Position Lateral Lumbar Interbody Fusion Surgery and Unilateral Percutaneous Pedicle Screw Fixation for Spondylolisthesis

Hui Lv1,2, Yu Sheng Yang1, Jian Hong Zhou1,2, Yuan Guo3, Hui Chen1,2, Fei Luo1,2, Jian Zhong Xu1,2, Zhong Rong Zhang1,2, Ze Hua Zhang1,2

1Department of Orthopaedic, Southwest Hospital, The First Affiliated Hospital of Army Medical University, Chongqing, China
2Department of Orthopaedic, Jiangbei Branch of Southwest Hospital, Chongqing, China

Objective: To evaluate the clinical and radiological efficacy of a combine of lateral single screw-rod and unilateral percutaneous pedicle screw fixation (LSUP) for lateral lumbar interbody fusion (LLIF) in the treatment of spondylolisthesis.

Methods: Sixty-two consecutive patients with lumbar spondylolisthesis who underwent minimally invasive (MIS)-TLIF with bilateral pedicle screw (BPS) or LLIF-LSUP were retrospectively studied. Segmental lordosis angle (SLA), lumbar lordosis angle (LLA), disc height (DH), slipping percentage, the cross-sectional areas (CSA) of the thecal sac, screw placement accuracy, fusion rate and foraminal height (FH) were used to evaluate radiographic changes postoperatively. Visual analogue scale (VAS) and Oswestry Disability Index (ODI) were used to evaluate the clinical efficacy.

Results: Patients who underwent LLIF-LSUP showed shorter operating time, less length of hospital stay and lower blood loss than MIS-TLIF. No statistical difference was found between the 2 groups in screw placement accuracy, overall complications, VAS, and ODI. Compared with MIS-TLIF-BPS, LLIF-LSUP had a significant improvement in sagittal parameters including DH, FH, LLA, and SLA. The CSA of MIS-TLIF-BPS was significantly increased than that of LLIF-LSUP. The fusion rate of LLIF-LSUP was significantly higher than that of MIS-TLIF-BPS at the follow-up of 3 months postoperatively, but there was no statistical difference between the 2 groups at the follow-up of 6 months, 9 months, and 12 months.

Conclusion: The overall clinical outcomes and complications of LLIF-LSUP were comparable to that of MIS-TLIF-BPS in this series. Compared with MIS-TLIF-BPS, LLIF-LSUP for lumbar spondylolisthesis represents a significantly shorter operating time, hospital stay and lower blood loss, and demonstrates better radiological outcomes to maintain lumbar lordosis, and reveal an overwhelming superiority in the early fusion rate.

Keywords: Spinal fusion, Minimally invasive surgical procedures, Single-position, Pedicle screws, Spondylolisthesis

INTRODUCTION

Degenerative diseases of the lumbar spine are common and the most classic procedure is still conventional posterior/transforaminal lumbar interbody fusion (TLIF),1,2 but for the past few years advances in minimally invasive (MIS) technology, indirect decompression as the core of the lateral lumbar interbody fusion (LLIF) that includes extreme lateral lumbar interbody fusion (XLIF) and oblique lateral lumbar interbody fusion (OLIF) have gained increasing attention for spine surgery.1,4

LLIF has many advantages including implantation a larger footprint to restore disc height (DH), and avoidance of posterior bone structure destruction and intraspinal thecal sac interference compared to posterior lumbar interbody fusion.5 How-
ever, the optimal supplemental fixation for LLIF is still controversial. Bilateral pedicle screw (BPS) fixation is a recognized and "gold standard" technique, but intraoperative repositioning prone needs to be operated for most surgeons without O-arm or robot, which significantly increases operative time and anesthetic-related complications. Hersey et al. found that the risk of postoperative complications increased with each additional hour of operative time. BPS fixation can be performed in a single position with the aid of an O-arm or a robot, but these devices cannot be distributed in all units. Lateral intervertebral fixation including 2 ways: lateral plate (LP) and screws is a modified solution which can achieve immediate fixation in the single-position but the effect of fixation in axial rotation is uncertain. Zhao et al. demonstrated a significant decrease in the DH of the anterolateral single screw-rod fixation for OLIF within 1 month postoperatively compared to the BPS for TLIF. In the study of Yingsakmongkol et al., supplementary fixation with anterolateral plate is considered to be a risk factor for indirect decompression failure of LLIF. Stand-alone LLIF surgery has the advantages of less trauma and decreased operative time on account of eliminating the use of additional internal fixation but the high rate of postoperative cage subsidence may expose more patients to the risk of a second operation.

Based on these, we believe that an excellent method of internal fixation in LLIF surgery needs to meet both the following conditions: implantation in single-position and biomechanical strength should be considerable. Inspired by reliability of multidimensional fixation, we designed a novel fixation scheme for LLIF which integrated both sagittal and coronal dimensions that was a combine of lateral single screw-rod and unilateral percutaneous pedicle screw fixation (LLIF-LSUP). To the best of our knowledge, we first report the clinical efficacy of this fixation modality for LLIF in the treatment of spondylolisthesis.

The present study introduced the key points of LLIF-LSUP, and compared postoperative complications, clinical and radiological outcomes of 2 ways fixation (LLIF-LSUP vs. MIS-TLIF-BPS) from a consecutive series of patients. Our goal was to generate referable information for improving the outcomes of supplemental fixation in LLIF.

**MATERIALS AND METHODS**

After being approved by the Ethics Committee of Jiangbei Branch of Southwest Hospital (KY-2022-41), a retrospective review of prospectively collected data was conducted. Sixty-two consecutive patients with lumbar degenerative disease who underwent MIS-TLIF or LLIF surgery between January 2021 to January 2022 met the inclusion and exclusion criteria and were enrolled in the present study. The detailed inclusion criteria included degenerative lumbar spondylolisthesis within Meyerding grade I or II, single segment at L2-L5. The exclusion criteria were as follows: (1) Diseases in which indirect decompression is not achieved, such as lumbar spinal stenosis of grade C and spondylolisthesis of grade III or IV; (2) Severe osteoporosis (T score less than -3.5), spinal neoplasms, and spinal injury; (3) Radiographic measurement indicated Cobb angle > 30° in the sagittal plane; (4) The shortest distance of oblique corridor between psoas muscles and abdominal vessels less than or equal to 1 cm in OLIF surgery. LLIF is determined based on dynamic clinical symptoms that the patient has significant pain relief at rest in the sitting or supine position compared with walking, and that spinal nerve compression due to disc herniation or fold of ligamentum flavum without bony lateral recess stenosis.

1. **Surgical Technique**

The OLIF is a 2-step procedure. After tracheal intubation and general anesthesia were satisfied, the patient was placed in the right lateral decubitus position (Fig. 1E), and the target intervertebral disc and "up-side" pedicles were identified by C-arm fluoroscopy and marked lines were drawn (Fig. 1A–D). First, the "up-side" percutaneous pedicle screws (Viper 2 System Guide, Depuy, Warsaw, IN, USA) placement was performed routinely. Briefly, a 1-cm longitudinal incision was made at the surface markers of the "up-side" pedicle. The pedicle is cannulated by manipulating the Jamshidi needle and K-wire was sequentially inserted with the aid of the C-arm fluoroscopy. The Jamshidi needle was removed and a suitable hollow pedicle screw was inserted along the K-wire with attention. Similarly, the mentioned above procedure was repeated in the surface markers of another pedicle. The precontoured rod was placed along the guided instrument. Subsequently, the screw cap of the inferior vertebra was gradually locked but the screw cap of the superior vertebra was incompletely locked for the subsequent reduction process (Fig. 1F–H). Second, a 5-cm longitudinal incision was made in the lateral abdominal region orientated 3 cm at the anterior edge of the target segment. The external oblique, internal oblique, and transverse abdominal muscles of the abdomen were bluntly dissected along the direction of intramuscular fibers. After entering the retroperitoneal space, the index finger was used to clean the retroperitoneal fat and identify the psoas major. Wet gauze with saline was given to protect the peritoneum, abdominal contents, and vessels from expandable retrac-
tors along the medial retroperitoneal space. The target intervertebral disc was carefully exposed to avoid iatrogenic injury to the femoral nerve, the sympathetic chain, and the ureter. Subsequently, discectomy was performed routinely but the contralateral annulus fibrosus should be released to allow the cage to be implanted smoothly in the bilateral peripheral endplates, and then the intervertebral endplate cartilage was scraped off carefully through specialized reamer. A PEEK cage (Oracle Cage System, Depuy, Warsaw, IN, USA) of appropriate size filled with allogeneic bone grafts (Bio-Gene, DastingBio-Tech Co., Ltd., Beijing, China) combination with bone marrow enrichment realized by selective cell retention technology following our previously reported procedure was implanted in the disc spaces and the target spondylolisthesis reduction was performed simultaneously. Subsequently, 2 lateral screws that was perpendicular to the direction of the pedicle screw were inserted above and below the adjacent endplates (diameter, 7 mm; length, 50 to 55 mm; Fig. 1I, J) and a connecting rod was applied (prominent from lateral edge of the vertebral about 15 mm; Fig. 1K, L). After the intervertebral space was compressed, all caps were final-

Fig. 1. A series of surgical photographs for key procedures of lateral lumbar interbody fusion combined lateral single screw-rod and unilateral percutaneous pedicle screw fixation. (A–D) Marked lines for the target intervertebral disc were obtained by C-arm fluoroscopy. (E–H) The patient underwent unilateral percutaneous pedicle screw fixation in single-lateral decubitus position. (I–L) Spondylolisthesis reduction, screws, cage, and connecting rod insertion were performed simultaneously.
ly locked. A drain was routinely placed and the wound was closed layer by layer. A schematic diagram was used to illustrate the key procedures of LLIF-LSUP (Fig. 2).

Most of the procedures of XLIF are similar to those of OLIF but the approach of XLIF was performed as described previously.\textsuperscript{17} The MIS-TLIF procedure was referring to the technique previously described.\textsuperscript{18} The Wiltse approach was used on the symptomatic side of the lower extremity. The facet joint is routinely excised and the ligamentum flavum was resected to reveal the dural sac and nerve roots. Discectomy was performed routinely in the Quadrant working channel. Routine endplate preparation, allogeneic bone grafting (Bio-Gene, DastingBio-Tech Co.), and cage (Fidji, Zimmer, Warsaw, IN, USA) placement were performed in sequence. The percutaneous screw fixation for the pedicle is identical with LLIF. A drain was routinely placed and the wound was closed layer by layer.

2. Postoperative Management

Antibiotics were routinely given to prevent infection and the drainage tube was removed within the first day postoperatively. All patients were required to wear a rigid brace at all times when they were up, for 3 months following surgery.

Follow-up time points were 3, 6, 9, 12 months postoperatively, respectively. All patients were required to complete x-ray and computed tomography (CT) examinations every 3 months prior to obtaining intervertebral bone fusion. For patients who are not available to come to the hospital, the information should be collected through telephone interview and radiographic examination should be performed in the local hospital and mailed to our office.

3. Therapeutic Evaluation

1) Clinical assessment

Visual analogue scale (VAS) was used to evaluate the pain of patients. Lower back function was evaluated using the Oswestry Disability Index (ODI). Operation time, intraoperative blood loss, length of hospital stay, fixation segments and postoperative complications were recorded during the operation.

2) Radiographic examinations

X-rays of all patients were taken standing up. Segmental lordosis angle (SLA), lumbar lordosis angle (LLA), disc height (DH), slipping percentage (SP), and foraminal height (FH) were used to evaluate radiographic changes postoperatively. SLA was defined as the Cobb angle between the superior endplate of the superior vertebra and the inferior endplate of the inferior vertebra. Similarly, LLA was defined as the Cobb angle between L\textsubscript{1} and S\textsubscript{1}. SP was defined as the ratio of the distance of spondylolisthesis to the length of the inferior vertebra. DH mainly refers to the method described by Ekman et al.\textsuperscript{19} FH was defined as the maximum distance between adjacent pedicles on the sagittal reconstructed CT images. Screw placement accuracy was evaluated according to the methods described by Spitz et al.\textsuperscript{20}

The cross-sectional areas (CSA) of the thecal sac were measured on T2-weighted axial magnetic resonance imaging according to the methods described by Nakashima et al.\textsuperscript{21} The bone fusion criteria described by Siepe et al.\textsuperscript{22} were used to evaluate interbody fusion status. Cage subsidence and endplate fracture were recorded. Cage subsidence was defined as more than 2 mm subsidence toward the endplate compared with the postoperative immediately. All radiological measurements were obtained by a picture archiving and communication system (JinYe Xiang Software, Beijing, China). All parameters were measured independently by 2 spine surgeons who were not involved in these surgeries and final measurement for each participant averaged the 2 measurements.

4. Statistical Analysis

Data are presented as mean ± standard deviation. Continuous variables between the 2 groups (e.g., body mass index [BMI],
bone mineral density [BMD], age, DH, SLA, LLA, FH, SP, CSA) were compared by t-test (IBM SPSS Statistics ver. 21.0, IBM Co., Armonk, NY, USA). Dichotomous variables from 2 groups (e.g., gender, Meyerding grade, smoker, segments distribution, screw placement accuracy and fusion rate) were analyzed by chi-square test or Fisher exact test. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 62 patients entered in this study. Of these, 26 patients underwent LLIF-LSUP and 36 patients MIS-TLIF-BPS. There was no statistical significance in age, sex, smoker, operation level, BMI, BMD, clinical symptoms, follow-up time and preoperative spondylolisthesis type between the patients underwnt LLIF and MIS-TLIF 2 groups (p > 0.05). The baseline demographic data are detailly described in Table 1.

1. Clinical Outcomes

The mean operation time was 100.5 minutes (85 to 127 minutes), and the mean blood loss was 68.8 mL (30 to 110 mL) in patients who underwent LLIF-LSUP, while that in patients with MIS-TLIF surgery was 140.3 minutes (103 to 200 minutes) and 244.7 mL (110 to 480 mL), respectively. There were significant differences between the 2 groups in operative time and blood loss (p < 0.05). The LLIF group had significantly short length of hospital stay compared with MIS-TLIF (p < 0.05). In terms of functional outcomes, the VAS in LLIF-LSUP decreased from a mean preoperative score of 6.5 to 1.8, 1.6, 1.6, and 1.5 and the ODI in LLIF-LSUP decreased from a mean preoperative score of 46.9 to 22.2, 15.8, 12.0, and 10.8 at each postoperative follow-up. The VAS in MIS-TLIF-BPS decreased from a mean preoperative score of 6.8 to 2.5, 2.0, 1.8, and 1.7 and the ODI in MIS-TLIF-BPS decreased from a mean preoperative score of 47.2 to 26.7, 18.5, 13.2, and 11.4 at each postoperative follow-up. Significant VAS decline was achieved between preoperation and postoperation through both procedures (p < 0.05). There was no significant difference in VAS and ODI between the 2 groups.

Table 1. Patient demographics and clinical characteristics

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<td>2 (5.6)</td>
<td>1 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L(_4)-L(_3)</td>
<td>5 (13.9)</td>
<td>4 (15.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L(_5)-L(_3)</td>
<td>29 (80.5)</td>
<td>21 (80.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>16.9 ± 3.5</td>
<td>15.6 ± 2.4</td>
<td>0.094</td>
<td>1.702</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). MIS-TLIF-BPS, minimally invasive transformaminal lumbar interbody fusion with bilateral pedicle screw; LLIF-LSUP, lateral lumbar interbody fusion combined lateral single screw-rod and unilateral percutaneous pedicle screw fixation; BMI, body mass index; BMD, bone mineral density.

Table 2. Clinical outcomes for all patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>MIS-TLIF-BPS (n = 36)</th>
<th>LLIF-LSUP (n = 26)</th>
<th>p-value</th>
<th>( t^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative duration (min)</td>
<td>140.3 ± 27.6</td>
<td>100.5 ± 13.3</td>
<td>0.000*</td>
<td>6.799</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>244.7 ± 101.1</td>
<td>68.8 ± 18.6</td>
<td>0.000*</td>
<td>8.748</td>
</tr>
<tr>
<td>Length of hospital stay (day)</td>
<td>9.2 ± 2.1</td>
<td>6.1 ± 1.9</td>
<td>0.000*</td>
<td>5.997</td>
</tr>
<tr>
<td>VAS</td>
<td>6.8 ± 1.5</td>
<td>6.5 ± 1.2</td>
<td>0.629</td>
<td>0.486</td>
</tr>
<tr>
<td>3 Months</td>
<td>2.5 ± 0.8</td>
<td>1.8 ± 0.6</td>
<td>0.000*</td>
<td>3.606</td>
</tr>
<tr>
<td>6 Months</td>
<td>2.0 ± 0.6</td>
<td>1.6 ± 0.5</td>
<td>0.001*</td>
<td>3.426</td>
</tr>
<tr>
<td>9 Months</td>
<td>1.8 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>0.101</td>
<td>1.667</td>
</tr>
<tr>
<td>12 Months</td>
<td>1.7 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>0.193</td>
<td>1.318</td>
</tr>
<tr>
<td>ODI</td>
<td>47.2 ± 10.0</td>
<td>46.9 ± 9.9</td>
<td>0.904</td>
<td>0.121</td>
</tr>
<tr>
<td>3 Months</td>
<td>26.7 ± 8.1</td>
<td>22.2 ± 6.5</td>
<td>0.022*</td>
<td>2.357</td>
</tr>
<tr>
<td>6 Months</td>
<td>18.5 ± 5.1</td>
<td>15.8 ± 4.4</td>
<td>0.033*</td>
<td>2.183</td>
</tr>
<tr>
<td>9 Months</td>
<td>13.2 ± 2.5</td>
<td>12.0 ± 3.2</td>
<td>0.118</td>
<td>1.587</td>
</tr>
<tr>
<td>12 Months</td>
<td>11.4 ± 1.7</td>
<td>10.8 ± 2.2</td>
<td>0.203</td>
<td>1.287</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. MIS-TLIF-BPS, minimally invasive transformaminal lumbar interbody fusion with bilateral pedicle screw; LLIF-LSUP, lateral lumbar interbody fusion combined lateral single screw-rod and unilateral percutaneous pedicle screw fixation; VAS, visual analogue scale; ODI, Oswestry Disability Index.

*p < 0.05, statistically significant differences.
at each follow-up point but a faint tendency was observed that more patients with MIS-TLIF-BPS complained of lower back pain (p > 0.05). No statistical difference was found between the 2 groups in screw placement accuracy (p > 0.05) (Table 2).

Overall, there are 8 patients with complications in MIS-TLIF surgery, including 3 cases of cage subsidence, 2 cases of dural sac tears, 2 cases of endplate fracture, 1 case of superficial wound infection, while 5 patients with complications in LLIF surgery, including 1 case of sympathetic chain injury, 1 case of cage subsidence, 1 case of endplate fracture, 2 cases of transient thigh numbness. No statistical difference was found between the 2 groups (p > 0.05). Most patients achieved satisfactory recovery of complications with conservative management, but 1 patient with cage subsidence in the MIS-TLIF group underwent reoperation and the pain in the lower limbs was finally relieved. Details are shown in Table 3.

2. Radiographic Outcomes

Compared with MIS-TLIF-BPS, LLIF-LSUP had a significant advantage in sagittal parameters including DH, FH, LLA, and SLA at each postoperative follow-up (p < 0.05). Meanwhile, these sagittal parameters in LLIF-LSUP had a statistical difference compared with those of preoperative (p < 0.05). Also, SP, DH, FH, and LLA in MIS-TLIF had a significant difference between preoperation and postoperation (p < 0.05). This difference, however, was not observed in LLA of MIS-TLIF-BPS between preoperation and postoperation (p > 0.05). No statistical difference was found between the 2 groups in SP. The CSA of MIS-TLIF-BPS had significantly better than that of LLIF-LSUP at each follow-up point and postoperative CSA in both groups was significantly expanded compared with preoperative CSA (p < 0.05). The fusion rate of LLIF-LSUP was significantly higher than that of MIS-TLIF-BPS at the follow-up of 3 months postoperatively.

### Table 3. Complications details for all patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>MIS-TLIF-BPS (n = 36)</th>
<th>LLIF-LSUP (n = 26)</th>
<th>p-value</th>
<th>( t^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall complications</td>
<td>8</td>
<td>5</td>
<td>0.775</td>
<td>0.082</td>
</tr>
<tr>
<td>Cage subsidence</td>
<td>3</td>
<td>1</td>
<td>0.853</td>
<td>0.035</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Endplate fracture</td>
<td>2</td>
<td>1</td>
<td>0.772</td>
<td>0.084</td>
</tr>
<tr>
<td>Sympathetic chain injury</td>
<td>0</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dural sac tear</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transient thigh numbness</td>
<td>0</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Screw placement accuracy, no/total (%)</td>
<td>135/144</td>
<td>99/104</td>
<td>0.627</td>
<td>0.236</td>
</tr>
</tbody>
</table>

MIS-TLIF-BPS, minimally invasive transforaminal lumbar interbody fusion with bilateral pedicle screw; LLIF-LSUP, lateral lumbar interbody fusion combined lateral single screw-rod and unilateral percutaneous pedicle screw fixation.

### Table 4. Radiographic details for all patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>MIS-TLIF-BPS (n = 36)</th>
<th>LLIF-LSUP (n = 26)</th>
<th>p-value</th>
<th>( t^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>DH</td>
<td>Pre 7.6 ± 1.3</td>
<td>7.3 ± 1.7</td>
<td>0.425</td>
<td>0.804</td>
</tr>
<tr>
<td></td>
<td>3 Days 9.7 ± 1.2</td>
<td>11.6 ± 1.4</td>
<td>0.000*</td>
<td>5.774</td>
</tr>
<tr>
<td></td>
<td>12 Months 8.7 ± 1.2</td>
<td>10.3 ± 1.2</td>
<td>0.000*</td>
<td>4.969</td>
</tr>
<tr>
<td>FH</td>
<td>Pre 16.2 ± 2.1</td>
<td>15.7 ± 2.6</td>
<td>0.409</td>
<td>0.832</td>
</tr>
<tr>
<td></td>
<td>3 Days 18.4 ± 2.3</td>
<td>20.3 ± 2.9</td>
<td>0.007*</td>
<td>2.783</td>
</tr>
<tr>
<td></td>
<td>12 Months 17.6 ± 2.1</td>
<td>19.2 ± 2.4</td>
<td>0.003*</td>
<td>3.028</td>
</tr>
<tr>
<td>LLA</td>
<td>Pre 34.5 ± 9.8</td>
<td>35.1 ± 9.2</td>
<td>0.809</td>
<td>0.242</td>
</tr>
<tr>
<td></td>
<td>3 Days 37.1 ± 6.4</td>
<td>40.8 ± 7.2</td>
<td>0.037*</td>
<td>2.131</td>
</tr>
<tr>
<td></td>
<td>12 Months 36.7 ± 6.3</td>
<td>40.1 ± 6.9</td>
<td>0.484</td>
<td>2.015</td>
</tr>
<tr>
<td>SLA</td>
<td>Pre 8.1 ± 2.3</td>
<td>8.4 ± 2.1</td>
<td>0.601</td>
<td>0.525</td>
</tr>
<tr>
<td></td>
<td>3 Days 10.9 ± 3.1</td>
<td>13.2 ± 2.9</td>
<td>0.004*</td>
<td>2.961</td>
</tr>
<tr>
<td></td>
<td>12 Months 10.5 ± 2.8</td>
<td>12.7 ± 2.8</td>
<td>0.003*</td>
<td>3.053</td>
</tr>
<tr>
<td>SP</td>
<td>Pre 22.4 ± 10.1</td>
<td>21.6 ± 7.9</td>
<td>0.738</td>
<td>0.336</td>
</tr>
<tr>
<td></td>
<td>3 Days 2.5 ± 1.0</td>
<td>2.1 ± 0.7</td>
<td>0.085</td>
<td>1.751</td>
</tr>
<tr>
<td></td>
<td>12 Months 2.8 ± 1.1</td>
<td>2.3 ± 0.8</td>
<td>0.054</td>
<td>1.970</td>
</tr>
<tr>
<td>CSA</td>
<td>Pre 80.3 ± 13.2</td>
<td>84.5 ± 7.7</td>
<td>0.152</td>
<td>1.452</td>
</tr>
<tr>
<td></td>
<td>3 Days 124.8 ± 16.7</td>
<td>105.4 ± 8.7</td>
<td>0.000*</td>
<td>5.409</td>
</tr>
<tr>
<td></td>
<td>12 Months 122.4 ± 16.1</td>
<td>113.2 ± 9.6</td>
<td>0.012*</td>
<td>2.600</td>
</tr>
<tr>
<td>Fusion rate</td>
<td>3 Months 13 (36.1)</td>
<td>15 (57.7)</td>
<td>0.045*</td>
<td>4.029</td>
</tr>
<tr>
<td></td>
<td>6 Months 21 (58.3)</td>
<td>19 (73.1)</td>
<td>0.231</td>
<td>1.434</td>
</tr>
<tr>
<td></td>
<td>9 Months 27 (75)</td>
<td>22 (84.6)</td>
<td>0.359</td>
<td>0.842</td>
</tr>
<tr>
<td></td>
<td>12 Months 31 (86.1)</td>
<td>24 (92.3)</td>
<td>0.723</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. MIS-TLIF-BPS, minimally invasive transforaminal lumbar interbody fusion with bilateral pedicle screw; LLIF-LSUP, lateral lumbar interbody fusion combined lateral single screw-rod and unilateral percutaneous pedicle screw fixation; DH, disc height; FH, foraminal height; LLA, lumbar lordosis angle; SLA, segmental lordosis angle; SP, slipping percentage; CSA, cross-sectional areas.

* \( p < 0.05 \), statistically significant differences.
(p < 0.05), but there was no statistical difference between the 2 groups at the follow-up of 6 months, 9 months, and 12 months (p > 0.05). The detailed data can be found in Table 4 and typical cases are presented in Fig. 3.

**DISCUSSION**

Remarkable progress of single position surgery in LLIF has been made in recent years, including early attempts at facet/unilateral pedicle screw fixation in the lateral decubitus position to address repositioning limitation, anterolateral single screw-rod/plate fixation and prone transpsoas (PTP) approach with BPS fixation in the nowadays technique. Although still no consensus on fixed method in LLIF, there’s little doubt that more effective surgical technique and lower complication is the goal of orthopedic surgeons. Consistent with recent article published by Zhu et al., a prospective study on the effect of OLIF-BPS versus MIS-TLIF-BPS in lumbar degenerative diseases, the operative time, blood loss, and length of hospitalization in the LSUP group were significantly decreased compared to conventional MIS-TLIF group in our series. However, the difference is that our results showed less operative time and trauma. We believe that single-position surgery plays a crucial role in these outcomes and relates to current theories of accelerated rehabilitation. Of note, Blizzard et al. indicated that OLIF combined with BPS can also be performed in a single position and the accuracy and efficiency rate for screw placement are similar to previously published studies of pedicle screws placement in the prone position. Contrary to what Blizzard et al. reported, however, the “down-side” pedicle screws placement in the lateral decubitus position are quite inconvenient compared to “up-side” screws placement as shown in Fig. 1G in our previous practice. Farber et al. also agreed that posterior screws placement in the lateral decubitus position was challenging and time-consuming. Additionally, while raising the position of the operating table makes it easier to place the screws, it may increase the complexity that the difficulty of intraoperative fluoroscopy and the probability of infection from contamination of
the sterile operating table. Therefore, current method of LSUP fixation is designed to avoid placing pedicle screws in the “down-side.” Moreover, our study showed a lower rate of screw breaches compared to existing studies.31,32 The possible reason is that LSUP has an active role in the efficiency and accuracy of anterolateral screws placement due to direct visualization of surgeon. In addition, it is important to note that the advantages of LSUP in the lateral decubitus position over PTP advocated by Professor Pineta are that the surgeons are used to implant the cage vertically and special tools are not required to open the space between the costal arch and the iliac spine. These factors may indicate LSUP procedure learning curve is lower compared to PTP. Still, attention should also be given to 3 key points in performing LLIF-LUSP. First, the lateral vertebral screw should be penetrated to the opposite side of the vertebral body within 2 mm to achieve bicaltoral fixation; Second, try to use the maximum diameter lateral vertebral screw (7–8 mm) available to maximize reduce cage subsidence; Finally, the caudal pedicle screw should be tilted enough to the cephalic side to allow sufficient space for placement of the vertebral screw.

Another important result of this study was a more optimistic improvement in sagittal parameters in the LLIF group and MIS-TLIF still has significant advantages in CSA index. The difference has been reported in previous articles and is determined by the inherent specificities of the 2 procedures that a cage of the larger footprint provides adequate height and segment lordosis for LLIF indirect decompression, and that the dural sac is anatomically exposed in direct visualization for MIS-TLIF direct decompression.33-35 However, the recent study of Woodward et al.36 demonstrated that MIS-TLIF can obtain more significant improvement in sagittal parameters that lumbar lordosis improved from 47.8° to 58.5°, and FH improved from 17.6 mm to 21.9 mm which is comparable with LLIF by using an expandable cage. Instead, Yee et al.37 suggested that there were similar improvements in segmental lordosis and lumbar lordosis when using expandable cage and static cage respectively. The application of expandable cages in MIS-TLIF is controversial. We believe that the application of a expandable cage should be considered carefully on a case-by-case basis. The first challenge with the use of expandable cage in MIS-TLIF is that the standard of bone graft volume cannot be accurately controlled. Excessive bone graft may lead to the difficulty of cage implantation, while too little bone graft may lead to low fusion rate due to insufficient bone volume after cage expansion. The second is intraoperative endplate injury especially in patients with osteoporosis. Combined release of the anterior longitudinal ligament may reduce the risk of endplate injury and improve sagittal parameters, but it is unfriendly to operate with MIS techniques. Likewise, Stickley et al.38 questioned the value of an expandable cage, which is associated with higher costs, no significant improvement in radiological parameters, and an increased risk of intraoperative subsidence. Further randomized controlled studies are needed to determine the benefits of expandable cage.

Generally, BPSs are the first choice and “gold standard” for circumferential fusion of the lumbar spine fixation. BPS fixation has been proven to have several well-known advantages but one of that the dual compression of BPS fixation is essential to reduce the possibility of cage migration early period of postoperation for LLIF. In addition, a larger cage in LLIF filled with more bone graft material provides greater contact cross-sectional area. These special factors may be associated with a markedly high fusion rate within the 3 months after surgery compared to MIS-TLIF group. On the other hand, compared with the fusion rate reported in previous articles that a series of study on the effect of anterolateral single screw-rod fixation in for OLIF,39,40 a relatively but not significantly high fusion rate was obtained in our study. Although there are many biases in the comparison of different studies, it is worth mentioning the great Wolff’s law or Perrin’s theory in a hundred of years ago that bone formation occurs at locations of high mechanical stimulus.41 The animal experiment study demonstrated that significantly higher pressure promoted the bone formation compared to quiescent areas.42 Theoretically, multidimensional fixation related to 4 screws allows stronger pressure in the intervertebral space and pressure dispersion to avoid internal fixation failure due to excessive stress concentration compared with anterolateral single screw-rod fixation, but these data need to be determined by finite element analysis or biomechanical analysis in further study. Alternatively, bone marrow enrichment procedure had a catalytic effect on osteogenesis and Shen et al.43 demonstrated that this technique has a faster healing time than conventional bone grafts in children with infectious bone defects. Such characteristics may lead to a higher fusion rate in the early. Also, cross-cross fixation has a robust fixation stiffness especially the axial rotation process in the early postoperative period, and provides structural support to the endplate thereby reducing the rate of cage subsidence in osteoporotic populations. These merits may contribute to fewer complications associated with cage.

The present study showed clinical function was comparable between the 2 groups at each postoperative follow-up consistent with the study of Zhu et al.27 Nevertheless, we noted that OLIF combined with lateral fixation alone had better clinical
outcomes in postoperative follow-up.\(^{15}\) This can be explained by the fact that posterior screws placement interfere with the normal structure of the paravertebral muscle soft tissue.\(^{44}\) And again it was shown that reducing the number of posterior screws was beneficial for the postoperative lower back.\(^{45}\) Significantly, in a biomechanical study of LLIF with secondary augmentation (stand-along, unilateral pedicle screws, BPS, LP, interspinous plate, LP combined with interspinous plate), the range of motion of LP combined with posterior interspinous fixation is second only to and infinitely close to BPS fixation in flexion, extension, lateral bending, and axial rotation.\(^{46}\) Similarly, Fogel et al.\(^{47}\) demonstrated that a combination of lateral and interspinous plate fixation in LLIF could achieve rigidity in all motion planes similar to that achieved with BPS fixation. Moreover, the reliability of unilateral pedicle screws fixation is significantly higher than that of interspinous fixation.\(^{46}\) Therefore, we reasonably speculate LSUP may provide biomechanically noninferior fixation forces compared to BPS. But this should be interpreted with caution until further biomechanical evidence is available. Furthermore, the overwhelming superiority of LLIF-LSUP was obtained in the management of lumbar spondylolisthesis that the posterior pedicle pulled screws played a crucial role in the reduction of spondylolisthesis compared to lateral fixation alone. The procedure of cage insertion and slip reduction can be performed simultaneously and the degree of reduction was observed in direct visualization. The LSUP fixation, a cross-cross fixation from an axial perspective, can provide multidimensional orientation of fixation and moderate the likelihood of screws pullout during the subsequent rehabilitation process especially in osteoporotic populations. In our study, satisfactory reduction results (SP 2.3%) were achieved by this fixation in all patients with spondylolisthesis and LSUP can achieve comparable effects with BPS.

This study involves several limitations. First, all patients enrolled were not randomly assigned to either group in this retrospective study with a low level of evidence. Second, a relatively small sample size correlated to extremely low complication result in a bias against the reality that longer operating time is associated with more complications. Thirdly, the population in our series was predominantly lumbar spondylolisthesis, which may have resulted in selection bias. This problem needs to be addressed by more diversified diseases in the future. Moreover, the relatively short follow-up time may have confounded the results that some complications were not apparent such as adjacent segment disorder, iatrogenic scoliosis and contralateral foraminal stenosis. Finally, the different surgical procedures may confound the comparison results between LUSP and BPS to some extent.

**CONCLUSION**

The overall clinical outcomes and complications of LLIF-LSUP were comparable to that of MIS-TLIF-BPS in this series and most patients in 2 groups achieved satisfactory results with few complications. Compared with MIS-TLIF-BPS, LLIF-LSUP for lumbar degenerative disease represents a significantly shorter operating time, hospital stay and lower blood loss, and demonstrates better radiological outcomes to maintain lumbar lordosis and indirect decompression, and reveals an overwhelming superiority in the early fusion rate that may be beneficial for patients returning to society early. LLIF-LSUP is an alternative and rigid surgical option that is comparable to BPS fixation for LLIF in a single-lateral decubitus position.

**NOTES**

**Conflict of Interest:** The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: FL, JZX, ZRZ, ZHZ; Data curation: HL, YSY, JHZ, YG, HC, FL; Formal analysis: HL, YSY, ZHZ; Funding acquisition: ZRZ, ZHZ; Methodology: JZX; Project administration: FL, JZX, ZRZ, ZHZ; Visualization: JZX, ZRZ, ZHZ; Writing - original draft: HL; Writing - review & editing: JZX, ZRZ, ZHZ.

**ORCID**

Hui Lv: 000-0003-2452-9251
Yu Sheng Yang: 0000-0001-5114-7983
Jian Hong Zhou: 0000-0003-2835-4102
Yuan Guo: 0009-0004-0260-4956
Hui Chen: 0009-0002-4697-4129
Fei Luo: 0000-0002-6368-6674
Jian Zhong Xu: 0000-0003-0434-5148
Zhong Rong Zhang: 0009-0002-4791-5411
Ze Hua Zhang: 0000-0002-5960-0890
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rod can maintain the surgical outcomes following oblique lumbar interbody fusion for double-segment disc disease. Orthop Surg 2022;14:1126-34.


Commentary on “Simultaneous Single-Position Lateral Lumbar Interbody Fusion Surgery and Unilateral Percutaneous Pedicle Screw Fixation for Spondylolisthesis”

Zafer Orkun Toktas

Department of Neurosurgery, Uskudar University School of Medicine, Istanbul, Turkey

The recent study1 entitled “Simultaneous Single-Position Lateral Lumbar Interbody Fusion Surgery and Unilateral Percutaneous Pedicle Screw Fixation for Spondylolisthesis” is worth interest in many aspects. This study is the first to compare “lateral lumbar interbody fusion (LLIF)+unilateral minimally invasive (MIS) screws” versus “MIS-transforaminal lumbar interbody fusion (TLIF)” in a single institution experience. In addition, the presentation of surgical methodology is excellent. I appreciate the authors’ efforts and their recommendations.

Since their introduction, interbody fusion techniques gained popularity and are now regarded as the first choice for several indications such as spondylolisthesis, degenerative pathologies, trauma and infection. The technique evolving rapidly, recent studies feature robotic approaches.2 Reviews and meta-analyses prove that TLIF, posterior lumbar interbody fusion, anterior lumbar interbody fusion MI-TLIF, oblique lumbar interbody fusion/anterior to psoas, and LLIF are all effective with comparable outcomes.3,4 Yet, the diversity of techniques and nuances inhibits access to unbiased data and higher levels of evidence. Studies that focus on a single variable such as “adjacent segment disease” or “fusion rate” promise clearer insight on selection of interbody technique.5

As discussed well in the paper, the foremost benefits of LLIF are the utility of larger interbody cages compared to posterior approach and the ease of end plate preparation. This certainly contributes to the favorable fusion rates and better disc height. In comparison, MIS-TLIF procedure yields limited vision of the endplate and curettage is more challenging. For LLIF, the authors encourage addition of unilateral posterior pedicle screws to prevent cage migration and improve biomechanics. This provides a 3-quarter stabilization if not a full 360°. Thanks to these factors, a 92% of fusion at 12 months is achieved. The untouched contralateral facet can be a weak spot in the case of spondylolisthesis (an interest for biomechanical testing). One typical downside for lateral approach is the shortage of autograft harvest. The authors suggested allografts enriched with bone marrow to achieve better fusion.

Considering the very low rate of complications and the short operative duration, we can estimate the surgeon(s) is highly experienced in LLIF-lateral single screw-rod and unilateral-
al percutaneous pedicle screw fixation (LSUP) approach. To prevent positive bias, specific complications have to be reminded. These include sympathectomy, vascular damage, ureteral injury. The local anatomy has to be carefully examined before surgery. On the other hand, obvious advantages of lateral approach include protection of posterior lumbar muscles and facet joints, spared dural sac and nerve roots, direct visualization of disc space. These factors favor selection of the LLIF approach.

We do not have the chance to compare the results of the study, due to the lack of similar reports. One study has strong resemblance though. Koike et al. compared oblique lateral interbody fusion with percutaneous posterior fixation in lateral position (OLIF-LPF) and MIS-TLIF for single-level degenerative spondylolisthesis. In a total of 92 cases, OLIF-LPF group proved superior to MIS-TLIF with lesser surgical duration and better disc height at follow-up.

In conclusion, this article provides valuable insight despite its limitations. The promising LLIF-LSUP technique needs further evaluation with larger cohorts and prospective trials. Long-term outcomes, effect on adjacent segment disease and the indication criteria must be validated.

**Conflict of Interest:** The author has nothing to disclose.

### REFERENCES

Original Article

Corresponding Author
Justin K. Scheer
https://orcid.org/0000-0003-2536-601X

Department of Neurological Surgery, University of California, San Francisco, 505 Parnassus Ave, Room M779, San Francisco, CA 94143, USA
Email: justin.scheer@ucsf.edu

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See the commentary on "Outcomes of Surgical Treatment for Patients With Mild Scoliosis and Age-Appropriate Sagittal Alignment With Minimum 2-Year Follow-up" via https://doi.org/10.14245/ns.2346926.463.

Objective: The goal of this study was to determine if patients with mild scoliosis and age-appropriate sagittal alignment have favorable outcomes following surgical correction.

Methods: Retrospective review of a prospective, multicenter adult spinal deformity database. Inclusion criteria: operative patients age ≥18 years, and preoperative pelvic tilt, mismatch between pelvic incidence and lumbar lordosis (PI–LL), and C7 sagittal vertical axis all within established age-adjusted thresholds with minimum 2-year follow-up. Health-related quality of life (HRQoL) scores: Oswestry Disability Index (ODI), 36-item Short Form health survey (SF-36), Scoliosis Research Society-22R (SRS22R), back/leg pain Numerical Rating Scale and minimum clinically important difference (MCID)/substantial clinical benefit (SCB). Two-year and preoperative HRQOL radiographic data were compared. Patients with mild scoliosis (Mild Scoli, Max coronal Cobb 10°–30°) were compared to those with larger curves (Scoli).

Results: One hundred fifty-one patients included from 667 operative patients (82.8% women; average age, 56.4 ± 16.2 years). Forty-two patients (27.8%) included in Mild Scoli group. Mild Scoli group had significantly worse baseline leg pain, ODI, and physical composite scores (p < 0.02). Mean 2-year maximum coronal Cobb angle was significantly improved compared to baseline (p < 0.001). All 2-year HRQoL measures were significantly improved compared to (p < 0.001) except mental composite score, SRS activity and SRS mental for the Mild Scoli group (p > 0.05). From the mild Scoli group, 36%–74% met either MCID or SCB for the HRQoL measures. Sixty-four point three percent had minimum 1 complication, 28.6% had a major complication, 35.7% had reoperation.

Conclusion: Mild scoliosis patients with age-appropriate sagittal alignment benefit from surgical correction, decompression, and stabilization at 2 years postoperative despite having a high complication rate.

Keywords: Adult spinal deformity, Complications, Mild scoliosis, Outcomes, Sagittal alignment
INTRODUCTION

Typically adult spinal deformity (ASD) patients present with reduced quality of life, disability, and pain. It has been well established that surgical management of these patients can provide significant improvements in their presenting symptoms as well as an increase in their spine-specific and overall health-related quality of life (HRQoL). However, these surgeries are technically challenging and are associated with a high complication rate ranging from 14%–71%. As a result, there have been many studies attempting to identify ASD patients that will benefit from surgery, including evaluating the major factors associated with the relationship between HRQoL and alignment in these patients.

The primary driver of poor HRQoL and disability in patients with ASD has been shown to be sagittal spine-pelvic malalignment, specifically global sagittal vertical axis (SVA), pelvic tilt (PT) and the mismatch between pelvic incidence and lumbar lordosis (PI–LL). These findings have been corroborated by many studies over the past 10 to 15 years beginning with the landmark studies by Glassman et al. that demonstrated the relationship between SVA and HRQoL. More recently, it has been determined that the sagittal malalignment thresholds for which a patient experiences disability varies by age. As patients age, they are able to tolerate a larger sagittal malalignment before reaching significant disability and thus correction to the prior sagittal alignment thresholds may result in unnecessary overcorrection. The association between sagittal alignment and HRQoL has been very well validated over the years and the management of such patients remains to be delineated.

To our knowledge, a study has yet to be conducted for these patients that demonstrated the results in HRQoL improvement. A study by Daubs et al. investigated preoperative coronal imbalance and HRQoL showing that correction of the coronal curve alone was not a factor for predicting improved functional outcomes and that sagittal malalignment was the strongest predictor. Furthermore, Buell et al. studied ASD patients with severe coronal curves of greater than 75° and found that patients had significant improvement in HRQoL. However these patients also had correction in the sagittal plane making it more difficult to isolate the effect of the coronal curve correction on HRQoL.

Based on our clinical experience, there exists a small population of ASD patients with minor coronal curves who are within their respective age-appropriate sagittal alignment parameters. Yet these patients still present with poor HRQoL, which may be from compression of neural elements and mechanical instability from degenerative changes given the small curves. It is unclear how these patients may do following surgical correction and the management of such patients remains to be delineated.

MATERIALS AND METHODS

1. Patient Population

This study is a retrospective review of a prospective multicenter ASD database, which is contributed to by 13 sites across the United States. All patients were consecutively enrolled into a protocol for which each site obtained Institutional Review Board approval. Patient data was then prospectively collected and entered into the database. Inclusion criteria for the database were: age ≥ 18 years and presence of spinal deformity, as defined by one or more of the following: scoliosis Cobb angle ≥ 20°, SVA ≥ 5 cm, PT ≥ 25°, and/or thoracic kyphosis (TK) ≥ 60°. Exclusion criteria included spinal deformity of a neuromuscular etiology and presence of active infection or malignancy.

In addition to the above database inclusion criteria, study patients were included if they had preoperative age-appropriate measurements for SVA, PT, and PI–LL. The method for determining patients age-appropriate sagittal alignment thresholds has been described in the literature, however, in brief, specific equations were developed in a prior study by Lafage et al. to predict a patient’s sagittal alignment threshold based on their age-adjusted Oswestry Disability Index (ODI) scores from population norms. Using those equations, the authors then calculated an age-adjusted sagittal alignment threshold for severe disability as defined by an ODI score of 40. Using those predetermined age-adjusted alignment thresholds for SVA, PT, and PI–LL, each patient in the present study was compared to those predetermined thresholds and if all 3 alignment parameters were below the established age-adjusted thresholds in the prior study, those patients were included in the present study. And of those, patients with mild scoliosis as defined by a maximum coronal Cobb angle of 10°–30° were also selected (Mild Scoli) and compared to the other scoliosis patients with larger curves.
The mild scoliosis definition was a consensus among multiple fellowship trained ASD surgeons and this range has also been used in the pediatric population.\textsuperscript{30–33}

2. Data Collection: Demographics, Radiographic Assessment, HRQoL, and Surgical data

The demographic and clinical data collected included patient age, sex, body mass index (BMI), number and type of comorbidities, and Charlson Comorbidity Index.\textsuperscript{34} Surgical data collected included: whether the index surgery was a primary or revision procedure, whether the surgery was an anterior or posterior fusion (and number of levels for each), the presence of a 3-column osteotomy (vertebral column resection or pedicle subtraction osteotomy), the uppermost instrumented vertebra (UIV), the lowermost instrumented vertebra, the number of posterior levels fused, and the ASD surgical invasiveness score.\textsuperscript{35} The presence of and the number of levels were also collected for the following: direct decompression, Smith-Petersen osteotomies (SPO), and interbody fusion (IBF). The surgical indications and decision to pursue surgery was left up to the discretion of the individual surgeon and their discussion with the patient.

Full-length free-standing lateral spine radiographs (36” cassette) at baseline were analyzed using validated software\textsuperscript{36} (Spineview, ENSAM, Laboratory of Biomechanics, Paris, France). All radiographic measures were performed at a central location based on standard techniques\textsuperscript{36} and included: coronal Cobb angles of thoracic and lumbar curves, maximum coronal Cobb angle, coronal plumbline (C7–S1), TK (T4–12; Cobb angle between superior endplate of T4 and inferior endplate of T12), LL (Cobb angle between superior endplate of L1 and superior endplate of S1), SVA (C7 plumbline relative to S1), PT, and PI–LL. The SRS-Schwab coronal curve type and sagittal modifiers were determined for all patients.\textsuperscript{37} And lastly, all patients were categorized based on previously published age-adjusted thresholds for PT, PI–LL, and SVA.\textsuperscript{19,24,28,29} Patients were required to have all 3 sagittal parameters within their respective age-adjusted thresholds to be included in the study.

Standardized HRQoL measures included the ODI, 36-item Short Form health survey (SF-36), and Scoliosis Research Society-22R (SRS-22R). Two standard summary scores were calculated based on the SF-36, the physical composite score (PCS) and the mental composite score (MCS). Furthermore, each patient was classified according to the ASD frailty index.\textsuperscript{36,39} The SRS-22R provides a total score and multiple subdomains, including activity, pain, appearance, mental, and satisfaction. A Numerical Rating Scale (NRS) score ranging from 0 (no pain) to 10 (most unbearable pain) was collected for back and leg pain separately. In order to place HRQoL outcomes in a clinically relevant context, minimal clinically import difference (MCID) values have been established for the HRQoL instruments.\textsuperscript{37,40} The proportions of patients reaching MCID for each HRQoL measure were also considered. Substantial clinical benefit (SCB) values for ODI, PCS and back and leg pain NRS have also been established.\textsuperscript{40} The MCID/SCB values used in the present study included: ODI (-16/-18.8), PCS (+5.2/+6.2), back and leg pain NRS (-2/-3).\textsuperscript{37,40–42}

3. Statistics

Continuous variables were described with the mean and standard deviation (SD). Baseline and 2-year variables were compared. Normality of data was determined using the Shapiro-Wilk test. Comparison of baseline means between the groups initially included an analysis of variance or Kruskal-Wallis test when appropriate, which was followed by pairwise comparisons using Tukey honest significant difference test to control for type I error or Wilcoxon rank-sum tests where appropriate. Frequency analyses for categorical variables were conducted via Pearson $\chi^2$ analysis. All statistical analyses were conducted using commercially available software (IBM SPSS Statistics ver. 22.0, IBM Co., Armonk, NY, USA) and the level of significance was set at $p < 0.05$ for all tests.

RESULTS

A total of 667 operative patients were eligible for inclusion and of those, 151 patients (22.6%) met these additional inclusion criteria (82.8% female; mean age, 56.4 ± 16.2 years). The mean BMI was 25.3 ± 4.9 kg/m$^2$. Of the 151 patients included, 42 of those (27.8%) met the additional inclusion criteria of having a maximum coronal Cobb angle of 10°–30° (Mild Scoli). Of the 42 Mild Scoli patients, 3 (7.1%) had their maximum coronal curve in thoracic spine, 13 (31.0%) in the thoracolumbar region and 26 (61.9%) in the lumbar spine. Only 27 study patients (17.9%) had a prior fusion. The rates of medical comorbidities for the Mild Scoli group ranged from 0%–52.4% (Table 1). The Mild Scoli group had a significantly higher preop frailty score, a higher distribution of number of comorbidities, higher rate of arthritis, and diabetes ($p < 0.05$ for all, Table 1). Most of the Mild Scoli patients underwent a posterior-only fusion (76.2%) with mean number of levels fused being 10.9 ± 4.2. Only 4.8% had a 3-column osteotomy and a over half (61.9%) underwent

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Table 1. Complete list of patient comorbidities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scoli</th>
<th>Mild Scoli</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline frailty index</td>
<td>2.6 ± 1.6</td>
<td>3.2 ± 1.6</td>
<td>0.04*</td>
</tr>
<tr>
<td>≥ 1 comorbidity</td>
<td>66 (60.6)</td>
<td>34 (81)</td>
<td>0.80</td>
</tr>
<tr>
<td># of comorbidities</td>
<td></td>
<td></td>
<td>0.002*</td>
</tr>
<tr>
<td>0</td>
<td>43 (39.4)</td>
<td>8 (19)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22 (20.2)</td>
<td>8 (19)</td>
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<tr>
<td>2</td>
<td>23 (21.1)</td>
<td>7 (16.7)</td>
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<tr>
<td>3</td>
<td>10 (9.2)</td>
<td>10 (23.8)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6 (5.5)</td>
<td>4 (9.5)</td>
<td></td>
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<tr>
<td>5</td>
<td>4 (3.7)</td>
<td>2 (4.8)</td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>1 (0.9)</td>
<td>3 (7.1)</td>
<td></td>
</tr>
</tbody>
</table>

Types

- Arthritis: 30 (27.5) vs. 22 (52.4) (p < 0.004)
- DVT: 2 (1.8) vs. 3 (7.1) (p = 0.10)
- Cancer: 8 (7.3) vs. 7 (16.7) (p = 0.09)
- Depression: 21 (19.3) vs. 13 (31) (p = 0.12)
- Diabetes: 0 (0) vs. 4 (9.5) (p = 0.001)
- Heart disease: 6 (5.5) vs. 8 (19) (p = 0.01)
- Hypertension: 22 (20.2) vs. 12 (28.6) (p = 0.27)
- Kidney disease: 3 (2.8) vs. 0 (0) (p = 0.28)
- Liver disease: 1 (0.9) vs. 1 (2.4) (p = 0.48)
- Pulmonary disease: 2 (1.8) vs. 2 (4.8) (p = 0.32)
- Neurological disease: 4 (3.7) vs. 2 (4.8) (p = 0.76)
- Osteoporosis: 19 (17.4) vs. 8 (19) (p = 0.82)
- Peripheral vascular disease: 2 (1.8) vs. 2 (4.8) (p = 0.32)
- Psychiatric disease: 4 (3.7) vs. 1 (2.4) (p = 0.69)
- Gastric ulcer: 13 (11.9) vs. 4 (9.5) (p = 0.68)

Values are presented as mean ± standard deviation or number (%).

* p < 0.05, statistically significant differences.

The 2-year postoperative mean maximum coronal Cobb angle was significantly lower surgical invasiveness score and mean number of posterior levels fused (p < 0.05 for both) (Table 2). The Mild Scoli group had a significantly higher percentage of patients with UIV in the thoracic and lumbar spine (p < 0.05). And lastly, the Mild Scoli group had a significantly higher rate of patients that received a direct decompression and higher mean number of levels decompressed with a significantly lower mean number of levels with an SPOs (p < 0.05 for all) (Table 2).

The 2-year postoperative mean maximum coronal Cobb angles were significantly reduced in the Mild Scoli group compared with baseline with a mean decrease of 8.8° ± 6.6° (p < 0.001) (Table 3). The Scoli group had a similar significant reduction in max coronal Cobb angle of 29.9° ± 14.4° (p < 0.001). However, the coronal C7 plumb line change was not significantly different for both groups (p > 0.05 for both). There were no significant changes in the sagittal alignment measures for SVA, PT, and PI–LL for both groups. However, the TK significantly increased at 2 years postoperative for the Scoli group by a mean of 4.8° ± 16.3° (p = 0.006) (Table 3). Of the 101 patients that had an increase in TK, 17 developed proximal junctional kyphosis (PJK) within the 2-year postoperative period for an overall rate of 11.3%.

All 2-year HRQoL measures were significantly improved compared to baseline for the Scoli group (p < 0.001) (Table 4). For the Mild Scoli group, all HRQoL measures were significantly improved at 2 years postoperative (p < 0.002) with the exception of MCS, SRS activity, and SRS mental (p > 0.05 for all 3). Compared with the Scoli group, the Mild Scoli group had a significantly worse baseline leg pain (5.2 ± 3.3 vs. 3.5 ± 3.3, p = 0.008), ODI (44.3 ± 14.7 vs. 36.6 ± 18.3, p = 0.012), and PCS (31 ± 8.5 vs. 36.2 ± 10.9, p = 0.011) scores. For the Mild Scoli group, many patients either met MCID or SCB at 2-year follow-up (36%–74%, Fig. 1). The greatest percentage of Mild Scoli patients that met MCID was for SRS pain, and back pain NRS with both rates being 74% (Fig. 1). All MCID and SCB rates were not statistically different between the Scoli and Mild Scoli groups with the exception of SRS Appearance MCID; the Mild Scoli group had a significantly lower rate of patients meeting MCID (Fig. 1).

There was a high complication rate within both groups. For the Mild Scoli patients, 64.3% had at least 1 complication with 28.6% having at least one major complication and 35.7% requiring a reoperation (Table 5). The indications for reoperation were the following (note: does not add up to total of 15 patients as some patients had multiple complications): Gastrointestinal: 1, Arthritis: 1, DVT: 1, Cerebral injury: 1, wound incisional hernia: 1, and PJK: 3. The most common type of complication was implant related at 28.6% with the second and third most common being neurologic (23.8%) and radiographic (21.4%, Table 5). Of the implant complications, the subcategories were the following: Loose implant: 4, painful/prominent implants: 2, rod fracture: 1, loose screw/medial breach: 3, wound infection: 1, epidural hematoma: 1, motor deficit/spinal cord injury: 2, cerebrospinal fluid leak: 1, visceral injury: 1, wound incisional hernia: 1, and PJK: 3. The most common type of complication was implant related at 28.6% with the second and third most common being neurologic (23.8%) and radiographic (21.4%, Table 5). Of the implant complications, the subcategories were the following: Loose implant: 4, painful/prominent implant: 2, rod/screw fracture: 3, and medial screw breach: 3. Of the neurologic complications, the subcategories were the following (note: does not add up to total of 15 patients as some patients had multiple complications): Epidural hematoma: 1, mental status changes: 2, motor deficit: 3, radiculopathy: 3, spinal cord injury: 1, sensory deficit: 1, and stroke: 1. Of
the radiographic complications, the subcategories were the following: postop sagittal malalignment: 1, and PJK: 8. There were no statistically significant differences in complication rates between Scoli and Mild Scoli groups (p > 0.05 for all) (Table 5).

Case example: The patient is a 75-year-old woman with mild scoliosis (Fig. 2) and baseline HRQoL scores of the following: back pain NRS: 8, leg pain NRS: 9, ODI: 56, PCS: 17.4, SRS activity: 1.75, pain: 1.2, appearance: 3.4, mental: 4, and satisfaction: 3.5. She underwent a T11-pelvis posterior instrumented fusion with significant correction of her lumbar scoliosis (Fig. 3). She had 1 major operative complication requiring a reoperation. Despite this, at 2 years postoperative she met MCID and SCB for all HRQoL measures except the SRS mental score.

**DISCUSSION**

It is now common knowledge amongst spine surgeons and evidenced throughout the literature that sagittal spinopelvic alignment is associated with patient reported HRQoL scores and that surgical correction of sagittal malalignment results in significantly improved function and quality of life. However, there exists a small population of ASD patients with mild scoliosis and sagittal alignment parameters within the age-appropriate thresholds who still present with significant disability and poor HRQoL. This is the first study of its kind investigating the 2-year surgical outcomes of such patients and demonstrated that symptomatic patients with only coronal deformities do well both radiographically and by HRQoL measures. More specifically, patients with mild scoliosis as defined by a maximum cor-
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onal curve of 10°–30° and with age-appropriate sagittal spinopelvic parameters have significant improvements in 2-year radiographic and HRQoL outcomes. The Mild Scoli patients are more frailer with a higher number of comorbidities and higher rates of arthritis and diabetes. The Mild Scoli patients had worse baseline leg pain, ODI, and PCS scores and underwent a less invasive surgery (less mean number of posterior fusion levels and SPOs) with a higher rate of direct decompressions. The mean Max coronal Cobb angle of the Mild Scoli patients was improved postoperatively and many patients met MCID or SCB despite having a relatively high overall complication rate of 64.3% and 28.6% for a major complication that was not different that the Scoli group.

The concept of age-appropriate sagittal alignment is a rela-

Table 3. Mean ± standard deviation for the preoperative, 2 years, and 2-year differences compared with preoperative values radiographic parameters for both the Scoli cohort and the Mild Scoli group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Max coronal Cobb (°)</th>
<th>Coronal C7 plumb (mm)</th>
<th>PT (°)</th>
<th>PI–LL (°)</th>
<th>TK (°)</th>
<th>SVA (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoli Preoperation</td>
<td>51.1 ± 19</td>
<td>24 ± 17.8</td>
<td>12.5 ± 6.3</td>
<td>-8.2 ± 11.4</td>
<td>40.1 ± 17.3</td>
<td>-3.3 ± 34.1</td>
</tr>
<tr>
<td>2 Years</td>
<td>21.7 ± 14.3</td>
<td>21.6 ± 18.3</td>
<td>14.1 ± 8.4</td>
<td>-7.8 ± 11.9</td>
<td>44.9 ± 15.4</td>
<td>-2.1 ± 41.6</td>
</tr>
<tr>
<td>2-Year changes</td>
<td>-29.9 ± 14.4</td>
<td>-2.5 ± 20.6</td>
<td>1.6 ± 6.1</td>
<td>0.4 ± 12.6</td>
<td>4.8 ± 16.3</td>
<td>1.2 ± 43.3</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001*</td>
<td>0.13</td>
<td>0.18</td>
<td>0.79</td>
<td>0.006*</td>
<td>0.88</td>
</tr>
<tr>
<td>Mild Scoli Preoperation</td>
<td>23.4 ± 4.8</td>
<td>29.2 ± 27.7</td>
<td>14.8 ± 7.7</td>
<td>-4.7 ± 13.1</td>
<td>45.6 ± 20.3</td>
<td>15.3 ± 33.4</td>
</tr>
<tr>
<td>2 Years</td>
<td>14.7 ± 6.9</td>
<td>23.6 ± 19.4</td>
<td>16.4 ± 9</td>
<td>-4.2 ± 12.7</td>
<td>50.4 ± 16.3</td>
<td>27.5 ± 43.1</td>
</tr>
<tr>
<td>2-Year changes</td>
<td>-8.8 ± 6.6</td>
<td>-5.1 ± 29.5</td>
<td>1.6 ± 4.9</td>
<td>0.5 ± 10.5</td>
<td>4.7 ± 17.4</td>
<td>12.2 ± 35.1</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001*</td>
<td>0.40</td>
<td>0.28</td>
<td>0.63</td>
<td>0.13</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
Scoli, patients with larger curves (greater than 30°); Mild Scoli, patients with mild scoliosis (10°–30°); PT, pelvic tilt; PI–LL, mismatch between pelvic incidence (PI) and lumbar lordosis (LL); TK, thoracic kyphosis; SVA, sagittal vertical axis.
*p < 0.05, statistically significant difference between the preoperative and 2-year postoperative values.

Fig. 1. The percentage of patients that reached minimal clinically important difference (MCID) and significant clinical benefit (SCB) from baseline to 2 years postoperative for the Scoli and Mild Scoli groups. Scoli, patients with larger curves (greater than 30°); Mild Scoli, patients with mild scoliosis (10°–30°); ODI, Oswestry Disability Index; PCS, physical composite score of the medical Short Form 36 (SF-36); MCS, mental composite score of the SF-36; SRS, Scoliosis Research Society-22 questionnaire; NRS, Numerical Rating Scale. *p < 0.05, statistically significant differences.
tively new idea in ASD and refers to the notion that as one ages, there tends to be a tolerance for a larger sagittal malalignment for a given level of disability. The study by Lafage et al. investigated this concept and defined new radiographic thresholds for surgical correction of sagittal malalignment based on age. They evaluated 773 ASD patients and their baseline HRQoL. Then, based on published PCS norms for a given age group, they created a regression analysis for PCS and ODI using severe disability as defined by an ODI of 40 to calculate the new age-adjusted thresholds for sagittal alignment. This is the same technique

<table>
<thead>
<tr>
<th>Variable</th>
<th>Scoli</th>
<th>Mild Scoli</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Total number of patients</td>
<td>109</td>
<td>42</td>
<td></td>
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<tr>
<td>Total number of complications</td>
<td>104</td>
<td>51</td>
<td>0.35</td>
</tr>
<tr>
<td>No. of patients with minimum 1 complication</td>
<td>61 (56.0)</td>
<td>27 (64.3)</td>
<td></td>
</tr>
<tr>
<td>No. of patients with intraoperative complications</td>
<td>18 (16.5)</td>
<td>8 (19.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>No. of patients with perioperative complications</td>
<td>17 (15.6)</td>
<td>7 (16.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>No. of patients with postoperative complications</td>
<td>43 (39.4)</td>
<td>21 (50.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>No. of patients with revisions</td>
<td>20 (18.3)</td>
<td>12 (28.6)</td>
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<td>No. of patients with reoperations</td>
<td>24 (22.0)</td>
<td>15 (35.7)</td>
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<td>37 (33.9)</td>
<td>14 (33.3)</td>
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<td>Major</td>
<td>19 (17.4)</td>
<td>12 (28.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>No. of complications</td>
<td>0.68</td>
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<table>
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<th>Types</th>
<th>Scoli</th>
<th>Mild Scoli</th>
<th>p-value</th>
</tr>
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<tr>
<td>Cardiopulmonary</td>
<td>11 (10.1)</td>
<td>3 (7.1)</td>
<td>0.58</td>
</tr>
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<td>Gastrointestinal</td>
<td>6 (5.5)</td>
<td>4 (9.5)</td>
<td>0.37</td>
</tr>
<tr>
<td>Implant</td>
<td>17 (15.6)</td>
<td>12 (28.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Infection</td>
<td>4 (3.7)</td>
<td>2 (4.8)</td>
<td>0.76</td>
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<td>Musculoskeletal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Neurologic</td>
<td>14 (12.8)</td>
<td>10 (23.8)</td>
<td>0.10</td>
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<td>Operative</td>
<td>17 (15.6)</td>
<td>7 (16.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.9)</td>
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<td>Renal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Wound</td>
<td>2 (1.8)</td>
<td>1 (2.4)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Values are presented as number (%). 
Scoli, patients with larger curves (greater than 30°); Mild Scoli, patients with mild scoliosis (10°–30°).
Surgical Treatment for Patients With Mild Scoliosis

Scheer JK, et al.

employed in the original study by Schwab et al. that defined the prior sagittal alignment thresholds for SVA, PT, and PI–LL. The concept of age-appropriate sagittal alignment has been expanded upon over the last few years. Specifically, there appears to be no benefit to overcorrecting patients based on their age-appropriate thresholds and furthermore, correction to age-appropriate alignment may reduce the incidence of PJK. Therefore, when attempting to isolate the effect of surgical correction for mild coronal curves, one must do this with respect to age-appropriate sagittal alignment.

In the context of age-appropriate sagittal alignment mentioned above, the results of this study were surprising and provide insight into this specific population that can aid in clinical decision making. The entire cohort presented with worse than expected baseline HRQoL metrics given the deformity was in the coronal plane and not the sagittal plane given we know that sagittal malalignment tends to be the primary diver of HRQoL.

The baseline mean ODI was 38.7 with a low PCS of 34.8 for the entire cohort and even worse for the Mild Scoli cohort with 44.3 and 31.0, respectively. Given that these patients had sagittal alignment that was within what would be predicted based on their age category, one might expect that their baseline pain and disability would be lower than that of ASD patients with sagittal malalignment. It is worth mentioning that these patients have worse baseline HRQoL than some of the major chronic disease states in the United States (US). A study by Bess et al. compared HRQoL of patients with ASD to US population norms and other chronic diseases. The authors found that the norm-based PCS value for the ASD population between ages 55–64 years was 38.7 and the US population norm was 47.4, both are better than the current study population with mild scoliosis. In addition, the mean PCS for the US population were the following for various chronic diseases: back pain 45.7, depression 45.4, diabetes 41.1, cancer 40.9, heart disease 38.9, and the lowest being lung disease at 38.3. Our current population of patients with mild scoliosis has a much lower mean PCS of 31.0 than all of those in comparison.
With regard to the radiographic correction in the present study, there was a significant reduction in the maximum coronal curve at 2 years postoperatively but not the C7 plumb line. The lack of significant change in the C7 plumb line is likely a result of the baseline offsets being relatively small (mean, 2.5 cm) with a high variation (SD, 2.1 cm). And thus, this was the same for the 2-year postoperative value resulting in a failure to reach statistical significance despite the mean reduction being 3 cm. There was a significant amount coronal deformity correction (mean decrease of 23.6° overall and only 8.8° in the Mild Scoli group) as the sagittal spinopelvic parameters remained the same at 2 years postoperative. Moreover, the mean 2-year PT and SVA even increased a small amount, yet was not statistically different. However, the Mild Scoli patients had a significantly higher mean leg pain and ODI scores as well as worse PCS mean scores than the Scoli patients. This is likely the reason for the surgical indication in these patients. This is in contrast to the study by Daubs et al. that investigated preoperative coronal imbalance and HRQoL. The authors demonstrated that correction of the coronal curve alone was not a factor for predicting improved functional outcomes and that sagittal malalignment was the strongest predictor. That population did have sagittal malalignment in addition to the coronal curves and was likely the driver of the improved outcomes. In the present study, we identified patients with only a coronal deformity that were within their age-appropriate sagittal alignment thresholds. The HRQoL improvement is also likely related to some patients receiving a direct decompression along with the deformity correction. This study has identified a small subset of ASD patients that have significant improvement in HRQoL with coronal correction and stabilization alone, even for mild scoliosis.

Given that historically coronal deformity correction has not shown as large of an improvement in HRQoL compared with sagittal deformity correction, the results of the present study were encouraging in that there was such a large improvement. There have been a number of studies looking at HRQoL improvement following surgical correction of ASD including MCID. Prior studies show that within a large cohort of ASD patients, the MCID improvements are ODI 49%, PCS 45%, SRS activity 63%, SRS pain 64%, SRS Appearance 74%, and SRS mental 43%. Another study focusing on back and leg pain showed 2-year MCID rates of back and leg pain were 71% and 46%, respectively and for SCB they were 62% and 39%, respectively. The mild scoliosis cohort had higher rates for all of those except SRS appearance and SRS mental scores, however they did have a significant improvement in mean SRS appearance. It was unexpected to have such high rates of MCID and SCB, however having lower SRS appearance and mental MCID rates and having the Mild Scoli group not meeting statistically significant improvement in SRS mental and MCS may be explained by their baseline status. The Mild Scoli cohort had small curves and had relatively higher MCS and SRS mental values. It is likely that the small curve did not play a role in their mental status and their poor HRQoL was more driven by pain and disability.

And lastly, the complication rate for the current study is higher compared with the means presented in the literature for ASD despite correcting smaller curves and having few 3-column osteotomies than the Scoli group. The rates reported in the literature from a large systematic review found that the mean overall complication rate was 55% with a major complication rate of 18.5%. The present study found a higher overall complication rate of 64.3% and a higher major complication rate of 28.6%. This could be explained by the fact that no matter the extent of surgical invasiveness, ASD comes with certain inherent and unavoidable risks. Surgically manipulating the spinal column remains technically challenging. Even though these were only coronal curves being corrected with few large 3-column osteotomies, the mean posterior levels fused was still high at 10.9 and 62.3% had at least one osteotomy with a mean EBL of 1.3 liters. These surgeries may not be as invasive as correcting large combined sagittal and coronal deformities, but they are still large surgeries that carry a high rate of complications. Despite this, the overall cohort and the Mild Scoli cohort had large improvements in HRQoL as mentioned above. The inherent risk in these technically demanding surgeries should not be a barrier to surgery but rather a discussion point between surgeon and patients as to the best surgical plan for their goals of care.

The study strengths include the large multicenter design and a large number of ASD patients with age-appropriate sagittal alignment, 151 total. The multicenter design from 13 high-volume ASD centers across the US allows for better generalizability of the results. In addition, a strength of the present study is the complete 2-year follow-up of the patients. However, there are limitations to this study, one of which includes the retrospective design which may have introduced selection or information biases. Additionally, the definition of mild scoliosis was defined as 10°–30°. This definition is arbitrary however there is no standard definition of “mild” and this was decided upon discussion with multiple fellowship trained ASD surgeons. The pediatric literature has also discussed “mild” scoliosis with varying ranges that include less than 20°–30°. The definition of “mild scoliosis” may differ in the adult population and vary across

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CONCLUSION

There exists a small population of ASD patients with coronal malalignment and age-appropriate sagittal spinopelvic parameters. They present with high baseline pain and disability, including patients with mild scoliosis of 10°–30° curves. The patients with mild curves have worse leg pain, ODI and PCS scores and likely the driver behind surgery. These patients benefit from surgical correction, decompression and stabilization at 2 years postoperative both radiographically and with significantly improved HRQoL and reduced disability. Of the mild scoliosis patients, 74% of them met MCID for SRS pain and back pain NRS despite having a high complication rate of 64.3%. This is the first study of its kind investigating the outcomes of this particular ASD population and provide the basis for future studies as well as important results for discussions between surgeons and patients to better inform decision making for preoperative planning.

NOTES

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ORCID

Justin K. Scheer: 0000-0003-2536-601X
Han Jo Kim: 0000-0002-7482-6994
Munish Gupta: 0000-0002-4711-4377
Christopher P. Ames: 0000-0003-2618-3098

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27. Savage JW. The optimal treatment for symptomatic neurogenic claudication or radiculopathy in the presence of mild degenerative scoliosis remains unclear. Spine J 2017;17:44-5.


Impacts of Adult Spinal Deformity Surgery on Coronal Malalignment: Commentary on “Outcomes of Surgical Treatment for Patients With Mild Scoliosis and Age-Appropriate Sagittal Alignment With Minimum 2-Year Follow-up”

Takashi Yurube
Department of Orthopedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

Adult spinal deformity (ASD), affecting the thoracic, thoracolumbar, or lumbar spine in the coronal and sagittal planes after skeletal maturity,\(^1\) has increased interest in the morbidity and burden with the population of rapid aging.\(^2\) The prevalence of ASD with the Cobb angle > 10° is notably high in elderly individuals of age ≥ 60 years, accounting for up to 68%.\(^3\) Then, ASD has a complex spectrum of disorders, principally consisting of adult idiopathic scoliosis, de novo degenerative scoliosis, and iatrogenic flatback.\(^1\) Age-related factors to accelerate ASD further include osteoporosis, vertebral fracture, spondylosis, spondylolisthesis, mobility restriction, body imbalance, and neurodegenerative disorders.\(^1\) Patients with ASD often complain of back pain, neurological disturbance, deformity, and disability, resulting in a negative influence on the health-related quality of life (HRQoL).\(^4\) Compared to nonoperative care, operative intervention provides significant improvements in the disability, pain, and HRQoL of ASD patients.\(^5\) However, favorable impacts of ASD surgery on HRQoL largely come from the restoration of sagittal spinopelvic alignment, while the magnitude of coronal malalignment and extent of coronal correction are less critical parameters.\(^6,7\) Integrated with consistent findings of following studies,\(^8\) the association between HRQoL and sagittal alignment has been well validated. More recently, the importance of age-adjusted sagittal alignment has been emphasized.\(^11,14\) Meanwhile, in a retrospective study of prospectively collected data, the correction of sagittal alignment was the most significant predictive factor for the improved HRQoL in patients with combined coronal and sagittal malalignment, although the correction of coronal alignment trended toward but did not reach the significance in those with coronal malalignment alone, due to the limited sample size.\(^15\) Therefore, effectiveness of coronal plane correction in the HRQoL improvement is still undetermined.

A retrospective case-control study from a prospective multicenter database of ASD, by Scheer et al.,\(^16\) investigated postoperative 2-year radiographic, HRQoL, and complication
outcomes of a unique cohort with scoliosis but also with age-appropriate sagittal alignment. These patients without sagittal malalignment were divided and compared based on the degree of the maximum coronal Cobb angle of 10°–30° and > 30°. Patients with 10°–30° mild scoliosis tended to be frailer with more comorbidities including arthritis, diabetes, and heart disease, who had worse preoperative leg pain Numerical Rating Scale (NRS), Oswestry Disability Index (ODI), and MOS 36-item Short Form health survey (SF-36) physical composite score than those with > 30° scoliosis. On preoperative radiographs, the maximum coronal curve of 10°–30° mild scoliosis existed mainly in the lumbar spine, but with a similar level of the coronal C7 plumb line change to > 30° scoliosis, indicating a short-segment but aggressive lumbar spine curve which would be difficult to compensate for the frailty. During correction surgery, patients with 10°–30° mild scoliosis had less surgical invasion, a smaller number of posterior fusion levels and Smith-Petersen osteotomy levels but larger number of decompression levels, and lower levels of the uppermost instrumented vertebra, whereas the most common location of the lowermost instrumented vertebra was the sacroiliac region. Postoperative 2-year radiographs presented the increased thoracic kyphosis in the group of > 30° scoliosis as well as the decreased maximum coronal Cobb angle in both the groups of 10°–30° and > 30° scoliosis. In patients with 10°–30° mild scoliosis, postoperative 2-year HRQoL measures of ODI, SF-36, Scoliosis Research Society-22R (SRS-22R), and back and leg pain NRS, except for the SF-36 mental composite score, SRS activity, and SRS mental, were improved with statistical significance compared to preoperative values; furthermore, surgical treatment significantly improved all HRQoL variables in those with > 30° scoliosis. The minimal clinically important difference (MCID) and substantial clinical benefit values for HRQol instruments were also well met in both the scoliosis groups of 10°–30° (36%–74%) and > 30° (39%–78%), although patients with 10°–30° mild scoliosis had a lower rate to meet SRS appearance MCID. Then, a high percentage of surgical complications occurred in both the scoliosis groups of 10°–30° (64.3%) and > 30° (56.0%). In particular, rates of reoperation, implant failure, and neurological deficit were higher with marginal significance in patients with 10°–30° mild scoliosis than with > 30° scoliosis, indicating technically demanding surgery for 10°–30° mild scoliosis but with a short-segment, sharp coronal curve. This study is noteworthy which, for the first time, provides statistically robust data on the preoperative impairment and postoperative improvement of HRQoL in > 30° scoliosis patients and even in 10°–30° mild scoliosis patients, both with ou sagittal malalignment, undergoing ASD surgery primarily through the sacroiliac region.

The multicenter nature of this study is valuable but should be alerted, as there is a possible small variation in surgical indication and strategy for approaches, techniques, and fusion levels. Unjustified instrumentation is at risk of over treatment, which can lead to a considerable socioeconomic burden, particularly in ASD surgery.\textsuperscript{17} Up to 3-level fusion and decompression surgery is commonly performed to treat degenerative spondylolisthesis with vertebral slippage and disc wedge or narrowing from L2 to L5 but with a relatively maintained harmony at L5–S1, providing substantial improvements in pain and function.\textsuperscript{18} Unlike conventional fusion and decompression surgery,\textsuperscript{19,20} long-term results of ASD surgery are not fully uncovered. Further prospective, randomized, controlled trials regarding HRQoL outcomes of short-segment fusion versus long-segment fusion are warranted to identify an acceptable indication of ASD surgery in patients with short-segment, sharp coronal but not sagittal malalignment. This paper,\textsuperscript{16} published in the September 2023 issue of the Neurospine, has opened up new avenues to debate about impacts of ASD surgery on mild scoliosis and age-appropriate sagittal alignment.

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**REFERENCES**


Osteoporotic vertebral fractures (OVFs) can hinder physical motor function, daily activities, and the quality of life in elderly patients when treated conservatively. Vertebral augmentation, which includes vertebroplasty and balloon kyphoplasty, is a commonly used procedure for OVFs. However, there have been reports of complications. Although serious complications are rare, there have been instances of adjacent vertebral fractures, cement dislocation, and insufficient pain relief due to cement failure, sometimes necessitating revision surgery. This narrative review discusses the common risks associated with vertebral augmentation for OVFs, such as cement leakage and adjacent vertebral fractures, and highlights the risk of revision surgery. The pooled incidence of revision surgery was 0.04 (0.02–0.06). The risks for revision are reported as follows: female sex, advanced age, diabetes mellitus, cerebrovascular disease, dementia, blindness or low vision, hypertension, hyperlipidemia, split type fracture, large angular motion, and large endplate deficit. Various treatment strategies exist for OVFs, but they remain a subject of controversy. Current literature underscores the lack of substantial evidence to guide treatment strategies based on the risks of vertebral augmentation. In cases with a high risk of failure, other surgeries and conservative treatments should also be considered as treatment options.

Keywords: Osteoporotic vertebral fracture, Vertebral augmentation, Revision, Complication

INTRODUCTION

Osteoporotic vertebral fractures (OVFs) can cause low back pain and inhibit physical motor function, activities of daily living, and quality of life in elderly patients treated conservatively.1-3 Furthermore, OVFs increase the risk of mortality in elderly women.4 Therefore, OVFs exert a significant health burden, especially in an aging society.5 While a decreasing trend in the incidence of hip fractures is observed in many countries, occurrence of OVFs is increasing.6,7 Recently, a declining trend in osteoporotic medication after OVFs is reported in the United States.8 The treatment for osteoporosis should be improved to preserve population health by increasing the medication rate. There is no universal conservative treatment including bed rest, spinal orthosis, and physical therapy. Basically, immobilization owing to bed rest can be harmful because of the deterioration in bone loss, progressive muscle weakness, thromboembolic disease, joint contracture, and skin ulcer in elderly population.4 Therefore, physical therapy under spinal orthosis is recommended after short immobilization period, although a recent prospective cohort study9 demonstrated that better compression ratio of vertebral body and lower surgical rate were obtained following 2 weeks of bed rest for patients with risk factors of poor prognosis. Physical therapy is effective to improve osteoporosis and pre-
Ventricular osteoporotic fracture (OF). In most cases, conservative treatment employing brace treatment is effective for the healing process of fractures. However, there is no apparent evidence regarding the type of spinal orthosis between soft and rigid brace. Despite conservative treatment, residual back pain and neurological deficit are observed due to nonunion, severe deformity, and global spinal imbalance. Particularly, nonunion is strongly associated with residual back pain compared to local alignment.

Vertebral augmentation comprising vertebroplasty and balloon kyphoplasty is a widely used procedure for OVFs, and its safety and usefulness have been reported in many papers. Vertebral augmentation provides pain relief and vertebral height restoration. As the population ages, cement augmentation is being considered as a treatment for patients who are increasingly older, specifically those who are more than 80 or 90 years old. Additionally, a database study demonstrated that vertebral augmentation can improve the survival rate. Cochrane systematic review shows weak evidence of vertebral augmentation for vertebral fracture in acute or subacute phase because randomized controlled studies could not find the difference between vertebroplasty and placebo procedure. Therefore, we considered the risk of vertebral augmentation to minimize the harm among elderly patients, which may improve the outcomes of this procedure. The timing of vertebral augmentation is important for surgical outcomes because there are changes in low back pain and compression ratio especially during the first 3 months. A prospective study demonstrated that the quality of life and low back pain improved until 3 months after injury and did not change thereafter until a mean follow-up of 5 years.

Previous papers suggest that late intervention worsen the severity of fracture as compared to early intervention. However, early intervention may include unnecessary cases with OVFs, which recovery by conservative treatment. Therefore, several papers demonstrated the predicting factors for poor prognosis after conservative treatments to minimize the surgical invasiveness in elderly patients. There have also been some reports of complications following surgery. Serious complications, which occur in less than 1% of cases, include cement leakage into the spinal canal, spinal cord injury, infection, and pulmonary embolization, which may require emergency treatment. Apart from serious complications, there have been cases of adjacent vertebral fractures or dislocation of cement and poor pain relief due to cement failure, which sometimes require revision surgery.

The purpose of this study was to investigate the incidence of revision after vertebral augmentation. In addition, we discuss the common risks of vertebral augmentation for OVFs, including cement leakage and adjacent vertebral fractures, and outline the risk of vertebral augmentation.

MATERIALS AND METHODS

We conducted a systematic review of the literature identifying revision surgery after vertebral augmentation in patients with vertebral fractures according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and with guidance from the Cochrane Handbook for Systematic Reviews of Interventions.

1. Literature Search

For the identification of eligible articles, the individual steps of title and abstract screening, full-text review, and data extraction were performed independently using the MEDLINE database, Cochrane library, and Scopus database. The search strategy included combinations of the terms “vertebroplasty” or “balloon kyphoplasty” or “vertebral augmentation” and “revision” or “reoperation” and “vertebral fracture.” To optimize data mining, word variations and exploded medical subject headings were included whenever feasible. The last literature search was performed on January 9, 2023.
Frailty was associated with increased total complications, Clavien-Dindo Grade IV complications, length of stay, and 30-day readmission rates. Split type fracture, angular motion ≥ 14°, and large endplate deficit were independently associated with mortality after VP/KP.

Patients with procedures performed by surgeons experienced lower odds of reoperation at 30 days and 1 year but the 5-year and overall rates were not significantly different.

Elevated creatinine levels and ASA PS classification grade IV were independently associated with mortality after VP/KP.

Patients with the following characteristics were at a greater risk for repeat VP: female sex, advanced age, diabetes mellitus, cerebrovascular disease, dementia, blindness or low vision, hypertension, and hyperlipidemia. Patients taking calcium/vitamin D, bisphosphonates, or calcitonin were less likely to undergo repeat VP/KP. Patients with the following characteristics were at a greater risk for repeat VP: female sex, advanced age, diabetes mellitus, cerebrovascular disease, dementia, blindness or low vision, hypertension, and hyperlipidemia. Patients taking calcium/vitamin D, bisphosphonates, or calcitonin were less likely to undergo repeat VP/KP.

The results indicate that patients with osteoporosis who undergo VP are significantly less likely to require a reoperation if treated with zoledronic acid infusion.

Patients withVF in a single center

KP

2.0% PVP/PKP procedures for OVF place a high economic burden for both the healthcare system and patients. Early detection and treatment of patients with osteoporosis is critical in China.

Combined anterior and posterior surgery seems to be the most secure salvage method to treat patients with severe osteoporosis in whom percutaneous VP initially failed.

VF, vertebral fracture; VP, vertebroplasty; KP, kyphoplasty; OVF, osteoporotic vertebral fracture; ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; ASA PS, American Society of Anesthesiologists (ASA) physical status classification.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>Procedure</th>
<th>Sample size</th>
<th>Age (yr)</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Revision rate</th>
<th>Author conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou et al.</td>
<td>Retrospective cohort study</td>
<td>Patients with VF in a single center</td>
<td>VP</td>
<td>843</td>
<td>75</td>
<td>&gt; 2 Years</td>
<td>Revision</td>
<td>1.70%</td>
<td>Location of fracture at the thoracolumbar junction, fracture type of intravertebral cleft, or wedge-type fracture, and material with nonintegrating properties injected into the fractured vertebra are risk factors associated with the occurrence of progressive kyphosis and neurological complications.</td>
</tr>
<tr>
<td>Hazzard et al.</td>
<td>Retrospective propensity score-matched cohort study</td>
<td>Thomson Reuters MarketScan database</td>
<td>VP/KP (n = 696), KP (n = 699)</td>
<td>78</td>
<td>2 Years</td>
<td>Revision</td>
<td>VP 11.4%, KP 8.9%</td>
<td>KP and VP have equivalent long-term costs to nonsurgical management.</td>
<td></td>
</tr>
<tr>
<td>Hogan et al.</td>
<td>Retrospective cohort study</td>
<td>PearlDiver</td>
<td>VP/KP</td>
<td>80,864</td>
<td>73</td>
<td>1–5 Years</td>
<td>Revision</td>
<td>1.5%</td>
<td>Patients with procedures performed by surgeons experienced lower odds of reoperation at 30 days and 1 year but the 5-year and overall rates were not significantly different.</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Retrospective cohort analysis</td>
<td>ACS-NSQIP dataset</td>
<td>VP/KP</td>
<td>1,932</td>
<td>74.9</td>
<td>&lt; 30 Days</td>
<td>Revision</td>
<td>3.2%</td>
<td></td>
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<tr>
<td>Korovessis et al.</td>
<td>Controlled comparative randomized study</td>
<td>Patients with OVF in a hospital</td>
<td>KP</td>
<td>86</td>
<td>72.3</td>
<td>14 Months</td>
<td>Salvage for cement leakage</td>
<td>2.3% in KP</td>
<td></td>
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<tr>
<td>Li et al.</td>
<td>Retrospective cohort study</td>
<td>Patients with OVF in 2 hospitals</td>
<td>VP</td>
<td>827</td>
<td>74.1</td>
<td>3 Months</td>
<td>Repeat VP</td>
<td>1.1%</td>
<td>Repeat PV is an effective option for patients with OVF with recurrent pain at the previously treated level.</td>
</tr>
<tr>
<td>Liang et al.</td>
<td>Retrospective population-based longitudinal observation study</td>
<td>National Health Insurance Research Database of Taiwan</td>
<td>VP/KP</td>
<td>79,225</td>
<td>&gt; 40</td>
<td>4–7 Years</td>
<td>Repeat VP/KP</td>
<td>11.3%</td>
<td>Patients with the following characteristics were at a greater risk for repeat VP/KP: female sex, advanced age, diabetes mellitus, cerebrovascular disease, dementia, blindness or low vision, hypertension, and hyperlipidemia. Patients taking calcium/vitamin D, bisphosphonates, or calcitonin were less likely to undergo repeat VP/KP.</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>Retrospective cohort study</td>
<td>Patients with VF in a single center</td>
<td>VP</td>
<td>1,646</td>
<td>76.7</td>
<td>1.16 Years</td>
<td>Repeat VP</td>
<td>4%–13%</td>
<td></td>
</tr>
<tr>
<td>Robinson et al.</td>
<td>Prospective cohort study</td>
<td>Patients with VF in a single center</td>
<td>KP</td>
<td>102</td>
<td>69</td>
<td>6 Months</td>
<td>Revision</td>
<td>2.0%</td>
<td>Major complications are rare. However, since severe acute complications requiring emergency treatment may occur, the procedure should be performed by a qualified spinal surgeon.</td>
</tr>
<tr>
<td>Segal et al.</td>
<td>Retrospective cohort study</td>
<td>Nationwide population</td>
<td>KP</td>
<td>2,465</td>
<td>74</td>
<td>30 Days</td>
<td>Revision</td>
<td>3.4%</td>
<td>Frailty was associated with increased total complications, Clavien-Dindo IV complications, length of stay, and 30-day readmission rates.</td>
</tr>
<tr>
<td>Takahashi et al.</td>
<td>Prospective cohort study</td>
<td>Patients with OVF in multiple centers</td>
<td>KP</td>
<td>109</td>
<td>74.0</td>
<td>6 Months</td>
<td>Revision</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Walter et al.</td>
<td>Retrospective cohort analysis</td>
<td>Patients with OVF in a single center</td>
<td>KP</td>
<td>173 Male, 70.1; Female, 77.8</td>
<td>2 Months</td>
<td>Salvage for cement leakage</td>
<td>1.7%</td>
<td>KP can be considered a safe procedure, even in the treatment of painful OVF of AO type A3.1.</td>
<td></td>
</tr>
<tr>
<td>Yang et al.</td>
<td>Population-based medical claims database</td>
<td>Population-based medical claims database</td>
<td>VP/KP</td>
<td>14,527</td>
<td>75</td>
<td>2 Years</td>
<td>Revision</td>
<td>7.9%</td>
<td>PVP/PKP procedures for OVF place a high economic burden for both the healthcare system and patients. Early detection and treatment of patients with osteoporosis is critical in China.</td>
</tr>
<tr>
<td>Yang et al.</td>
<td>Retrospective study</td>
<td>Patients with OVF in multiple centers</td>
<td>VP</td>
<td>1,523</td>
<td>69.2</td>
<td>NA</td>
<td>NA</td>
<td>1.4%</td>
<td>Combined anterior and posterior surgery seems to be the most secure salvage method to treat patients with severe osteoporosis in whom percutaneous VP initially failed.</td>
</tr>
</tbody>
</table>
2. Study Selection and Quality Assessment

First, incomplete articles and non-English language articles were removed (Fig. 1). Next, review articles and case reports were excluded. Additionally, the articles that included only vertebral augmentation with instrumentation, only trauma cases, ankylosing spondylitis, pathological fracture, cervical spine, and sacral fracture were excluded. Next, the articles on only revision cases after vertebral augmentation were excluded because of lacking revision rate. Finally, we evaluated prospective or retrospective cohort studies to assess the incidence of revision surgery and the risks\textsuperscript{31,33-35} (Table 1). The initial screening of titles and abstracts for relevance was conducted by a single reviewer (ST). Full texts of the remaining articles were obtained and assessed for eligibility by comparison with the inclusion criteria. Data were extracted from the included studies by 2 independent reviewers (ST and MI). Any discrepancies during the screening or extraction process were resolved by consensus agreement or adjudication with another author (KT). The risk of bias in each study was evaluated by 2 reviewers (ST and KT). The post intervention biases for selection and reporting were judged using the Risk Of Bias In Non-randomized Studies of Interventions tool as follows: low, moderate, serious, and critical\textsuperscript{34} (Table 2). Confounding and information biases were excluded from the assessment because the reviewed articles were not compatible.

3. Data Extraction

Information on the study population, type of intervention, original sample size, average or median age, follow-up period, outcome of the study, revision rate, and risk of revision was collected. Revision surgery included failure of vertebral augmentation, repeated vertebral fracture for new fractures, and salvage surgery for cement leakage. The authors’ main conclusions regarding revision or repeated surgery were summarized.

4. Data Analysis

Pooled incidence of revision after vertebral augmentation was obtained by random-effect meta-analysis using a normal-binomial generalized linear mixed model method in the R packages “meta” (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria).\textsuperscript{46}

RESULTS

A flow diagram of the systematic literature search is provided in Fig. 1. The database search yielded 206 eligible articles after the removal of incomplete, duplicated and non-English articles. During the title and abstract screening, 206 articles were excluded for not meeting the inclusion criteria or for meeting the exclusion criteria. Of the remaining 19 articles, a further 5 records were excluded during full-text screening because they analyzed only revision cases. Finally, 14 articles were used for qualitative synthesis.

Six articles were nationwide or insurance database studies. Five studies were retrospective cohort and 2 were prospective cohort studies. One article was a randomized controlled trial that evaluated KIVA system, which is a novel polyether ether ketone implant, and balloon kyphoplasty.\textsuperscript{31} Several studies confirmed osteoporosis as the cause of vertebral fractures, while the other studies included patients who underwent vertebral augmentation for vertebral fracture. The median age in most studies was > 70 years. Although the definition of revision surgery was different due to differences in the purpose of the studies, it was divided into revision surgery, repeat vertebral augmentation, and salvage surgery for cement leakage. In several articles, revision surgery included repeat vertebral augmentation and salvage surgery. The rate of revision ranged from 1.1% to 13%. Repeat vertebral augmentation was relative frequent.\textsuperscript{35-37} Repeat vertebral augmentation was performed for new fractures. Salvage surgery was rarely performed for infection (0.36%). The frequency of salvage surgery for cement leakage was 1.7% to 2.3%.\textsuperscript{34,40} The pooled incidence of revision surgery was 0.04 (0.02–0.06) (Fig. 2).

The risk factors for revision were reported in several studies.\textsuperscript{36,39,42} Chou et al.\textsuperscript{42} demonstrated location of fracture at the

Table 2. Evaluation of postintervention biases

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou et al.\textsuperscript{42}</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Hazzard et al.\textsuperscript{33}</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hogan et al.\textsuperscript{44}</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Kim et al.\textsuperscript{45}</td>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td>Korovessis et al.\textsuperscript{34}</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Li et al.\textsuperscript{35}</td>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td>Liang et al.\textsuperscript{36}</td>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td>Lin et al.\textsuperscript{37}</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Robinson et al.\textsuperscript{33}</td>
<td>Moderate</td>
<td>Low</td>
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<tr>
<td>Segal et al.\textsuperscript{34}</td>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td>Takahashi et al.\textsuperscript{39}</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Walter et al.\textsuperscript{40}</td>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td>Yang et al.\textsuperscript{41}</td>
<td>Moderate</td>
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</tr>
<tr>
<td>Yang et al.\textsuperscript{31}</td>
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<td>Moderate</td>
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</table>
thoracolumbar junction, fracture type of intravertebral cleft, or wedge-type fracture, and material with nonintegrating properties injected into the fractured vertebra were risk factors associated with the occurrence of progressive kyphosis and neurological complications. Database study demonstrated the following other risk factors for repeat vertebral augmentation: female sex, advanced age, diabetes mellitus, cerebrovascular disease, dementia, blindness or low vision, hypertension, and hyperlipidemia. Patients taking calcium/vitamin D, bisphosphonates, or calcitomin were less likely to undergo repeat vertebral augmentation. Another study\(^{39}\) showed that split type fracture, greater angular motion, and large endplate deficit increased the risk for revision surgery. Additionally, frailty, elevated creatinine levels, and American Society of Anesthesiologists physical status classification grade IV were independently associated with mortality and complications\(^{38,45}\); treatment of osteoporosis, an experienced surgeon, and prophylactic vertebral augmentation may reduce the risk.\(^{36,37}\) Vertebroplasty and kyphoplasty showed similar revision rates.\(^{43}\)

**DISCUSSION**

Revisions following vertebral augmentation have been reported previously. However, few reports have investigated the risk factors for revision. The risks for revision are as follows: female sex, advanced age, diabetes mellitus, cerebrovascular disease, dementia, blindness or low vision, hypertension, hyperlipidemia, split type fracture, angular motion ≥ 14°, and large endplate deficit.\(^{36,39,42}\) Furthermore, intradiscal leakage may lead to secondary adjacent vertebral fractures\(^{29,47}\) and a greater angular motion of the fractured vertebra may be associated with greater vertebral height reduction in vertebral augmentation.\(^{39}\) A significant reduction in vertebral height is also known to be a risk factor for adjacent vertebral fracture.\(^{48}\) Additionally, the presence of an intravertebral cleft with angular motion has been reported as a poor prognostic indicator after vertebroplasty.\(^{49}\) A greater angular motion might indicate breakage or dysfunction of the anterior spinal elements, including the anterior longitudinal ligament and annulus, which may lead to failure in retaining the cement with the vertebral body. Anterior dislodgment of cement causes a loss of vertebral height and stability.

There is no standard classification of OVFs. Genant grading has been used for screening and evaluating the impact of OVFs on population health based on a semiquantitative assessment.\(^{50}\) AO spine classification for thoracolumbar injury is also widely used to evaluate the fracture type and to aid therapeutic and surgical decision making.\(^{51}\) However, the classification is adequate for trauma because OVFs are fragile fractures caused by minor injury. Recently, the new classification of OVFs, the OF classification, which is a morphologic classification of different types of OF, was developed by the German Orthopedic and Trauma Society and was also adopted by AO Spine.\(^{51}\) The classification comprises 5 subgroups as per the OF severity including endplate fracture and posterior wall injury assessment: OF 1, no deformation (vertebral body edema in MRI-STIR); OF 2, deformation of one endplate without or with only minor posterior wall involvement; OF 3, deformation of one endplate with distinct posterior wall involvement; OF 4, deformation of both endplates with/without posterior wall involvement; and OF 5, injuries with anterior or posterior tension band failure. Additionally, a scoring system was developed for making decisions regarding surgical intervention using the information on severity of osteoporosis, deformity progression, pain, neurological symptoms, mobilization, and health status. The severity of OF was associated with the frequency of surgery and 2% patients required revision surgery. Further research is necessary to investigate the surgical outcome depending on this new classifi-
Vertebral augmentation carries the risk of bone cement leakage and pulmonary embolism. Although symptomatic pulmonary embolism is a rare condition, pulmonary cement embolism leading to death can occur after uncontrolled leakage. Pedicle violation caused by epidural cement leakage further carries the potential risk of neurological deficit. Therefore, vertebral augmentation should only be performed by experienced surgeons following the identification of critical indications under fluoroscopic or computed tomography (CT) monitoring.

Minor cement leakage is frequently noted on CT but is asymptomatic in most cases. Indeed, leakage has been reported to occur in 30%–65% of cases. Decreased integrity of vertebral walls and the volume of injected cement significantly boost the potential risk of cement leakage. Cement leakage adjacent to a disc is frequently encountered, while symptomatic neurological complications due to compression of a nerve root or the spinal cord are less frequent. Vertebral augmentation is also a viable option for the treatment of OVF s, even with posterior wall involvement. High-viscosity cement results in lower bone cement leakage rate and better VAS score improvement compared with low-viscosity cement. Application of a large void volume using the balloon and the smaller injected cement than that void might be useful to avoid leakage. The unilateral approach may decrease the incidence of cement leakage due to lower cement dosage. Symptomatic bone cement displacement, which causes poor outcomes after vertebral augmentation is reported to be approximately 2% along with the risks of intravertebral cleft, anterior leakage, and cement distribution.

Several reports have investigated the difference between vertebroplasty and kyphoplasty. A meta-analysis that evaluated 121 reports demonstrated that the rate of asymptomatic cement leaks per treated patient was significantly higher for vertebroplasty than for kyphoplasty, although both procedures were effective in symptomatic vertebral compression fractures and there was no difference in mortality. Another meta-analysis further demonstrated that kyphoplasty has a reduced risk of cement leakage and it increases the postoperative vertebral height compared to vertebroplasty; however, it is more expensive and requires longer operative time durations. However, several papers in the current review showed no differences in clinical outcomes and complications between vertebroplasty and kyphoplasty.

The incidence ratio of adjacent vertebral fracture after vertebral augmentation has been calculated as approximately 10%–40% in previous reports. Most fractures occur within a few months. Vertebral augmentation is known to reduce vertebral
cation.

Progressive kyphosis after vertebroplasty is a risk factor for revision surgery and the incidence is reported as 1.5% in a retrospective study. There are risk factors associated with the occurrence of progressive kyphosis and neurological complications after vertebral augmentation, including location of fracture at the thoracolumbar junction, fracture type of intravertebral cleft, or wedge-type fracture, and material of nonintegration properties injected into the fractured vertebra. Additionally, significant associations were found between cement distribution patterns and progressive kyphosis in cemented vertebrae, which affected the clinical outcome in patients after vertebral augmentation. The cement distribution included uninterlocked solid pattern, discontinuous trabecular pattern, and solid lump cement pattern. The distribution of cement in vertebrae contributes to noncemented cancellous bones without load transfer causing recollapse. Another report stated that insufficient cement distribution is responsible for unrelieved pain. Location of the fractured area is an independent risk factor for the occurrence of insufficient cement distribution; if the fracture is located in the superior portion of the index vertebra, there is a higher incidence of insufficient cement distribution. The recollapse after vertebral augmentation may lead to recurrent back pain and revision surgery; the latter is sometimes necessary to avoid serious consequences. Multiple balloon dilation, location of cement and cement volume may be important to avoid the recollapse.

A previous study summarized the possible revision strategies for failed vertebral augmentation. The surgical strategy to treat cement leakage into the spinal canal causing neurological deficit is urgent laminectomy and fusion. Cement dislodgement or fragmentation also requires anterior or posterior surgery. For infection, extensive debridement is necessary, with combined anterior and posterior surgery being the safest method to treat this complication. Augmentation of pedicle screw fixation, using various bone cements, is less evident, although its use as an initial procedure to improve fatigue strength of instrumentation among patients with severe osteoporosis has been previously investigated. Major complications are rare. However, since severe acute complications requiring emergency treatment may occur, the procedure should be performed by a qualified spinal surgeon. Additionally, for patients with symptomatic failed vertebral augmentation, posterior transpedicular approach surgery with circumferential removal of leaked cement and anterior or reconstruction show low complication rate and good clinical outcomes; this can be considered as an alternative method combining anterior and posterior approaches.

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kyphotic deformity at the fractured vertebrae, as reported in several previous studies.\textsuperscript{99,101} However, correction after vertebral augmentation should be considered in the area including the upper and lower spinal segments. Even if correction can be achieved by kyphoplasty, correction loss may occur following adjacent vertebral fracture or correction loss of the vertebral body. Hard cement may further result in increased mechanical pressure, eventually causing a new fracture of the endplate in the adjacent vertebral body.\textsuperscript{79} More severe wedge angle before surgery, correction degree, old OVF presence, and thoracolumbar levels were identified as predictive factors of adjacent vertebral fracture in previous studies.\textsuperscript{85,82} Furthermore, a change in Cobb angle after operation and diabetes have been reported as a risk factor for postoperative adjacent vertebral fracture.\textsuperscript{65} A correction degree of $> 10^\circ$ was further reported as an independent risk factor for adjacent vertebral fracture.\textsuperscript{82} Several papers\textsuperscript{71,75,83} have shown that decreased bone mineral density (BMD) increases the risk of adjacent vertebral fracture following vertebroplasty. Furthermore, cement leakage has been reported as the primary risk factor for new vertebral compression fractures.\textsuperscript{79,84} However, if the cement is not in close contact with the endplates, it does not increase endplate deformation in the adjacent vertebrae, thereby minimizing the risk of adjacent vertebral fracture.\textsuperscript{85} Several studies have developed scoring systems to predict adjacent vertebral fracture based on the identified risk factors.\textsuperscript{82,86,87} The usefulness of these scoring systems may be revealed in the future.

Most adjacent vertebral fractures heal by conservative treatment.\textsuperscript{82} The application of smaller volumes of cement has been shown to be effective in decreasing the risk of adjacent vertebral fractures, while maintaining sufficient stability.\textsuperscript{88} Prophylactic augmentation into non-fractured vertebra may be effective to prevent further fractures and minimize the risk of revision surgery in osteoporotic patients.\textsuperscript{89} However, several studies indicated that the cause of adjacent fracture was mainly related to the progression of osteoporosis rather than the vertebral augmentation\textsuperscript{89} and the efficacy is inconsistent across the studies. Recent meta-analysis suggested that prophylactic augmentation could not reduce the risk of revision surgery.\textsuperscript{21} The therapeutic effects of teriparatide were better than those of the combined vertebroplasty and an antiresorptive agent in fracture prevention, BMD increase, and sustained pain relief.\textsuperscript{101} However, considering that most of the adjacent vertebral fractures occur within a few months, and the effect of increasing BMD appeared at least 3 months after the start of teriparatide use,\textsuperscript{82} teriparatide should be administered at least before surgery. A randomized controlled trial\textsuperscript{93} showed that teriparatide might prevent adjacent vertebral fracture due to stimulation of bone formation and faster improvement of bone strength and quality than antiresorptive agents. Teriparatide may offset the pharmacy cost due to the reduction of the inpatient admission and repeat vertebral augmentation.\textsuperscript{84} In addition, a reduced BMD might be a surrogate marker in patients with reduced activity of daily living because mechanical loading can inhibit bone resorption and increase bone formation.\textsuperscript{95}

As the limitation of this study, the criteria for revision surgery is not consistent according to the study population and surgeon’s decision. The lack of uniform definition in a heterogeneous topic can limit the generalizability of the study findings. However, it is important to recognize the possibility and risk for revision surgery after vertebral augmentation in OVF. Furthermore, the follow-up period is relatively short, and the long-term outcomes of the revision surgery are not evaluated. Additionally, publication bias may exist in this review. The investigators who did not identify the revision cases might not submit their data. Finally, this study did not assess the cost-effectiveness of revision surgery, which could have provided valuable information for healthcare providers and policy makers.

**CONCLUSION**

There are numerous treatment strategies for OVF\textsubscript{s}, which remain controversial. Current reviews have documented the low level of evidence currently available to inform the treatment strategy based on the risk of vertebral augmentation. Therefore, it is necessary to carefully evaluate the fracture to determine all relevant surgical indications. In cases with a high risk of failure, other surgeries and conservative treatments should also be considered as treatment options. However, implant complications such as cage subsidence, screw loosening, pull-out, and junctional failure are common in older patients with osteoporosis. Therefore, further investigation is necessary to create treatment strategies for OVF\textsubscript{s}.

**NOTES**

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REFERENCES


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Proximal Junctional Kyphosis or Failure After Adult Spinal Deformity Surgery - Review of Risk Factors and Its Prevention

Byung-Jou Lee¹, Sung Soo Bae², Ho Young Choi², Jin Hoon Park³, Seung-Jae Hyun⁴, Dae Jean Jo², Yongjae Cho⁵; Korean Spinal Deformity Society (KSDS)

¹Department of Neurosurgery, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
²Department of Neurosurgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, Korea
³Department of Neurosurgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
⁴Department of Neurosurgery, Spine Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
⁵Department of Neurosurgery, Ewha Womans University School of Medicine, Seoul, Korea

Proximal junction kyphosis (PJK) is a common imaging finding after long-level fusion, and proximal junctional failure (PJF) is an aggravated form of the progressive disease spectrum of PJK. This includes vertebral fracture of upper instrumented vertebra (UIV) or UIV+1, instability between UIV and UIV+1, neurological deterioration requiring surgery. Many studies have reported on PJK and PJF after long segment instrumentation for adult spinal deformity (ASD). In particular, for spine deformity surgeons, risk factors and prevention strategies of PJK and PJF are very important to minimize reoperation. Therefore, this review aims to help reduce the occurrence of PJK and PJF by updating the latest contents of PJK and PJF by 2023, focusing on the risk factors and prevention strategies of PJK and PJF. We conducted a search on multiple database for articles published until February 2023 using the search keywords “proximal junctional kyphosis,” “proximal junctional failure,” “proximal junctional disease,” and “adult spinal deformity.” Finally, 103 papers were included in this study. Numerous factors have been suggested as potential risks for the development of PJK and PJF, including a high body mass index, inadequate postoperative sagittal balance and overcorrection, advanced age, pelvic instrumentation, and osteoporosis. Recently, with the increasing elderly population, sarcopenia has been emphasized. The quality and quantity of muscle in the surgical site have been suggested as new risk factor. Therefore, spine surgeon should understand the pathophysiology of PJK and PJF, as well as individual risk factors, in order to develop appropriate prevention strategies for each patient.

Keywords: Proximal junctional kyphosis, Proximal junctional failure, Proximal junctional disease, Adult Spinal deformity, Risk factor
root and spinal cord caused by deformation of the coronal and sagittal alignment, and the quality of life decreases. These symptoms are an important factor in determining correction surgery. Correction surgery using long segment instrumentation for ASD requires high skill among spine surgeons. Therefore, it is mainly performed by experienced spine surgeons. Nevertheless, the overall complication rate of correction surgery for ASD is 13%, and the revision rate in long term follow-up is about 9%. Proximal junctional kyphosis (PJK) and proximal junctional failure (PJF) are common complications that occur in about 46% of cases after correction surgery of ASD, but revision surgery is required in severe cases of PJK and PJF. Additional revision surgery in patients who have undergone a long segmentation instrument for ASD can be another disaster. Therefore, in order to reduce the incidence of PJK and PJF, this paper focuses on the risk factors and prevention of PJK and PJF after correction surgery of ASD, and aims to provide overall information about PJK and PJF through current literature review. Based on this, it is hoped that it will be helpful to establish prevention strategies for PJK and PJF.

MATERIALS AND METHODS

We conducted a search across multiple databases, including PubMed, Embase, CENTRAL, and Web of Science for papers published by February 2023. The search keywords were "proximal junctional kyphosis," "proximal junctional failure," "proximal junctional disease," and "adult spinal deformity." In this study, a search strategy was employed using keywords, medical subject headings (MeSH) terms alone, or a combination of both. The MeSH terms included "kyphosis" and "spinal diseases" used. 438 papers in PubMed were identified, 425 articles in Web of Science, 292 in Embase, and 18 in CENTRAL. A total of 1,173 articles were identified, of which 412 were duplicate articles. Papers written in languages other than English, and case reports & articles were excluded (n = 356), and studies not focusing on PJK and PJF were also excluded from this study (n = 302). Finally, 103 articles were included in this review. The details of this process are highlighted in Fig. 1. Each article title and/or abstract was screened for relevance by 2 reviewers. Subsequently, the same reviewers conducted a full-text review of the relevant articles and determined whether each article satisfied the criteria for inclusion.

1. Definition, Pathophysiology, Incidence, Classification

PJK is a complication that commonly occurs in the uppermost instrumented vertebra of long-level instruments and indicates the presence of abnormal kyphosis at that level. There are various methods of measuring PJK. The most common way to measure PJK is to measure the sagittal Cobb’s angle between the inferior endplate of the upper instrumented vertebra (UIV) and the superior endplate of the vertebra 2 levels above the UIV. This method is mainly used because of its high reproducibility with intraclass and interclass correlations ranging from 0.78 to 0.92 and 0.55 to 0.80. In 1989, Bernhardt and Bridwell reported on the normal sagittal alignment of thoracic kyphosis, thoracolumbar junction, and lumbar lordosis (LL) in normal individuals. Then, in 1999, Lee et al. reported abnormal kyphotic angles of the proximal level of instrumented fusion of at least 5 degrees during a follow-up period of at least 2 years after posterior spinal fusion surgery. Subsequently, based on the study findings that there should be a difference of at least 11 degrees in radiologic measurements after long-level fusion to have 95% confidence in kyphosis, Glattes et al. redefined the angle of PJK to be greater than 10°. To date, it is most commonly used to define PJK as an increase in the angulation of the PJK by at least 10° greater than the preoperative measurement in literature. Despite numerous studies, no consensus has been reached on the optimal PJK angle after adult spinal deformity surgery, with many studies proposing a critical cutoff value of either 15° or 20°. PJK is commonly seen in fusion surgery, and there is much controversy about its clinical significance, as it rarely results in significant neurological outcomes or requires...
revision surgery. Some studies consider PJK to be a simple radiological finding, as there is no difference in its association with clinical symptoms regardless of its presence or absence.\textsuperscript{2,16,22} PJK is a progressive condition that has been observed to continue even after 2 years following surgery.\textsuperscript{23,24} PJF refers to the worsened form of the PJK disease spectrum and is characterized by mechanical failure and/or spinal instability at the UIV or UIV+1, including vertebral fracture, subluxation, and fixation failure. This can cause pain, neurological deficits, and may require revision surgery in up to 47% of affected patients.\textsuperscript{11,18,21,23,25} PJK and PJF are not separate diseases but rather included in one disease spectrum. In analogy to tumor, depending on the severity of the disease, they can be classified into benign PJK without significant clinical relevance and malignant PJF with important clinical significance (Fig. 2).

The pathophysiology of PJK and PJF may differ slightly. PJK is believed to occur due to partial damage to the posterior tension band near the UIV during long-level instrumentation surgery, as well as the action of deformity correction force during surgery and compensation for reduced kyphosis in the thoracic region.\textsuperscript{18,26} This kyphosis, which is thus induced or compensated, increases loading near the UIV. In addition, biomechanically, long-level instrumentation induces stress increase near the UIV due to the long lever arm and nonphysiological center of motion. This causes force to occur near the UIV, and motion near the UIV increases to distribute this force. As a result, degenerative changes progress more rapidly near the UIV, and vertebral bodies that cannot withstand the force may also experience fractures and instrumentation failure, leading to PJF.\textsuperscript{27-29}

The incidence of PJK varies widely due to various factors such as its definition, follow-up period, and characteristics of the patient population. Many studies report the incidence of PJK to be within 20%–40%.\textsuperscript{2,12,23,30,31} According to a recent paper published in Korea, among 78 ASD surgical patients who were followed up for more than 2 years from January 2012 to December 2017, 25 patients (32.1%) were reported to have developed PJK.\textsuperscript{32} In contrast, the incidence of PJF is reported to be lower than that of PJK, ranging from 1.4% to 35%.\textsuperscript{21,33,34} It is important to know not only the incidence of PJK and PJF but also the timing of their occurrence. PJK is usually diagnosed within 1 year after surgery, and when PJK occurs, approximately 53% of PJK progression angle occurs within 3 months of occurrence.\textsuperscript{23} In other study, it has been reported that approximately 59% of PJK progression angle occurs within 8 weeks of occurrence.\textsuperscript{24} Although PJF is an aggravated finding of PJK, PJF progresses rapidly. The average time for revision surgery with PJF was 10 months, and 87% of these cases underwent revision within 2 years.\textsuperscript{34} Similarly, in another study, PJF was diagnosed within an average of 3 months after surgery and revision surgery was performed within 7 months.\textsuperscript{21}

There have been few studies on the classification of PJK. Yagi et al.\textsuperscript{23} classified PJK based on type and grade, and spondylolisthesis. This method provided a simple and easy means of communicating PJK type among clinicians, but had a major drawback in that it did not provide decision criteria for management, including revision surgery.\textsuperscript{11} To address this issue, Hart et al.\textsuperscript{25} and the International Spine Study Group (ISSG) classified PJK and provided decision criteria for management. They used a PJK severity scale consisting of 6 components, including neurological deficit, focal pain, instrumentation problem, change in kyphosis/posterior ligament complex integrity, fracture location, and level of UIV. This scale had good reliability and repeatability, and its score showed a strong correlation with clinical outcomes and indication for revision surgery. A score of 7 or higher was recommended for revision surgery (Table 1).

2. Risk Factors and Prevention

PJK and PJF can be caused by various factors, but can be broadly classified into 3 categories: patient-related, radiographic, and surgical risk factors.

1) Patient-related risk factors

Patient-related risk factors include old age, osteoporosis, high

Fig. 2. Whole spine lateral x-ray and computed tomography image of proximal junctional kyphosis (A) and failure (B).
Many studies have reported old age as a risk factor for PJK after long-level instrumentation in adult spinal deformity. While age of 50 or older is often mentioned as a risk factor, other studies have also reported age of 60 or older as a risk factor. Along with advanced age, important risk factors for PJK/PJF are osteoporosis and low bone mineral density (BMD). Patients with low BMD, including osteoporosis and osteopenia, have a 30.9% increased risk of developing PJK compared to those with normal BMD. Furthermore, osteoporosis and age over 60 are considered as risk factors for PJK. Mikula et al. measured the bone density of UIV and UIV+1 with Hounsfield units (HU) using computed tomography and reported that low HU was the risk factor for PJK and PJF with an optimal cutoff of 159 HU. Moreover, it has recently been reported that high vertebral body quality (VBQ) is related to the occurrence of PJK/PJF by measuring bone quality with MRI-based VBQ scoring. Yagi et al. compared the changes in average BMD and the incidence of PJK between the postoperative teriparatide (TP) group and control group among osteopenia patients who underwent long segment fusion with ASD. Hip BMD increased by 6.7%+4.9% in the TP group, but decreased by 1.4%+4.2% in the control group at 2 years follow-up. The incidence of PJK type 2 was also significantly lower in the TP group (4.6%) than in the control group (15.2%, p = 0.02). There are studies that have applied cement augmentation to prevent proximal junctional complications in patients with osteoporosis. In one study, prophylactic vertebroplasty was performed on UIV and UIV+1, resulting in a decrease of PJK and PJF by 8% and 5%, respectively, at 6 months follow-up, but at 5-year follow-up, the incidence of PJK was not significantly different (28.2%). Another study reported no junctional complications during the follow-up period after cement augmentation at all instrumented levels and UIV+1. There is currently no guideline that determines up to which level prophylactic cement augmentation should be performed for PJK and PJF. However, considering the changes in biomechanical loading, shearing, and vertebral body/disc nutrition due to cement augmentation, many authors recommend performing cement augmentation at the UIV and/or UIV+1. Bridwell et al. reported that high BMI (median, 25.6 kg/m²) and the presence of comorbidities are related to the development of PJK of 20° or more. However, other studies have explained that BMI is not related to PJK/PJF. Recently, the importance of muscles has been emphasized, and the concept of sarcopenia has been introduced. Furthermore, many studies have reported the association between paraspinal muscles and the risk of PJK. In 2016, Hyun et al. proposed that lower thoracolumbar muscularity and higher fatty degeneration could induce PJK. Subsequently, Pennington et al. measured the cross-sectional area of paraspinal muscles at the UIV and reported that smaller paraspinal muscle at the UIV strongly predicted PJK. Recently, the importance of muscles has been emphasized, and the importance of multifidus among paraspinal muscles has also been integrated. Lower HUs and severe multifidus sarcopenia at the UIV are proposed as independent predictors of PJK and PJF. Therefore, the state of muscle as well as bone should

<table>
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<tr>
<td>Level of UIV</td>
<td></td>
</tr>
<tr>
<td>Thoracolumbar junction</td>
<td>0</td>
</tr>
<tr>
<td>Upper thoracic</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. The Hart-International Spine Study Group proximal junctional kyphosis severity scale

VAS, visual analogue scale; PLC, posterior ligamentous complex; UIV, upper instrumented vertebrae.
be evaluated before long-level instrumentation in ASD patients. In addition, the concept of frailty was also presented. Frailty is a new medical concept that represents an individual’s vulnerability to external injury due to physiological age increase and physiological function decrease.\textsuperscript{51} Health deteriorates at varying rates among individuals, and from a medical perspective, there is a discrepancy between physiological age and chronological age. Assessment of frailty has been developed as a method to quantify an individual’s physiological age.\textsuperscript{51,52} Recently, these frailty indices have shown good results in predicting complications after surgery.\textsuperscript{53,54} In a study, the researchers utilized the ISSG ASD prospective patient database to develop the adult spinal deformity frailty index (ASD-FI). They reported that patients with greater frailty measured by ASD-FI had a higher incidence of major complications such as PJK and were associated with worse outcomes.\textsuperscript{51,55} Recently, the Frailty-Adjusted Realignment Score was proposed by combining the ASD-FI and GAP scores, and it was reported to be useful in minimizing the risk of mechanical complications.\textsuperscript{56}

2) Radiographic risk factors

After undergoing deformity surgery, if the load distribution is not stabilized in the implants and spine alignment, a compensation mechanism occurs. Therefore, spine surgeons should perform instrumented fusion to minimize the occurrence of compensation mechanisms following surgery.\textsuperscript{57} Malalignment of the thoracolumbar spine can cause compensatory changes, including cervical hyperlordosis, pelvic shift, knee flexion, hip extension, and pelvic retroversion. Cervical alignment can be influenced by thoracic alignment, and there is a correlation between global sagittal alignment and reciprocal changes with the magnitude of sagittal deformities.\textsuperscript{58,59} T1 slope is associated with cervical lordosis and C7 sagittal vertical axis (SVA), and changes in each parameter can influence the others. Cervical lordosis increases after greater iatrogenic reduction in thoracolumbar deformity surgery.\textsuperscript{60} There is a reciprocal relationship between LL and thoracic kyphosis. Thoracic kyphosis and pelvic retroversion can be corrected after restoration of LL.\textsuperscript{61} The magnitude of the T1 pelvis angle is strongly associated with reciprocal changes in knee angle, hip extension, and posterior pelvic shift. If sagittal malalignment is corrected, posterior pelvic shift, knee flexion, and hip extension are also corrected.\textsuperscript{62} Therefore, an important factor in the occurrence of PJK and PJF is the presence of radiographic abnormalities of global spinal alignment. As performance of spine surgery involves artificially fixing a dynamic spine structure, it is crucial to balance the loading distribution of the inherent gravitational force of the spine both before and after the surgery. Many radiological risk factors have been reported for PJK and PJF; which can be classified into preoperative and postoperative factors.\textsuperscript{63} Maruo et al.\textsuperscript{64} reported that preoperative thoracic kyphosis (TK) of 30° or more is an important predictive factor for PJK, and a meta-analysis study identified TK > 40° as a risk factor for PJF.\textsuperscript{23,65} Additionally, other studies have reported that preoperative proximal junctional angle of 10° or more and pelvic incidence > 55° are associated with a higher risk of PJF.\textsuperscript{66} Regarding the occurrence of PJK and PJF, several studies have emphasized the changes in spinal alignment after surgery. Yagi et al.\textsuperscript{23} reported that postoperative changes in SVA of 50 mm or more are related to increased incidence of PJK. Another study showed that postoperative SVA of less than 50 mm is significantly associated with a risk of PJF.\textsuperscript{33} Furthermore, a change in LL of 30° or more before and after surgery has also been reported as a risk factor for the occurrence of PJF.\textsuperscript{64}

The Scoliosis Research Society (SRS)-Schwab classification suggested that the targets for obtaining satisfactory alignment and good clinical outcome were pelvic incidence-LL (PI-LL) $< \pm 10^\circ$, pelvic tilt $< 20^\circ$, and SVA $< 40$ mm.\textsuperscript{66-68} However, it was not clear how achieving Schwab goal affected the occurrence of mechanical complications, and mechanical complications were common despite achieving the ideal correction of the Schwab criteria. One study reported that Implant-related complications occurred in 31.7%, even though Schwab’s target value was achieved, and 52.6% of them required reoperation.\textsuperscript{69} In addition, the Schwab criteria were simply measured with radiologic curves, angles, and distant parameters, and the definitions of “normal” and “pathologic” alignment were unclear. These radiologic parameters are purely descriptive rather than analytic. So, correlations with these parameters do not necessarily imply causation. When using SVA, PI-LL, and pelvic tilt, using only the linear numerical value without considering the correlation of each parameter can lead to misleading, especially in patients whose PI value is close to the upper-normal or lower normal limit.\textsuperscript{57} Examples of causing misleading in each parameter are as follows. Patients with higher PI may have higher PT and SS, and higher PT do not necessarily imply increased retroversion and disability. A pelvic tilt of $> 20^\circ$ can be interpreted as a pathologic condition under the Schwab criteria, but may be an anatomical characteristic or reflect a large PI. So, the ideal target of pelvic tilt $< 20^\circ$ cannot be applied to all types of PI. A lower PT may be required in patients with low PI, but pelvic tilt $< 20^\circ$ in patients with high PI may be disabling. Ultimately, in the Schwab
criteria, PT did not consider anteversion, which could be the cause of mechanical failure. PI-LL < ±10 has limitations when applied to patients with extreme PI values. Additionally, incorrect load distribution during surgical correction of LL can lead to mechanical failure, so the lordosis distribution in the lower (L4–S1) and upper (L1–3) lumbar spine which is important for changing the load distribution should be considered. However, the Schwab criteria did not take this into account. SVA < 40 mm can be masked by compensatory pelvic retroversion without considering negative malalignment, which is a potential cause of mechanical failure. In order to overcome these limitations of the Schwab criteria, a new method has been proposed for predicting mechanical complications after surgery in ASD patients called the global alignment and proportion (GAP) score. Since PI is a relatively constant parameter, other parameters can be evaluated in relation to PI. Therefore, GAP score uses PI-based proportional parameter rather than absolute numeric. Furthermore, the GAP score indicates the standing sagittal alignment and shape as either “normal” or “pathological” for every magnitude of PI. This involves considering each individual’s ideal global spinopelvic alignment, considering appropriate alignment goals based on the complexity of their spinal structure. Measurements such as relative LL, relative pelvic version, relative spinopelvic alignment, lordosis distribution index, and age factor are used to score postoperative alignment characteristics and classify them into proportionate, moderately disproportionate, and severely disproportionate categories. This classification demonstrated that patients with proportionate alignment had mechanical complication rates of 6%, moderate disproportionate in 47%, and severe disproportionate alignment in 95%. Therefore, understanding the GAP score within the current concept of spine balance is important for preventing PJK. However, external validation of the GAP score for the association between proportional alignment categories and mechanical failure has not been consistent across studies. Furthermore, since this method was developed and analyzed postoperatively, it is difficult to apply it reliably before surgery. Therefore, there are still differing opinions on whether the GAP score reflects mechanical failure or not. Recently, in order to improve the predictive ability of mechanical complication, Modified GAP scoring with BMI and BMD (GAPB), which combines BMI and BMD with the GAP score, has been proposed. Furthermore, Noh et al. reported that they further improved the predictive ability of mechanical complications using machine learning based on GAPB.

With the increase in the elderly population, there has been a growing discussion regarding the definition of ideal sagittal balance in elderly patients. As age increases, LL tends to decrease with an increase in pelvic tilt to maintain whole sagittal balance following lumbar spine degeneration. Roussouly et al. classified the spine shape of normal adults into 5 types and presented an algorithm for restoring sagittal alignment, considering the association between pelvic incidence and lumbar degenerative changes. Degenerative loss in LL shifts the gravity line forward, and consequently compensatory mechanisms such as pelvic retroversion, knee flexion, and ankle extension occur to shift the gravity line posteriorly, resulting in posterior pelvic shift. Due to these reasons, sagittal parameters in the normal population can vary with aging. The ideal target of LL relative to PI may be lower in elderly patients. Therefore, age-adjusted targets for sagittal alignment have been proposed. In a study, it was reported that despite undergoing deformity surgery based on the previous target in elderly patients, there was a high incidence of PJK. This was attributed to overcorrection according to the age-adjusted target. Additionally, it was found that overcorrection was more commonly observed in the smaller PI group, which increased the occurrence of PJK. Therefore, while achieving sufficient correction is crucial for patients with high PI. Spine surgeons should be cautious about overcorrection in elderly patients with lower PI due to the high correlation with PJK. Lafage et al. reported effective prediction of PJK and surgical outcome through sagittal age-adjusted score considering inspired by SRS classification, the concept of the GAP score, and age-adjusted alignment targets. However, there is no universal target for spinopelvic measurement that considers all of these yet.

3) Surgical risk factors

It is also very important for spine surgeons to consider the surgical aspect in predicting and preventing PJK and PJF. The surgical risk factors of PJK and PJF include the following; Selection of UIV/lowest instrumented vertebra (LIV), surgical approach, proximal implant construction, rod characteristics, and posterior soft tissue (muscle, posterior ligamentous complex [PLC], facet capsules) injury. Choosing an appropriate UIV can be a challenging issue. In general, neutral and stable vertebrae are chosen as UIV. Some studies have reported a lower incidence of PJF when the UIV is located in the upper thoracic (UT) region compared to the lower thoracic (LT), thoracolumbar, or lumbar region. However, the UIV in the UT region can lead to PJK caused by subluxation and soft tissue injury, while the UIV in the LT region can lead to PJF and secondary vertebral body fractures. Since thoracic hyperkyphosis is a risk factor for proximal junctional problems, fusion extended to the UT region...
level in patients with thoracic hyperkyphosis can reduce the occurrence of PJK and PJF.\textsuperscript{43,83} Additionally, several studies have reported that long-level instrumentation extending to S1 can increase the incidence of PJK.\textsuperscript{24,33,84} However, if the LIV is L5, revision surgery can be increased by accelerating the degeneration of the L5–S1 disc.\textsuperscript{85} Therefore, the decision to choose the LIV at L5 or S1 remains controversial. The incidence of PJK is more than 3 times higher in patients who have undergone a combined anterior-posterior approach than in those who have undergone a posterior-only fusion. It is speculated that this is because the combined approach involves an anterior release, allowing for greater correction and resulting in a larger difference in sacral sagittal vertical line. However, the exact reason for this is unclear.\textsuperscript{31,11,86} One important aspect in the occurrence of PJK and PJF is also what to use for proximal implant construction. Pedicle screw is commonly used, but it is rigid and can cause PJK by increasing facet violations at the proximal level.\textsuperscript{16,20,87} Therefore, various other methods for semirigid fixation have been devised. It has the concept of topping off, which reduces peak stress by creating a gradual transition of motion at the proximal end of the rigid spinal construct.\textsuperscript{12,88} One of the representative methods is the spinal hook, which theoretically reduces facet violation and provides dynamic motion, thus decreasing the risk of PJK. In a study involving 47 patients who underwent transverse hook or pedicle screw fixation at the UIV and were followed up for 2 years, the spinal hook group showed a PJK incidence of 0%, while the pedicle screw group showed an incidence of 29.6%, demonstrating that spinal hooks significantly reduce the occurrence of PJK.\textsuperscript{28} In a biomechanical study using cadavers, the loading stress at the proximal level after long-level instrumentation was compared among the groups using supralaminar hooks (17% ± 11.5%), hybrid constructs (19% ± 8.2%), and unilateral screws (23% ± 8.3%). The loading stress in supralaminar hook group was the lowest, indicating that it is effective in reducing loading stress at the proximal level.\textsuperscript{89} There is a method to reconstruct the PLC by providing Mersilene tape (polyester fiber) to the lamina or spinous process of UIV–1, UIV, and UIT+1 to reduce the loading stress at this level; tether, sublaminar tape.\textsuperscript{12,88,90,91} Doodkorte et al.\textsuperscript{12} conducted a systematic review of biomechanical studies and found that tether showed a gradual increase in the transition zone of range of motion (ROM) compared to pedicle screws, and also demonstrated a decrease in intradiscal pressure. In a systematic review of clinical studies, the incidence of PJK was significantly lower in the tether group compared to the pedicle screw group (18% vs. 45%, \(p = 0.045\)).\textsuperscript{18} Sublaminar tape, like tether, also reduced the ROM of flexion-extension and lateral bending at the index level and decreased the intradiscal pressure.\textsuperscript{12} In a prospective study that included 40 consecutive patients who underwent sublaminar tape application at UIV+1, 7.5% of PJK and no cases of radiological PJF occurred during a median follow-up period of one year.\textsuperscript{92} The role of the rod is also important in the development of PJK and PJF due to the influence of the long-level arm of instrumentation. Using a stiff rod such as cobalt chromium (CoCr) can increase stability, but due to higher rigidity, it can cause PJK by increasing loading and increasing ROM at both ends of the rod, especially proximal.\textsuperscript{86,90} In actual clinical practice, PJK occurred more frequently in the CoCr rod group than in the titanium alloy (Ti) rod group (CoCr 60% vs. Ti 26.5%).\textsuperscript{93} Not only the stiffness of the rod, but also its shape is important in construct design. Contouring of the rod at the proximal level can reduce additional loading forces on the construct and decrease screw pullout strength and junctional stress.\textsuperscript{29,4} Kim et al.\textsuperscript{45} recommend careful kyphotic bending of the proximal portion of the rod to ensure complete seating of the rod within the screw head at the proximal 2 levels and to prevent additional loading at this level. In addition, the use of a transition rod within a single rod that varies in diameter and strength to modify the rigidity of the construct has been reported to reduce the incidence of PJK.\textsuperscript{94} However, due to the difficulty in fitting a rod to individual patients and the lack of clinical data, transition rods are not widely used in actual clinical field. Multiple rod constructs have been used to improve stiffness and stability at pedicle subtraction osteotomy sites in adult deformity correction,\textsuperscript{96} but a recent study reported that multiple rod constructs did not reduce pseudoarthrosis and rod fracture after PSO for ASD correction.\textsuperscript{97} Finally, the easiest but arguably most difficult aspect that a deformity surgeon must be cautious about is posterior soft tissue injury, which is an iatrogenic injury caused by the surgeon. Damage to the paraspinal muscles and posterior ligament complex at the proximal level during surgery has been identified as a risk factor for PJK and PJF in many studies.\textsuperscript{11,18,23,90,98,99} Therefore, when exposing the proximal level, it is essential to preserve the inter-spinous ligaments, supraspinous ligaments, proximal facet, and capsule. This has led to the proposal of minimally invasive surgery as an approach to reduce the risk of injury.\textsuperscript{100,101} The risk factors mentioned above are summarized in Table 2. Recently, the application of minimal invasive surgery (MIS) in ASD has been reported because of the relatively short surgical incision, short hospital stays, reduced bleeding loss. Although open surgery demonstrates powerful correction results, it is associated with a higher incidence of PJK due to factors such as
more damage to the normal spinal structures and larger implants compared to MIS. MIS offers advantages in reducing iatrogenic injuries and minimizing the occurrence of mechanical complications, as it does not require large incisions and extensive muscle dissection. It preserves the muscles, ligaments, and nerves associated with mechanical complications, which can help reduce the incidence of PJK. While MIS cannot currently replace open surgery in ASD, further attempts are needed, and selection of MIS in appropriate patients can minimize PJK.

**CONCLUSION**

Advances in implant technology and surgical skills have enabled long-level fusion and instrumentation for treating adult spine deformity, but these advancements have also led to new complications including PJK and PJF. PJK and PJF occur due to a combination of various factors, including surgical, radiological, and patient-related risk factors. Therefore, spine surgeon should understand the pathophysiology of PJK and PJF, as well as individual risk factors, in order to develop appropriate prevention strategies for each patient.

**NOTES**

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**Author Contribution:** Conceptualization: BJL, DJJ, JHP; Korean Spinal Deformity Society (KSDS); Formal Analysis: BJL, DJJ, JHP; Investigation: BJL, DJJ, JHP, KSDS; Methodology: BJL, DJJ, JHP, KSDS; Project Administration: BJL, DJJ, JHP, KSDS; Writing – Original Draft: BJL, DJJ; Writing – Review & Editing: BJL, DJJ, SSB, HYC, SJH, JHP, YC, KSDS.

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**Table 2. Risk factors and potential prevention strategies for proximal junctional kyphosis and proximal junctional failure**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Risk factor</th>
<th>Prevention</th>
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<tbody>
<tr>
<td><strong>Patient-related</strong></td>
<td>Old age: age of 50 or older/age of 60 or older&lt;br&gt;Sarcopenia: total muscle-fat index of PSE &gt; 4.08**</td>
<td>Teriparatide before/after surgery**&lt;br&gt;Prophylactic VP on UIV/UIV+1**&lt;br&gt;Weight loss before surgery</td>
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<tr>
<td><strong>Radiographic</strong></td>
<td>TK &gt; 40°&lt;sup&gt;20,53&lt;/sup&gt;&lt;br&gt;Proximal junctional angle &gt; 10°&lt;sup&gt;10&lt;/sup&gt;&lt;br&gt;Pelvic incidence &gt; 55°&lt;sup&gt;10&lt;/sup&gt;</td>
<td>GAP score&lt;sup&gt;22,58&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Surgical</strong></td>
<td>Selection of UIV/LIV</td>
<td>UIV: UT recommend (controversy)&lt;sup&gt;14,34&lt;/sup&gt;&lt;br&gt;UT (hyperkyphosis)&lt;sup&gt;43,62&lt;/sup&gt;&lt;br&gt;LIV: L5 or S1 (controversy)&lt;sup&gt;31,53,65,66&lt;/sup&gt;</td>
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PSE, paraspinal extensor muscles; HU, Hounsfield units; VP, vertebroplasty; UIV, upper instrumented vertebra; BMI, body mass index; TK, thoracic kyphosis; SVA, sagittal vertical axis; GAP, global alignment and proportion; LL, lumbar lordosis; PI, pelvic incidence; LIV, lowest instrumented vertebra; UP, upper thoracic; SH, spinal hook; ST, sublaminar tape.
REFERENCES


40:1414-21.
Adult spinal deformity (ASD) surgery aims to correct abnormal spinal curvature in adults, leading to improved functionality and reduced pain. However, this surgery is associated with various complications, one of which is proximal junctional failure (PJF). PJF can have a significant impact on a patient's quality of life, necessitating a comprehensive understanding of its causes and the development of effective management strategies. This review aims to provide an in-depth understanding of PJF in ASD surgery. PJF is a complex complication resulting from a multitude of factors including patient characteristics, surgical techniques, and postoperative management. Age, osteoporosis, overcorrection of sagittal alignment, and poor bone quality are identified as significant risk factors. The clinical implications of PJF are substantial, often requiring revision surgery and causing a considerable decrease in patients' quality of life. Prevention strategies include careful preoperative planning, appropriate patient selection, and optimization of surgical techniques. Treatment often necessitates a multifaceted approach, including surgical intervention and the management of underlying risk factors. Predictive modeling is an emerging field that may offer a promising avenue for the risk stratification of patients and individualized preventive strategies. A thorough understanding of PJF's pathogenesis, risk factors, and clinical implications is essential for surgeons involved in ASD surgery. Current preventive measures and treatment strategies aim to mitigate the risk and manage the complications of PJF, but the complication cannot be entirely prevented. Future research should focus on the development of more effective preventive and treatment strategies, and predictive models could be valuable in this pursuit.

**Keywords:** Proximal junctional failure, Adult spinal deformity surgery, Postoperative complications, Risk factors, Prevention, Treatment
DEFINITION AND CLASSIFICATION OF PJK/PJF

PJF represents a severe form of proximal junctional kyphosis (PJK), a postoperative complication characterized by an increase in the kyphotic angle at the junction between the fused and the adjacent unfused vertebrae. However, while PJK refers to this radiographic change, PJF involves additional serious complications. The main difference between PJK and PJF lies in the extent of the problem and its clinical impact. While PJK primarily involves radiographic changes (increased kyphotic angle at the junctional level), PJF represents a mechanical failure at the junction. This failure could involve fractures, listhesis, hardware failure, and is typically associated with significant clinical symptoms and often necessitates surgical revision. While PJK and PJF are related entities and part of a continuum, PJF represents a more severe and clinically impactful condition that often necessitates more aggressive interventions. These definitions are crucial in guiding therapeutic strategies and assessing outcomes in ASD surgery.

1. Proximal Junctional Kyphosis

PJK is essentially a radiographic diagnosis, characterized by an increase in the kyphotic angle between the lower endplate of the upper instrumented vertebra (UIV) and the upper endplate of the vertebra 2 levels above the UIV. A kyphotic angle increase of more than 10° to 20°, depending on the definition used, is typically considered indicative of PJK. This change may or may not be accompanied by clinical symptoms.

2. Proximal Junctional Failure

PJF is considered a severe form of PJK that is associated with mechanical failure at the proximal junction of a spinal instrumentation. It is defined by the presence of one or more of the following: (1) Fracture of the UIV or the vertebra 1 level above (UIV+1) (2) Failure of the posterior elements of UIV or UIV+1 leading to listhesis (3) Neurological deficit (4) The need for revision surgery due to clinical deterioration

While there’s no universal classification, PJF might be categorized based on the type and severity of the mechanical failure and clinical symptoms. Recently, PJF is widely recognized as the any form of PJK requiring revision surgery.

Several classification systems have been described. Among them, the Yagi-Boachie PJK/PJF classification is a widely recognized system for categorizing PJK/PJF based on the pathogenesis. The classification is as follows (Fig. 1).

1) Type 1: disc and ligamentous failure

This type is characterized by a kyphotic deformity that occurs at the junctional level but without any signs of instrumentation failure, screw pullout or junctional listhesis (displacement between UIV and UIV+1). This type is typically managed conservatively with observation, pain management, and physical therapy.

Fig. 1. Representative radiographs illustrating the types of PJK according to the Yagi-Boachie PJK/PJF Classification System. (A) Representative radiograph of Yagi-Boachie type 1 PJK: ligamentous failure. (B) Representative radiograph of Yagi-Boachie type 2 PJK: bone failure. (C) Representative radiograph of Yagi-Boachie type 1 PJK: implant and bone interface failure. PJK, Proximal Junctional Kyphosis; PJF, proximal junctional failure.
2) Type 2: bone failure
This type involves a kyphotic deformity with fracture of either UIV or UIV+1 vertebra and can cause junctional listhesis. Patients with type 2 PJK often require revision surgery to extend the fusion and restore spinal alignment.

3) Type 3: implant/bone interface failure
This type is characterized by a kyphotic deformity that occurs at the junctional level due to bone/implant interface failure, such as pedicle screw loosening. Type 3 PJK typically asymptomatic and does not necessitate revision surgery.

By using this classification, clinicians can accurately describe the severity of PJK, predict potential complications, and determine the most appropriate treatment.

INCIDENCE OF PJF

Although the incidence of PJK is relatively well-documented, the incidence of PJF is less so due to its definition variability and the need for revision surgery to confirm the diagnosis. The reported incidence rates range between 2% and 18% following ASD surgery.\(^8,12,17,22\) A multicenter study by Crawford et al.\(^22\) showed an incidence rate of PJF of approximately 7% at 2 years. Another study by Yagi et al.\(^8\) suggested a slightly higher incidence, reporting a rate of 8.8%. However, Maruo et al.\(^12\) found an incidence rate of 2.4% after 2 years. The variability in incidence rates can be attributed to the differences in the patient population, surgical techniques, and the specific definitions used for PJF.

PATHOGENESIS AND RISK FACTORS OF PJF

The exact pathogenesis of PJF remains unclear, yet it is a multifactorial complication related to an intricate interplay of biomechanical, surgical, patient-related, and radiographic factors:

1. Biomechanical Factors
A notable transition from a rigid, instrumented spine to a more flexible, noninstrumented area produces a “stress-riser” at the junction. The subsequent change in rigidity, coupled with increased mechanical stress and movement, can lead to junctional region failure.\(^23-25\)

2. Surgical Factors
Surgical factors such as overcorrection of the spinal deformity, aggressive facetectomy at the UIV, or the selection of an unsuitable UIV (e.g., in a region with preexisting degenerative changes or deformity) can heighten PJF risk.\(^26-29\)

3. Patient-Related Factors
Certain patient characteristics, such as advanced age, osteoporosis, and high body mass index (BMI), are linked to a heightened risk of PJF. These factors are likely attributed to the diminished bone quality and increased mechanical stress they induce.\(^20,26-28,30\)

Recognizing these risk factors is vital for effective preoperative planning, patient counseling, and the development of strategies to potentially mitigate the risk of PJF. The interplay of these factors can often be complex, which necessitates a comprehensive, holistic approach when considering these risks. However, the development of PJF is a significant complication following ASD surgery, making it crucial to understand its definition, pathogenesis, and risk factors for effective prevention and management strategies.

ROLE OF RADIOLOGICAL PARAMETERS AND PREDICTIVE MODELS IN PJF

Implementing various predictive models and radiological parameters can provide critical insights into the management and prevention of PJK and PJF. These parameters serve as important guidelines for optimal correction in ASD surgery. Here, we elaborate on the Scoliosis Research Society (SRS)-Schwab classification, age-adjusted sagittal alignment goals, the global alignment and proportion (GAP) score, and the Roussouly algorithm.\(^2,6,7,9,31-40\)

1. SRS-Schwab Classification
The SRS-Schwab classification system is a widely recognized tool for quantifying the severity of ASD.\(^34\) It considers 3 sagittal plane modifiers (sagittal vertical axis, pelvic tilt, and pelvic incidence minus lumbar lordosis) and quantifies deformity based on these modifiers. The strength of this system lies in its incorporation of global parameters, enabling comprehensive evaluation of spinal alignment. However, it does not provide explicit guidance on age-adjusted alignment goals or predict the risk of complications such as PJF.

2. Age-Adjusted Sagittal Alignment Goals
Age-adjusted sagittal alignment aims to guide spinal correction surgery by accounting for natural changes in spinal alignment with aging. According to a study by Lafage et al.,\(^35\) this age-adjusted model was validated in terms of PJF and clinical outcomes in ASD. However, it has limitations and may not be
universally applicable to all patients. They found a higher incidence of PJK in older age groups and suggested the incorporation of age-specific alignment targets into preoperative planning to optimize surgical outcomes and prevent PJK.

3. GAP Score

The GAP score is another important tool that provides guidelines for individualized patient alignment to achieve balanced sagittal alignment and minimize complications. Yilgor et al. developed and validated the GAP score, demonstrating high predictive accuracy for mechanical complications. Patients with proportioned spinopelvic alignment according to the GAP score had a significantly lower rate of mechanical complications compared to those with disproportioned alignment. Conversely, a study by Yagi et al. found that the GAP score was not predictive of mechanical failure or revision surgery in an Asian cohort of patients with ASD, suggesting the need for further research to assess its predictive ability in different patient populations.

4. Roussouly Classification

The Roussouly classification is a 4-type classification based on the shape and alignment of the sagittal spinal profile. It can assist surgeons in understanding the patient's natural alignment and planning surgery accordingly. Although useful for assessing preoperative alignment, it does not inherently include any predictive elements for postoperative complications like PJF. Each of these systems provides valuable insights into optimal correction goals and patient stratification in ASD surgery. However, none can singularly predict the occurrence of complications such as PJF. Therefore, a multifactorial approach, incorporating patient-specific characteristics, clinical variables, radiological parameters, and predictive models, is essential to provide the best surgical outcomes.

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**BONE QUALITY AND SARCOPENIA: THEIR ROLE IN PJK/PJF AFTER ASD SURGERY**

Emerging evidence indicates that poor bone quality and muscle mass (sarcopenia) are significant risk factors for the development of PJF after ASD surgery, especially in the Asian population.

1. Bone Quality

Bone quality, often compromised in patients with low bone mineral density (BMD) or osteoporosis, has been identified as a crucial factor influencing the risk of PJF in recent studies. Yagi et al. conducted a propensity-matched analysis to investigate BMD as a risk factor for PJF in patients who underwent corrective surgery for ASD. They categorized the 113 ASD patients based on T scores into 2 groups: mildly low to normal BMD (M group) or significantly low BMD (S group). They found that PJF occurred in 19% of patients, but significantly more frequently in the S group compared to the M group (33% vs. 8%, respectively). The odds ratio of 6.4 indicated a notable risk for PJF in the group with lower BMD, highlighting the necessity of considering prophylactic treatments for patients with low BMD during ASD correction.

Building on this, Kuo et al. conducted a retrospective chart review to assess the predictive power of the MRI-based vertebral bone quality score (VBQ) for PJF after corrective surgery for ASD. In a sample of 116 patients who underwent surgery involving 5 or more thoracolumbar levels, they found that patients with higher VBQ scores were significantly more likely to develop PJF. Their multivariate analysis found that the VBQ score was the only significant predictor of PJF, with an increased odds ratio of 1.745 associated with higher VBQ scores, demonstrating a predictive accuracy of 94.3%.

Lastly, Mikula et al. explored the relationship between BMD, as estimated by Hounsfield units (HU), and PJF in the upper thoracic spine. The study found that among a total of 81 patients who underwent instrumented fusion, 33% developed PJF. On multivariable analysis, they discovered that a lower HU at the UIV/UIV+1 was the only independent predictor of PJF, with a lower HU indicating an increased risk. Patients with HU < 147 at the UIV/UIV+1 had a 59% rate of PJF, emphasizing the need to assess BMD using HU measurements to identify high-risk patients and implement preventive measures.

These studies underscore the critical role of bone quality in the onset of PJF, urging increased focus on bone health in the management and surgical intervention strategies for patients with ASD.

2. Sarcopenia

Recent research suggests a significant link between sarcope-
nia, a condition characterized by the loss of skeletal muscle mass and function, and various spinal disorders. A study conducted by Yagi et al., aimed to explore the role of the multifidus (MF) and psoas (PS) muscles in the maintenance of global spinal alignment in patients with degenerative lumbar scoliosis (DLS). In a cohort of 120 female patients, the cross-sectional areas (CSAs) of the MF and PS muscles were significantly smaller in the DLS group compared to the lumbar spinal stenosis group. The DLS group also exhibited a larger percentage difference in CSA between the right and left sides. Importantly, the average CSA of the MF showed moderate correlations with global spinal alignment and spinopelvic alignment in the DLS group. The MF CSA was also found to be correlated with postoperative kyphosis progression at the unfused thoracic vertebrae in the DLS group.

In a different study by Guo et al., the characteristics of para-vertebral muscles (PVMs) in ASD patients were studied with regard to pelvic incidence minus lumbar lordosis (PI–LL) match or mismatch. Out of 67 ASD patients, the PVM on the concave side was found to be larger than on the convex side in both PI–LL match and mismatch groups. The mismatch, however, exacerbated this asymmetry. More concerning was that the average degeneration degree of the MF, visual analogue scale scores for pain, symptom duration, and Oswestry Disability Index for disability were significantly higher in the PI–LL mismatch group. Babu et al. conducted a retrospective study to determine if sarcopenia is an independent risk factor for complications in ASD patients undergoing pedicle subtraction osteotomy (PSO). In a cohort of 73 ASD patients, it was found that patients with complications had a lower psoas-lumbar vertebral index (PLVI) on average compared to those without complications. Patients with lower PLVI values had significantly greater odds of developing complications such as proximal junctional kyphosis, wound infection, and dural tear. Krenzlin et al. conducted a study to examine the impacts of sarcopenia and bone density on implant failures (IFs) and complications in patients with spondylodiscitis due to osteoporotic vertebral fractures (OVFs). Out of 68 patients with OVF s, sarcopenia was detected in 47.1%, myosteatosis in 66.2%, and osteoporosis in 72%. Lower skeletal muscle area (SMA) z-scores adjusted for height and BMI (zSMAHT) were significantly associated with IFs, suggesting that the presence of sarcopenia and osteoporosis increased the likelihood of an IF. The study also established sarcopenic obesity as the main determinant for IF occurrence.

Recognizing and addressing these risk factors is crucial. Improving bone quality and treating sarcopenia could potentially reduce the risk of PJF. This could involve comprehensive management including nutritional supplementation, pharmacotherapy for osteoporosis, and physical rehabilitation to improve muscle mass and strength. Further research is necessary to determine the best strategies to manage these risks.

**CLINICAL IMPLICATIONS OF PJF**

PJF can significantly impact patients' quality of life due to associated pain, functional impairment, and the potential requirement for revision surgery. Studies have shown that patients with PJF report lower scores on health-related quality of life measures compared to those without PJF. In severe cases, PJF can lead to neurological deficits, which can have debilitating outcomes.

1. **Pain and Physical Discomfort**

One of the most immediate implications of PJF is the significant pain and discomfort it can cause. This can severely restrict a patient's mobility and physical capabilities. Often, the pain is localized at the upper part of the instrumentation and can be exacerbated by movement. While the exact incidence is challenging to quantify due to variations in individual pain thresholds and reporting, most patients with PJF experience significant pain and discomfort.

2. **Neurological Complications**

The reported incidence of neurological complications related to PJF varies widely, with some studies suggesting an incidence of around 10%–15%. For example, if the failure involves a fracture of the UIV or the UIV+1 and there is posterior displacement, the spinal cord or nerve roots could be compressed, leading to symptoms such as numbness, weakness, or even paralysis.

3. **Revision Surgery**

PJF often necessitates revision surgery, which can carry its own set of risks and complications. The reported rate of revision surgery due to PJF is around 10%–20%. This includes a higher risk of infection, blood loss, and perioperative complications. The additional surgery can also lead to prolonged hospital stays and increased healthcare costs. The need for revision surgery is a significant clinical implication of PJF.

4. **Impaired Quality of Life**

The combination of pain, reduced mobility, neurological symptoms, and the psychological stress of facing additional surgeries can significantly impair a patient's quality of life.
affect various aspects of life, including mental health, social relationships, and the ability to work or perform daily activities. The incidence of impaired quality of life is difficult to quantify as it involves subjective and varied measures. However, most patients with PJF are likely to experience some decrease in quality of life due to pain, disability, and the need for further surgery.

5. Impaired Spinal Alignment

PJF can lead to a loss of the corrective alignment achieved during the initial surgery, leading to a recurrence of the original deformity symptoms. This can further exacerbate pain and disability.6,7

6. Psychological Impact

The diagnosis of PJF, coupled with the potential requirement for additional surgery and the associated complications, can have a significant psychological impact on patients, leading to stress, anxiety, and potentially depression.5,8,10,11

Overall, PJF can have profound clinical implications affecting various aspects of a patient’s life, highlighting the importance of appropriate preventive and treatment strategies.

PREVENTION STRATEGIES FOR PJK/PJF

Prevention strategies are primarily directed towards risk modification. While PJF cannot be entirely prevented, several strategies may help to reduce its risk. This includes optimization of bone health, careful patient selection, appropriate surgical technique, and maintaining a balanced spinal alignment. The role of prophylactic vertebroplasty, cement augmentation of the UIV, and the use of hook or transitional rods are currently being investigated.9

1. Preoperative Planning and Patient Selection

Careful patient selection and preoperative planning are crucial. This includes optimizing the patient’s health before surgery, managing comorbidities such as osteoporosis using teriparatide, and carefully assessing the patient’s spinal alignment.6,9,10,49 Correct selection of the level of the UIV based on individual patient anatomy and alignment can also reduce the risk of PJF.50

2. Management Strategies for Improving Bone Quality in ASD Surgery

Management strategies for improving bone quality, especially in the context of ASD surgery, are essential to prevent instrumentation-related complications. Both in preoperative and postoperative phases, several pharmacological therapies have shown promise. These therapies primarily aim to either increase bone formation or decrease bone resorption, thereby enhancing overall bone density and quality. Recently, several therapeutic agents such as teriparatide, romosozumab, abaloparatide, and denosumab have shown promise in enhancing bone quality and preventing complications.51-57

Teriparatide, a recombinant form of parathyroid hormone, is known to enhance bone formation. A study by Yagi et al.51 revealed that teriparatide therapy initiated immediately after surgery improved the volumetric BMD (vBMD) and fine bone structure at the vertebra above the UIV+1. After 6 months of treatment, the teriparatide group showed a significant increase in hip-BMD and vBMD at UIV+1 compared to the control group. Moreover, a lower incidence of vertebral-failure-type proximal junctional kyphosis (PJK type 2) was reported in the teriparatide group at the 2-year follow-up, suggesting its potential in preventing PJK.

Abaloparatide, similar to teriparatide, abaloparatide is an anabolic agent that promotes bone formation. Clinical trials have shown its efficacy in reducing the risk of fractures and improving BMD in patients with osteoporosis.57 Further studies are warranted to validate its utility in the preoperative setting of ASD surgery.

Romosozumab, a monoclonal antibody, functions by increasing bone formation and decreasing bone resorption. It has shown beneficial effects in increasing BMD and reducing fracture risk. This could potentially translate to a reduced risk of instrumentation failure in ASD surgery.

Denosumab, another monoclonal antibody, inhibits bone resorption by binding to RANKL (receptor activator of nuclear factor kappa-β ligand). Studies have shown it increases BMD and decreases vertebral and nonvertebral fractures in postmenopausal women. It could provide similar benefits in the context of ASD surgery.

Bisphosphonates, an antiresorptive agents inhibit osteoclast-mediated bone resorption, thus improving bone quality. Several studies have demonstrated that bisphosphonates can reduce the risk of postoperative vertebral fractures and enhance fusion rates, while the effect is limited.

Further, combining therapies could offer superior outcomes. For instance, combining teriparatide and denosumab has been shown to produce a more significant increase in BMD than either agent alone.

In conclusion, employing these therapies in both the preoperative and postoperative phases could contribute to enhanced
bone quality and lower the risk of postoperative complications in ASD surgery. However, the application of these therapies should be individualized and based on thorough patient evaluation.

3. Surgical Technique

1) Mitigating overcorrection and limiting fusion length

Surgical techniques can be fine-tuned to help prevent PJF. These adjustments could involve mitigating the overcorrection of sagittal alignment, favoring a gradual correction of deformities over an abrupt change, and aiming to limit the length of fusion where viable. Attention is increasingly being drawn to prophylactic measures, such as vertebroplasty, cement augmentation, and the implementation of hooks, transitional rods, or sub-laminar tethering (Table 1).19,23,50,58-67

2) Cement-augmented pedicle screws at the UIV and UIV+1

The application of cement-augmented pedicle screws at the UIV and UIV+1 is a strategic approach aimed at reinforcing the stability of fixation, especially beneficial for patients with diminished bone quality.19,61,62 Cement augmentation notably enhances the pullout strength of pedicle screws, which is advantageous for patients with low BMD or osteoporosis. Numerous studies have suggested that by fortifying the fixation at the UIV and UIV+1, cement augmentation might help mitigate mechanical stress at these junctional levels, potentially lowering the risk of PJF. While the initial cost of cement-augmented pedicle screws may be higher than traditional pedicle screws, the potential decrease in revision surgeries due to PJF could render this approach cost-effective in the long run. However, it’s important to acknowledge potential drawbacks associated with this method. A risk exists for cement leakage into the spinal canal or vascular system, which can lead to serious complications, including neurological deficits or pulmonary embolism. Additionally, it is theorized that cement augmentation increases the construct’s stiffness, which might redistribute increased stress to the adjacent levels and potentially result in adjacent segment disease. Furthermore, in situations where revision surgery becomes necessary, the extraction of cement-augmented pedicle screws could prove challenging and may possibly lead to supplementary complications.

3) Ligament augmentation using polyethylene tape at the upper instrumented levels

A newly described procedure to constrain excessive movement and reduce the likelihood of PJF is ligament augmentation at the upper instrumented levels using polyethylene tape.66-68 In this technique, a polyethylene tape with high tensile strength and durability is looped around the spinous processes or lamina at the UIV and the adjacent level (UIV and UIV+1 or UIV+2). The tape is tensioned to a certain degree and secured, creating a

Table 1. Descriptive summary of the studies related to the surgical prevention of PJF

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Age (yr)</th>
<th>Follow-up (yr)</th>
<th>Type of prevention</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raman et al.62</td>
<td>41 ASDs</td>
<td>66</td>
<td>5</td>
<td>Cement augmentation</td>
<td>5.1% PJF</td>
</tr>
<tr>
<td>Ghobrial et al.64</td>
<td>38 ASDS</td>
<td>64</td>
<td>2</td>
<td>Cement augmentation</td>
<td>0% PJF</td>
</tr>
<tr>
<td>Viswanathan et al.65</td>
<td>40 ASDs</td>
<td>64</td>
<td>2</td>
<td>Sublaminar tethering</td>
<td>0% PJF</td>
</tr>
<tr>
<td>Rodnoi et al.66</td>
<td>23 ASDs</td>
<td>63</td>
<td>2</td>
<td>Sublaminar tethering</td>
<td>0% PJF</td>
</tr>
<tr>
<td>Yagi et al.67</td>
<td>32 ASDs</td>
<td>67</td>
<td>2</td>
<td>Sublaminar tethering</td>
<td>3% PJF</td>
</tr>
<tr>
<td>Hassanzadeh et al.68</td>
<td>20 ASDs</td>
<td>46</td>
<td>2</td>
<td>Transverse process hooks</td>
<td>0% PJF</td>
</tr>
</tbody>
</table>

PJF, proximal junctional failure; ASD, adult spinal deformity.
posterior tension band effect (Fig. 2). This technique aims to provide additional support and stability to the junctional region, thereby reducing abnormal motion and stresses that could lead to PJF. The rationale behind this method is that it attempts to mimic and augment the function of the posterior tension band—the supraspinous and interspinous ligaments—which are often disrupted during surgery. However, while initial studies show promising results, long-term data and larger studies are needed to validate the safety and efficacy of this technique. Furthermore, technical considerations such as the optimal tension on the tape and the ideal anchoring points for maximum effect are yet to be established.

4) Contouring of the terminal rod and fusion length considerations

The contouring of the terminal rod represents another intraoperative technique designed to circumvent the occurrence of acute junctional kyphosis between the UIV and UIV+1, offering a potential advantage over the use of a flat terminal rod (Fig. 3). Moreover, the surgeon’s decision to terminate the construct at a specific level should be carefully considered, given that extended fusions are known risk factors for PJF.

4. Postoperative Care

After surgery, maintaining adequate bone health is important, especially in patients with osteoporosis. Postoperative bracing may be helpful in some patients, though evidence for its efficacy in preventing PJF is mixed.67,68

### Diagnostic and Management Algorithm of PJK/PJF:

<table>
<thead>
<tr>
<th>Diagnostic and Management Algorithm of PJK/PJF:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Assessments:</strong> Prior to the surgery, conduct a comprehensive assessment including a detailed clinical history, physical examination, and assessment of bone quality. Use imaging techniques (e.g., X-ray, CT, and MRI) to establish a baseline and for further comparisons.</td>
</tr>
<tr>
<td><strong>Postoperative Monitoring:</strong> Following surgery, perform regular clinical and radiological evaluations. Monitor for early signs of PJK, such as changes in sagittal alignment, worsening back pain, or a significant increase in kyphosis at the proximal junction.</td>
</tr>
<tr>
<td><strong>Diagnosis of PJK:</strong> PJK is diagnosed when there is an increase of &gt;10 deg. in the kyphotic angle between the lower endplate of the UIV and the upper endplate of UIV+2, compared to the immediate postoperative period.</td>
</tr>
<tr>
<td><strong>Early Onset PJK without Failure:</strong> If there's evidence of early PJK without instrumentation failure or neurologic deficits, conservative management including physical therapy, bracing, and analgesics should be tried initially.</td>
</tr>
<tr>
<td><strong>Progressive PJK or PJF:</strong> If there is progressive worsening of kyphosis, failure of the instrumentation, or development of neurological symptoms, revision surgery might be warranted. The type of surgery would depend on the severity and cause of PJK/PJF. This could include extension of fusion to higher levels, use of stronger or more stable constructs, correction of sagittal imbalance, and in some cases, vertebral column resection.</td>
</tr>
<tr>
<td><strong>Postoperative Management:</strong> After revision surgery, continue with physical therapy, bracing, pain management, and regular follow-up with imaging. Monitor for any signs of recurrence or other complications.</td>
</tr>
<tr>
<td><strong>Long-term Management:</strong> Ongoing rehabilitation and exercise programs to improve strength and flexibility, along with regular clinical evaluations, are essential components of long-term management.</td>
</tr>
</tbody>
</table>

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**Fig. 3.** Intraoperative view demonstrating the use of flat bend-er for the rod contour.

**Fig. 4.** Diagnostic and management algorithm of PJK/PJF. PJK, Proximal Junctional Kyphosis; PJF, proximal junctional failure; CT, computed tomography; MRI, magnetic resonance imaging; UIV, upper instrumented vertebra.

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TREATMENT OF PJF

Treatment of PJF often necessitates a multidisciplinary approach (Fig. 4). The initial step often involves conservative measures, including pain management, bracing, and physiotherapy. However, these measures may be insufficient in PJF cases. Surgical intervention is considered in patients with progressive neurological deficits, persistent pain, or those who experience significant deterioration in their quality of life. Additionally, further PJF commonly developed after revision surgery for PJF. Surgery typically involves extension of the fusion to more proximal levels, revision of the instrumentation, or even vertebral column resection (VCR) in severe cases. Revision surgery for PJF after ASD surgery is a complex procedure and should be tailored to the individual patient’s anatomy, symptoms, and overall health status. Various strategies can be utilized depending on the specifics of the PJF presentation.

1. Surgical Approach
   The surgical approach to PJF revision surgery can be posterior, anterior, or a combined approach. The decision depends on several factors, including the location and severity of the failure, the need for neural decompression, the patient’s overall health, and the surgeon’s expertise.

2. Extension of Fusion
   One common strategy in PJF revision surgery is extending the fusion to more proximal levels. However, it’s important to be mindful of the potential for creating additional stress at the new junctional level.

3. Osteotomies
   In cases where PJF has resulted in significant kyphosis at the junctional level, an osteotomy may be necessary to correct the alignment. This could involve a PSO or a VCR, depending on the severity of the deformity.

4. Reinforcement of UIV and UIV+1
   Reinforcing the fixation can also be beneficial in PJF revision surgery to avoid further PJF. This could involve using larger or longer pedicle screws, adding additional screws or hooks, posterior laminar tethering, or using cement augmentation to decrease the integrity of the posterior ligamentum complex.

5. Anterior Column Support
   In some cases, particularly where there has been substantial vertebral body collapse or fracture, adding anterior column support can be beneficial. This could involve an anterior or lateral lumbar interbody fusion or the placement of a cage.

6. Addressing Bone Health
   In patients with osteoporosis or other conditions affecting bone health, it’s crucial to address this as part of the revision strategy. This could involve medical management such as teriparatide and bisphosphonate to improve bone density or the use of bone grafts or bone morphogenetic proteins to enhance fusion.

It’s important to note that revision surgery for PJF carries significant risks, and the decision to proceed should be made after careful consideration of the potential benefits and risks. Furthermore, the best strategy will depend on the individual patient’s situation and the surgeon’s judgement and expertise.

ARTIFICIAL INTELLIGENCE IN PREDICTING AND PREVENTING PJF/PJF: INSIGHTS FROM RECENT STUDIES

Artificial intelligence (AI) holds great promise in the management of spinal conditions such as PJK and PJF. Recent research has been focused on leveraging AI for predictive analysis, imaging assessment, and personalized treatment planning.

1. Predictive Analysis
   In a multicenter study, Scheer et al. developed a predictive model for PJK and PJF in ASD surgery, achieving an accuracy of 86.3%. They identified several factors, including age, lowest instrumented vertebra (LIV), preoperative sagittal vertical axis, UIV implant type, preoperative pelvic tilt, and preoperative PI–LL, as strong predictors. This model can aid in preoperative decision-making and risk stratification in ASD surgery. Yagi et al. further validated and refined this predictive model by including BMD as an additional variable. Their model achieved 100% accuracy in the testing sample. Key predictors identified were pelvic tilt, BMD, LIV level, UIV level, PSO, global alignment, BMI, PI–LL, as strong predictors. This model can aid in preoperative decision-making and risk stratification in ASD surgery. Yagi et al. further validated and refined this predictive model by including BMD as an additional variable. Their model achieved 100% accuracy in the testing sample. Key predictors identified were pelvic tilt, BMD, LIV level, UIV level, PSO, global alignment, BMI, PI–LL, as strong predictors. This model can aid in preoperative decision-making and risk stratification in ASD surgery. Another study by Noh et al. developed a machine learning model based on GAPB (GAP scoring with BMI and BMD) factors for predicting mechanical complications in ASD surgery. The random forest algorithm employed in this study displayed the highest performance, suggesting its utility in surgical risk prediction.
2. Imaging Analysis

AI has also shown potential in imaging analysis. Grover et al.\textsuperscript{78} evaluated an AI-based algorithm for determining sagittal balance parameters in patients with and without spinal instrumentation. The algorithm demonstrated excellent agreement with human raters, particularly on preoperative images, suggesting its efficiency for large-scale imaging analysis.

Similarly, Orosz et al.\textsuperscript{79} introduced an AI algorithm that accurately measures spinopelvic parameters on lumbar radiographs. The AI measurements displayed excellent interrater reliability and provided precise measurements, proving it to be a valuable tool for clinical practice and research.

Taken together, these studies demonstrate the significant potential of AI in predicting PJK/PJF risk and guiding surgical decision-making. It offers the advantage of analyzing large datasets and imaging efficiently, accurately, and objectively. However, further research is needed to ensure the generalizability of these AI models across diverse patient populations and settings.

FUTURE DIRECTIONS

While considerable progress has been made in understanding PJF, significant knowledge gaps still exist. Future research should focus on further elucidating the pathophysiology of this complex disorder. Additionally, it is crucial to establish a standard definition of PJF to facilitate consistent reporting and comparison across studies.

The development and validation of a risk prediction model could help identify patients at high risk for PJF preoperatively. This could guide surgical decision-making and patient counseling, and aid in the development of personalized prevention strategies. Moreover, investigating the role of novel biomarkers and advanced imaging techniques in predicting PJF warrants attention. In the therapeutic realm, efforts should be directed towards refining surgical techniques and the development of advanced spinal implants to prevent PJF. Additionally, assessing the efficacy of minimally invasive surgery (MIS) in preventing PJF could be promising, as MIS techniques are associated with less tissue damage and potentially fewer postoperative complications.

Finally, conducting long-term follow-up studies will help understand the natural history of PJF and the true impact of various prevention and treatment strategies on patient outcomes.

CONCLUSION

PJF is a multifaceted complication of ASD surgery with significant implications for patients’ quality of life. Our understanding of its pathogenesis is still evolving, but current efforts are directed towards developing effective prevention and treatment strategies. Future research is critical to filling the existing knowledge gaps and improving patient outcomes in ASD surgery.

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ORCID

Mitsuru Yagi: 0000-0002-2324-3780

REFERENCES


Severe Obesity Is an Independent Risk Factor of Early Readmission and Nonhome Discharge After Cervical Disc Replacement

Tejas Subramanian¹², Daniel Shinn¹², Pratyush Shahi¹, Izzet Akosman¹², Troy Amen¹, Omri Maayan¹², Eric Zhao¹², Kasra Araghi¹, Junho Song¹², Sidhant Dalal¹, James Dowdell¹, Sravisht Iyer¹, Sheeraz Qureshi¹

Hospita for Special Surgery, New York, NY, USA

Weill Cornell Medicine, New York, NY, USA

Objective: Despite growing interest in cervical disc replacement (CDR) for conditions such as cervical radiculopathy, limited data exists describing the impact of obesity on early postoperative outcomes and complications. These data are especially important as nearly half of the adult population in the United States is expected to become obese (body mass index [BMI] ≥ 30 kg/m²) by 2030. The goal of this study was to compare the demographics, perioperative variables, and complication rates following CDR.

Methods: The 2005–2020 American College of Surgeons National Surgical Quality Improvement Program datasets were queried for patients who underwent primary 1- or 2-level CDR. Patients were divided into 3 cohorts: Nonobese (BMI: 18.5–29.9 kg/m²), Obese class-I (BMI: 30–34.9 kg/m²), Obese class-II/III (BMI ≥ 35 kg/m²). Morbidity was defined as the presence of any complication within 30 days postoperatively. Rates of 30-day readmission, reoperation, morbidity, individual complications, length of stay, frequency of nonhome discharge disposition were collected.

Results: A total of 5,397 patients were included for analysis: 3,130 were nonobese, 1,348 were obese class I, and 919 were obese class II/III. There were more 2-level CDRs performed in the class II/III cohort compared to the nonobese group (25.7% vs. 21.5%, respectively; p < 0.05). Class-II/III had more nonhome discharges than class I and nonobese (2.1% vs. 0.5% vs. 0.7%, respectively; p < 0.001). Readmission rates differed as well (nonobese: 0.5%, class 1: 1.1%, class II/III: 2.1%; p < 0.001) with pairwise significance between class II/II and nonobese. Class II/III obesity was an independent risk factor for both readmission (odds ratio [OR], 3.32; p = 0.002) and nonhome discharge (OR, 2.51; p = 0.02). Neither 30-day reoperation nor morbidity rates demonstrated significance. No mortalities were reported.

Conclusion: Although obese class-II/III were risk factors for 30-day readmission and nonhome discharge, there was no significant difference in reoperation rates or morbidity. CDR procedures can continue to be safely performed independent of obesity status.

Keywords: Cervical disc replacement, Obesity, Risk factors

INTRODUCTION

Patients with cervical myelopathy and radiculopathy have been classically treated with anterior cervical discectomy and fusion (ACDF) after failure of conservative measures.¹⁻³ ACDF has shown admirable efficacy over the years, but the procedure is associated with numerous complications, including pseudoarthrosis, adjacent segment disease, dysphagia, and loss of cervical range of motion as well as inherent risks of harvesting bone graft.¹⁻⁴ In recent decades, an alternative method, cervical disc
replacement (CDR), has gained popularity due to its potential to reduce the postoperative risks associated with ACDF. Unlike ACDF, CDR preserves range of motion, decreases adjacent segment disease, and does not require a plating graft. CDR has also shown comparable efficacy, safety, and overall outcomes to ACDF. However, despite the growing body of literature supporting CDR, there has been little investigation into the impact of obesity on early postoperative outcomes and complications of this procedure. This is a significant knowledge gap, given that obesity is a growing public health crisis in America with 49% of the United States (US) adults predicted to be obese by 2030, and the prevalence of severe obesity (body mass index [BMI] ≥ 35 kg/m²) is expected to spike to 24.2% in the US adults within the same timeframe.

Obesity is a well-known risk factor for numerous postsurgical complications in spine surgery, including venous thromboembolism, surgical site infection, and blood loss, and severe obesity has been shown to correlate with a higher risk of early complications. Obese patients may be especially prone to poorer outcomes in specifically anterior cervical surgery as different cardiopulmonary risks, difficult approaches, and retraction in obese patients have previously described in these surgeries even compared to lumbar spine surgery. So, while there have been previous studies describing obesity as a risk factor for early postoperative complications in ACDF, to our knowledge, to date, no study has described these outcomes in CDR. ACDF and CDR are technically very different surgeries and impact biomechanics of the spine in different ways. Obesity may be even more crucial to understand in CDR than ACDF since the replaced intervertebral disc has a very different function than a functionally temporary graft used in ACDF procedures. The rising relevance of both CDR and obesity presents a crucial need for further inquiry. Therefore, the purpose of this study was to (1) investigate perioperative complication profiles, readmission rates, and mortality following CDR for obese patients, and (2) outline patient demographic variables in obese patients that may be associated with higher complications.

MATERIALS AND METHODS

1. Study Population

Data was collected via the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. The NSQIP database is a validated, multicenter, prospective database designed to measure quality of surgical care and track early patient outcomes. Patients undergoing primary 1 or 2 level CDR procedures between 2005 and 2020 were queried for this analysis. This was extracted via current procedural terminology (CPT) codes 22856 and 22858 for CDR. Patients undergoing revision CDR (22861) and removal CDR (22864) were excluded. ACDF (22551, CPT2552), anterior cervical fusion (22554, 22585), posterior cervical fusion (22590, 22600, 22614), cervical laminoplasty (63050) procedures were also excluded. Consistent with prior methods, emergent/non-elective cases, fractures, and infection cases were all excluded from the NSQIP query.

Following data was pulled from the NSQIP database. Patients with missing demographics were excluded.

(1) Preoperative data: surgical setting (outpatient [length of stay < 24 hours], inpatient [length of stay ≥ 24 hours]), patient demographics (age, BMI, sex, race, ethnicity, functional status, smoking status, American Society of Anesthesiologists [ASA] physical status classification, comorbidities [i.e., diabetes, congestive heart failure, chronic obstructive pulmonary disease, bleeding disorders], laboratory values [creatinine, hematocrit, white blood, and platelet cell count]).

(2) Operative data: type of surgery, number of levels, operation time, and length of stay.

(3) Postoperative data: discharge disposition (home, nonhome), 30-day morbidity (complications including wound infections, urinary tract infection, pneumonia, sepsis, unplanned intubation, renal insufficiency/failure, stroke, myocardial infarction, thrombosis/embolism, transfusions), readmission, and reoperation.

BMI was the primary independent variable of interest. To fully appreciate the effect of BMI on the patient’s surgical risk profile, patients were categorized into nonobese (BMI: 18.5–29.9 kg/m²), obese class I (BMI: 30–34.9 kg/m²), and obese class II/III (BMI ≥ 35 kg/m²) in accordance with the World Health Organization BMI classification. Severe obesity can be defined as patients obese class II/III. Any patients with BMI < 18.5 kg/m² were excluded.

2. Statistical Analysis

Across BMI groups, demographic factors and postoperative outcomes for categorical variables were compared with Pearson chi-square test or Fisher exact test when applicable. Analysis of variance and Kruskal-Wallis tests were used for continuous normally and nonnormally distributed variables respectively. Post hoc, pairwise t-tests were conducted if there was a significant difference among the 3 cohorts. Univariate logistic regression and multivariable logistic regressions were then carried out to
investigate independent predictors of morbidity, reoperation, readmission, and nonhome discharge disposition. Significance was defined with a p-value ≤ 0.05. All analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Demographics
A total of 5,397 patients were included in this analysis; 3,130 (58%) were nonobese, 1,348 (25%) were obese class I, and 919 (17%) were obese class II/III (Table 1). Nonobese patients had significantly lower rates of diabetes (class I: 5%, class II: 11.4%, class III: 18.2%, p < 0.001), dyspnea (1.3%, 1.5%, 3.9%, p < 0.001), hypertension (19.6%, 32.8%, 44.3%, p < 0.001), and bleeding disorder (0.2%, 0.6%, 0.9%, p = 0.012) compared to obese class I and obese class II/III patients. The percentage of patients with ASA physical status classification grade ≥ III was also significantly lower for nonobese patients compared to obese patients (14.5%, 25.1%, 49.9%, p < 0.001).

2. Perioperative and 30-Day Outcomes
A greater percentage of obese class II/III underwent 2-level CDR procedures compared to nonobese patients (25.7% vs. 21.5%, p = 0.021). While there were no differences in surgical

Table 1. Demographical and clinical characteristics (n = 5,397)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonobese (n = 3,130)</th>
<th>Obese class I (n = 1,348)</th>
<th>Obese class II/III (n = 919)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.2 ± 11&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>47 ± 10.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47 ± 10.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.004&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 2.7&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>32.3 ± 1.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>40 ± 5.6&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female sex</td>
<td>1,491 (47.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>594 (44.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>511 (55.6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Black race</td>
<td>187 (6)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>122 (9.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>102 (11.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>99 (3.2)</td>
<td>58 (4.3)</td>
<td>34 (3.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Outpatient surgery setting</td>
<td>1,753 (56)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>799 (59.3)</td>
<td>590 (64.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dependent functional status</td>
<td>11 (0.4)</td>
<td>8 (0.6)</td>
<td>6 (0.7)</td>
<td>0.308</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>155 (5)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>153 (11.4)&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>167 (18.2)&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Current smoker within 1 year</td>
<td>666 (21.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>240 (17.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>172 (18.7)</td>
<td>0.016&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>40 (1.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23 (1.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>36 (3.9)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>47 (1.5)</td>
<td>17 (1.3)</td>
<td>21 (2.3)</td>
<td>0.138</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (&lt;0.1)</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>0.261</td>
</tr>
<tr>
<td>Hypertension requiring medication</td>
<td>613 (19.6)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>442 (32.8)&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>407 (44.3)&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dialysis</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>2 (0.2)</td>
<td>0.188</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>74 (2.4)</td>
<td>28 (2.1)</td>
<td>23 (2.5)</td>
<td>0.773</td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td>7 (0.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (0.6)</td>
<td>8 (0.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.012&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>ASA PS classification grade &gt; III</td>
<td>455 (14.5)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>339 (25.1)&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>459 (49.9)&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wound class &gt; 2</td>
<td>9 (0.3)</td>
<td>8 (0.6)</td>
<td>3 (0.3)</td>
<td>0.314</td>
</tr>
<tr>
<td>Preoperative laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>197 (7.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>115 (10.4)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>55 (7.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.015&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Elevated white blood cell count</td>
<td>106 (4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64 (5.6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69 (8.8)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low hematocrit</td>
<td>105 (3.9)</td>
<td>41 (3.5)</td>
<td>36 (4.5)</td>
<td>0.534</td>
</tr>
<tr>
<td>Low platelet count</td>
<td>67 (2.5)</td>
<td>27 (2.4)</td>
<td>26 (3.3)</td>
<td>0.401</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA PS, American Society of Anesthesiologists physical status. Superscripts a, b, and c denote statistically significant (p < 0.05) post hoc pairwise analysis. Elevated creatinine defined as ≥ 1.2 mg/dL. Elevated white blood cell count defined as ≥ 11 k/μL. Low hematocrit defined as ≤ 35%. Low platelet count ≤ 50 k/μL. *p < 0.05, statistically significant differences.
complications among the 3 groups, the percent of patients with a nonhome discharge disposition (0.5%, 0.7%, 2.1%, \( p < 0.001 \)) and 30-day readmission (0.5%, 1.1%, 2.1%, \( p < 0.001 \)) were significantly higher for obese patients compared to nonobese patients. While not statistically significant, there was a trend towards higher rates of reoperations for obese patients (0.4%, 0.5%, 1%, \( p < 0.094 \)). Length of stay and total operation time were not significantly different between the groups (\( p < 0.05 \) for both) (Table 2).

### 3. 30-Day Readmission

On a univariate analysis, age (odds ratio [OR], 1.04; \( p = 0.005 \)), BMI as a continuous variable (OR, 1.06; \( p < 0.001 \)), obese class I (OR, 2.06; \( p = 0.042 \)), obese class II/III (OR, 3.87; \( p < 0.001 \)), Hispanic ethnicity (OR, 3.02; \( p < 0.021 \)), dependent functional status (OR, 9.45; \( p = 0.003 \)), ASA physical status classification grade \( \geq III \) (OR, 2.54; \( p = 0.001 \)) were all significant predictors of 30-day readmission. Comorbidities including dyspnea, hypertension, and dialysis all also had significantly higher odds of readmission (Supplementary Table 1). Outpatient surgery setting

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonobese (n = 3,130)</th>
<th>Obese class I (n = 1,348)</th>
<th>Obese class II/III (n = 919)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Level CDR</td>
<td>672 (21.5)(^a)</td>
<td>315 (23.4)</td>
<td>236 (25.7)(^a)</td>
<td>0.021(^*)</td>
</tr>
<tr>
<td>30-Day outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readmission</td>
<td>17 (0.5)(^a)</td>
<td>15 (1.1)</td>
<td>19 (2.1)(^a)</td>
<td>&lt; 0.001(^*)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>12 (0.4)</td>
<td>7 (0.5)</td>
<td>9 (1)</td>
<td>0.094</td>
</tr>
<tr>
<td>Morbidity</td>
<td>25 (0.8)</td>
<td>17 (1.3)</td>
<td>13 (1.4)</td>
<td>0.156</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Individual complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial wound infection</td>
<td>8 (0.3)</td>
<td>5 (0.4)</td>
<td>4 (0.4)</td>
<td>0.589</td>
</tr>
<tr>
<td>Deep incisional infection</td>
<td>1 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>0.374</td>
</tr>
<tr>
<td>Organ/space infection</td>
<td>0 (0)</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>0.091</td>
</tr>
<tr>
<td>Wound disruption</td>
<td>0 (0)</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>0.091</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (0.1)</td>
<td>0 (0)</td>
<td>2 (0.2)</td>
<td>0.206</td>
</tr>
<tr>
<td>Unplanned intubation</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Ventilator requirement &gt; 48 hr</td>
<td>1 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Progressive renal insufficiency</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (0.2)</td>
<td>2 (0.1)</td>
<td>5 (0.5)</td>
<td>0.144</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (&lt; 0.1)</td>
<td>1 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>0.664</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (&lt; 0.1)</td>
<td>1 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>0.652</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>1 (&lt; 0.1)</td>
<td>3 (0.2)</td>
<td>0 (0)</td>
<td>0.166</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>2 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>0.553</td>
</tr>
<tr>
<td>Sepsis/septic shock</td>
<td>2 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>0.553</td>
</tr>
<tr>
<td>Perioperative variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total RVUs</td>
<td>23.8 ± 1.8</td>
<td>23.8 ± 1.8</td>
<td>23.7 ± 2.1</td>
<td>0.337</td>
</tr>
<tr>
<td>Total operation time (min)</td>
<td>111.1 ± 52.1</td>
<td>111.7 ± 49.9</td>
<td>113.5 ± 48.5</td>
<td>0.118</td>
</tr>
<tr>
<td>Length of hospital stay (day)</td>
<td>1.03 ± 1.45</td>
<td>0.98 ± 2.06</td>
<td>1.03 ± 1.8</td>
<td>0.323</td>
</tr>
<tr>
<td>Nonhome discharge disposition</td>
<td>16 (0.5)(^a)</td>
<td>9 (0.7)(^b)</td>
<td>19 (2.1)(^ab)</td>
<td>&lt; 0.001(^*)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation.

CDR, cervical disc replacement; RVU, relative value unit.

Superscripts (a, b, c) denote statistically significant (\( p < 0.05 \)) post hoc pairwise analysis.

\(^*\)\( p < 0.05 \), statistically significant differences.
was a protective factor for readmission (OR, 0.5; p = 0.015). On multivariable analysis, BMI as a continuous variable (OR, 1.06; p < 0.001) and obese class II/III (OR, 3.32; p = 0.002) both remained significant predictors of readmission. Outpatient surgery setting remained a protective factor for readmission (OR, 0.55; p = 0.049) (Table 3).

4. Nonhome Discharge Disposition

On a univariate analysis, age (OR, 1.06; p < 0.001), BMI as a continuous variable (OR, 1.06; p < 0.001), obese class II/III (OR, 4.12; p < 0.001), Hispanic ethnicity (OR, 5.32; p < 0.001), dependent functional status (OR, 10.99; p < 0.001), ASA physical status classification grade ≥ III (OR, 4.85; p < 0.001) were all significant predictors of nonhome discharge disposition. Comorbidities including dyspnea, hypertension, and dialysis all also had significantly higher odds of nonhome discharge. Outpatient surgery setting was a protective factor for nonhome discharge (OR, 0.3; p < 0.001) (Supplementary Table 1). On multivariable analysis, BMI as a continuous variable lost significance, but obese class II/III (OR, 2.51; p = 0.027) remained a significant independent predictor. Hispanic ethnicity (OR, 6.76; p < 0.001) and ASA physical status classification grade ≥ III (OR, 3.37; p = 0.001) both remained significant predictors. Outpatient surgery setting remained a protective factor for nonhome discharge (OR, 0.31; p = 0.002) (Table 4).

5. 30-Day Morbidity

On univariate analysis, BMI as a continuous variable (OR, 1.04; p = 0.01) and ASA physical status classification grade ≥ III (OR, 2.23; p = 0.004) were significant predictors of 30-day morbidity. Obesity class II/III, though not significant, did have an elevated odds ratio (OR, 1.78; p = 0.093). Comorbidities includ-

### Table 3. Multivariable regression: 30-day readmission

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.01</td>
<td>0.98–1.04</td>
<td>0.443</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.06</td>
<td>1.03–1.10</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BMI (categorical)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonobese</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Obese class I</td>
<td>1.87</td>
<td>0.87–4.01</td>
<td>0.11</td>
</tr>
<tr>
<td>Obese class II/III</td>
<td>3.32</td>
<td>1.56–7.08</td>
<td>0.002*</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>2.77</td>
<td>0.99–7.77</td>
<td>0.053</td>
</tr>
<tr>
<td>Outpatient surgery setting</td>
<td>0.55</td>
<td>0.30–1.00</td>
<td>0.049*</td>
</tr>
<tr>
<td>Dependent functional status</td>
<td>2.51</td>
<td>0.31–20.43</td>
<td>0.391</td>
</tr>
<tr>
<td>2-Level CDR</td>
<td>1.57</td>
<td>0.84–2.95</td>
<td>0.159</td>
</tr>
</tbody>
</table>

### Table 4. Multivariable regression: nonhome discharge disposition

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.04</td>
<td>1.01–1.08</td>
<td>0.022*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.04</td>
<td>1.00–1.09</td>
<td>0.064</td>
</tr>
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<td>BMI (categorical)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonobese</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Obese class I</td>
<td>0.79</td>
<td>0.29–2.15</td>
<td>0.643</td>
</tr>
<tr>
<td>Obese class II/III</td>
<td>2.51</td>
<td>1.11–2.15</td>
<td>0.027*</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>6.76</td>
<td>2.48–18.18</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Outpatient surgery setting</td>
<td>0.31</td>
<td>0.15–0.66</td>
<td>0.002*</td>
</tr>
<tr>
<td>Dependent functional status</td>
<td>4.08</td>
<td>0.78–21.28</td>
<td>0.010*</td>
</tr>
<tr>
<td>2-Level CDR</td>
<td>1.6</td>
<td>0.76–3.34</td>
<td>0.214</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; BMI, body mass index; CDR, cervical disc replacement; COPD, chronic obstructive pulmonary disease; ASA PS, American Society of Anesthesiologists physical status. Elevated creatine defined as ≥ 1.2 mg/dL. Low hematocrit defined as ≤ 35%.

*p < 0.05, statistically significant differences.
**Table 5. Multivariable regression: 30-day morbidity**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>1.02</td>
<td>0.98–1.07</td>
<td>0.248</td>
</tr>
<tr>
<td>BMI (categorical)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nonobese</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Obese class I</td>
<td>1.21</td>
<td>0.60–2.46</td>
<td>0.589</td>
</tr>
<tr>
<td>Obese class II/III</td>
<td>1.37</td>
<td>0.64–2.94</td>
<td>0.421</td>
</tr>
<tr>
<td>Outpatient surgery setting</td>
<td>0.49</td>
<td>0.27–0.89</td>
<td>0.019*</td>
</tr>
<tr>
<td>Dependent functional status</td>
<td></td>
<td></td>
<td>0.998</td>
</tr>
</tbody>
</table>

Comorbidities

<table>
<thead>
<tr>
<th>_variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.71</td>
<td>0.80–3.66</td>
<td>0.165</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>4.26</td>
<td>1.62–11.23</td>
<td>0.003*</td>
</tr>
<tr>
<td>ASA PS classification grade &gt; III</td>
<td>1.64</td>
<td>0.86–3.12</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Preoperative laboratory values

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated creatinine</td>
<td>1.75</td>
<td>0.77–4.01</td>
<td>0.185</td>
</tr>
<tr>
<td>Elevated white blood cell count</td>
<td>4.06</td>
<td>1.91–8.64</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status.

Elevated creatine defined as ≥1.2 mg/dL. Elevated white blood cell count defined as ≥11 k/µL.

Dashed lines represent failed univariate analysis due to perfect correlation (complete separation).

*p < 0.05, statistically significant differences.

**Table 6. Multivariable regression: 30-day reoperation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>1.04</td>
<td>1.00–1.09</td>
<td>0.065</td>
</tr>
<tr>
<td>BMI (categorical)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nonobese</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
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<td>1.39</td>
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<td>2.46</td>
<td>0.97–6.25</td>
<td>0.059</td>
</tr>
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<td>0.37</td>
<td>0.17–0.80</td>
<td>0.011*</td>
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</table>

Comorbidities

<table>
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<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>4.65</td>
<td>1.31–16.55</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

ASA PS classification grade > III | 1.23 | 0.52–2.89 | 0.634 |

*OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status.

*p < 0.05, statistically significant differences.

**DISCUSSION**

As the rates of obesity continue to rise, there is high demand to understand its effect on surgical outcomes. While there exists strong evidence broadly supporting obesity as a risk factor for various spinal pathologies, there remains relatively little exploring the effect of obesity clinical outcomes of CDR. In the present study we looked to investigate if obesity is associated with a higher risk for early postoperative complications and outcomes following CDR. Utilizing the ACS-NSQIP database, we have shown that obesity was associated with an independent risk for 30-day readmission and nonhome discharge disposition. However, obesity was not significantly associated with the risk of postoperative morbidity outcomes.

Obesity was found to be a risk factor for 30-day readmission following CDR. When categorized, severe obesity (class II/III) was associated with a 3.32-fold increased 30-day readmission risk. Understanding risks of readmission has recently become of great interest. These unplanned readmissions for Medicare patients alone cost the federal government an estimated $17.4 billion annually, and so it is a point of focus to improve healthcare efficiency and affordability. Obesity as a risk factor for readmission risk has not yet been fully understood. While obesity has been shown as a risk for readmission in various surgical specialties, other analyses have found it as an insignificant factor. Here we have found that within the setting CDR, obesity does increased risk of readmission. 30-day reoperation rates were also analyzed. While obesity was not significantly associated with increased rates of reoperation, it is worth noting that.
with each class of obesity, the percentage of patients reoperated on increased. Obesity has been long shown in spine surgery to increase rates of operative complications.\textsuperscript{7,8,20,21} Jiang et al.\textsuperscript{21} conducted a meta-analysis of 32 studies and almost 100,000 patients looking at rates of complications amongst obese patients undergoing spine surgery. They found that various complications including surgical site infection, venous thromboembolism, mortality, revision rate, and blood loss were all increased amongst obese patients. Readmission and reoperation risks are highly associated with operative or postoperative complications.\textsuperscript{17,22} The increased risk of complications likely yields the outcomes of increased readmissions amongst obese patients. In an effort to improve patient quality of life and increase health care efficiency, further understanding how obesity mediates this increased risk of readmission and potential reoperation could be helpful. Obesity was also found as an independent risk factor for nonhome discharge disposition following CDR. In the multivariable analysis, obesity as a continuous variable was not associated with an increased risk for nonhome discharge but as a categorical variable, obesity class II/III was. In a similar way, it is likely obese patients have a higher comorbidity burden which is a significant factor in deciding the need for a nonhome discharge disposition.

Our analysis found various comorbidities associated with obesity that are in line with existing literature. Obesity was significantly associated with diabetes, dyspnea, hypertension, and bleeding disorders. It is also worth noting that when stratifying obesity by BMI, higher classes of obesity had even greater risks for these comorbidities. These findings are well in alignment with existing literature regarding the risks associated with obesity\textsuperscript{23,24} which provides some additional external validation of the data presented here. These various comorbidities were also associated with various complications. ASA physical status classification grade $\geq$ III was an independent risk factor for nonhome disposition and was a significant risk factor for readmission and morbidity on the univariate analysis. Individual co-morbidities were also analyzed. Dyspnea for example was a significant independent risk factor for 30-day reoperation. In the univariate analysis, various other comorbidities were associated with the worse outcomes investigated: dyspnea (readmission, nonhome discharge reoperation), hypertension (readmission, nonhome discharge), dialysis (readmission, nonhome discharge), diabetes (morbidity). So, while is possible that these other co-morbidities play an independent role, obesity was the only one constantly measure remaining significant across all the outcome measures in the multivariable analysis. In fact, these likely mediate the elevated risk of readmission and nonhome discharge seen in obese patients. In a similar way, we show that patients that underwent surgeries in ambulatory settings had decreased odds of readmission, reoperation, morbidity, and nonhome discharge. Patients whose surgeries are done in ambulatory centers tend to have lower comorbidity burdens, and thus we would expect them to be at lower risk for these complications.\textsuperscript{25}

Another potential explanation for the poorer outcomes found here independently associated with obesity following CDR is the increased surgical complexity associated with a larger body habitus. Previous studies have described longer set up times with more difficult patient positioning, the necessity for larger incisions, and more difficult retraction associated with more subcutaneous fat in spine surgery.\textsuperscript{26-28} Rosenfeld et al.\textsuperscript{29} additionally reported that preoperative and intraoperative radiographs were less accurate in obese patients and potentially required higher radiation doses, increasing the surgical difficulty in those cases. Anterior cervical surgery specifically may be additionally more challenging in patients with shorter necks and large neck circumferences. In ACDF surgeries, Qi et al.\textsuperscript{30} reported that neck circumference, neck length, and associated increased BMI were all risk factors for complications. The increased rates of readmission and nonhome discharge disposition for obese class II/III patients following CDR therefore may be partially explained by the increasing difficulty of surgeries in this population.

This study did have several limitations worth noting. Despite the large initial sample size of patients included in this analysis, the rates of various complications were very low. These complications may be too infrequent to elucidate significant differences without much larger sample sizes. This study is also prone to various limitations associated with the retrospective methodology employed. NSQIP is a prospective database that we have retrospectively reviewed. This methodology can lead to potential for selection bias in the analysis. Similarly, this study is prone to limitations associated with the usage of the NSQIP database itself. The database was curated from certain participating centers, which may not result in a representative sample of the whole population of patients undergoing CDR. Additionally, the differences in patient care are inevitable with such a database, and with such small rates of complications, such variances can affect the reproducibility of the data. Additionally, other comorbidities and complications were not recorded in this database, and these other factors may be important in assessing the risk of complications for obesity in CDR. Despite these limitations, we believe that the large sample size and quality data from NSQIP make the findings presented here valid and applicable for
Impact of Obesity on CDR Outcomes
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CDR. We additionally acknowledge that obesity can be part of a broader spectrum of metabolic disease so further research may be necessary to isolate obesity as an independent risk factor or analyze metabolic syndrome's impact on early outcomes following CDR.

CONCLUSION

Obesity is an epidemic and growing public health concern that costs the US an estimated $209.7 billion dollars annually. As such, it becomes increasingly important to truly understand the effects and risks on medical care and surgical procedures. Although the negative impacts of obesity have been reported as a general surgical risk factor for spine surgery, to our knowledge, our study is among the first to analyze its risk for early postoperative complications following CDR. In this analysis of over 5,000 patients, obesity was found to be a risk factor for readmission and nonhome discharge but was not associated with morbidity in these patients. Based on this analysis, we believe patients can safely undergo CDR without a significantly increased risk of complications, but appropriate counseling is still necessary.

NOTES

Supplementary Material: Supplementary Table 1 can be found via https://doi.org/10.14245/ns.2346442.221.

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Author Contribution: Conceptualization: TS, DS, JD, SI, SQ; Data curation: DS, IA, OM, EZ, KA; Formal analysis: TS, DS, IA, OM, EZ, KA; Methodology: TS; Project administration: JD, SI; Writing - original draft: TS, DS; Writing - review & editing: TS, PS, TA, JS, SD, JD, SI, SQ.

ORCID
Tejas Subramanian: 0000-0003-0323-6716
Daniel Shinn: 0000-0002-6729-4352
Pratyush Shahi: 0000-0003-4903-9697
Troy Amen: 0000-0003-0792-9739
Izzet Akosman: 0000-0002-1433-9078
Omri Maayan: 0000-0002-2581-5447
Eric Zhao: 0009-0000-0869-9379
Kasra Araghi: 0000-0003-0061-2640
Junho Song: 0000-0002-4853-4736
Sidhant Dalal: 0000-0002-4114-6116
James Dowdell: 0000-0001-9852-4133
Srvatisht Iyer: 0000-0002-8338-9757
Sheeraz Qureshi: 0000-0002-7177-1756

REFERENCES


### Supplementary Table 1. Univariate regression

<table>
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<tr>
<th>Variable</th>
<th>30-Day readmission</th>
<th>Nonhome discharge</th>
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<th>30-Day morbidity</th>
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<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.04 (1.01–1.06)</td>
<td>0.005*</td>
<td>1.06 (1.04–1.09)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.07 (1.04–1.1)</td>
<td>&lt; 0.001*</td>
<td>1.06 (1.03–1.1)</td>
<td>&lt; 0.001*</td>
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<tr>
<td>BMI (categorical)</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
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<tr>
<td>Nonobese</td>
<td>2.06 (1.03–4.14)</td>
<td>0.042*</td>
<td>1.31 (0.58–2.97)</td>
<td>0.52</td>
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<td>Obese class I</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
<td></td>
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<tr>
<td>Obese class II/III</td>
<td>3.87 (2.7–7.47)</td>
<td>&lt; 0.001*</td>
<td>4.12 (2.11–8)</td>
<td>&lt; 0.001*</td>
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<tr>
<td>Female sex</td>
<td>1.04 (0.6–1.8)</td>
<td>0.895</td>
<td>0.75 (0.41–1.36)</td>
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<tr>
<td>Black race</td>
<td>0.76 (0.24–2.44)</td>
<td>0.64</td>
<td>1.22 (0.43–3.41)</td>
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</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>3.02 (1.18–7.68)</td>
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<td>5.32 (2.34–12.05)</td>
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<td>0.5 (0.29–0.87)</td>
<td>0.015*</td>
<td>0.3 (0.16–0.57)</td>
<td>&lt; 0.001*</td>
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<td>Dependent functional status</td>
<td>9.45 (2.17–4.17)</td>
<td>0.003*</td>
<td>10.99 (2.52–47.62)</td>
<td>0.001*</td>
</tr>
<tr>
<td>2-Level CDR</td>
<td>1.57 (0.87–2.84)</td>
<td>0.139</td>
<td>1.78 (0.95–3.32)</td>
<td>0.073</td>
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<td>Comorbidities</td>
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<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.66 (0.74–3.7)</td>
<td>0.217</td>
<td>1.98 (0.88–4.44)</td>
<td>0.101</td>
</tr>
<tr>
<td>Current smoker within 1 year</td>
<td>1.24 (0.65–2.37)</td>
<td>0.524</td>
<td>0.89 (0.41–1.92)</td>
<td>0.765</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.42 (1.05–11.17)</td>
<td>0.042*</td>
<td>4 (1.22–13.16)</td>
<td>0.022*</td>
</tr>
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<td>Severe COPD</td>
<td>2.59 (0.62–10.82)</td>
<td>0.193</td>
<td>-</td>
<td>0.997</td>
</tr>
<tr>
<td>Hypertension requiring medication</td>
<td>-</td>
<td>0.999</td>
<td>-</td>
<td>0.999</td>
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<tr>
<td>Dialysis</td>
<td>35.62 (0.82–8.71)</td>
<td>0.102</td>
<td>41.67 (4.24–500)</td>
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<td>Chronic steroid use</td>
<td>2.68 (0.82–8.71)</td>
<td>0.127</td>
<td>0.98 (0.13–7.19)</td>
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<td>Bleeding disorder</td>
<td>4.84 (0.64–36.61)</td>
<td>0.001*</td>
<td>-</td>
<td>0.998</td>
</tr>
<tr>
<td>ASA PS classification grade &gt; III</td>
<td>2.54 (1.45–4.43)</td>
<td>0.001*</td>
<td>4.85 (2.65–8.85)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Wound class ≥ 2</td>
<td>-</td>
<td>0.999</td>
<td>-</td>
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<td>Preoperative laboratory values</td>
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<tr>
<td>Elevated creatinine</td>
<td>1.99 (0.88–4.48)</td>
<td>0.097</td>
<td>2.29 (0.95–5.56)</td>
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<td>Elevated white blood</td>
<td>1.74 (0.62–4.9)</td>
<td>0.293</td>
<td>2.7 (1.05–6.99)</td>
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<td>Low hemocrit</td>
<td>2.3 (0.82–6.48)</td>
<td>0.115</td>
<td>4.42 (1.83–10.64)</td>
<td>&lt; 0.001*</td>
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<tr>
<td>Low platelet</td>
<td>1.7 (0.41–7.1)</td>
<td>0.467</td>
<td>1.97 (0.47–8.26)</td>
<td>0.354</td>
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OR, odds ratio; CI, confidence interval; BMI, body mass index; CDR, cervical disc replacement; COPD, chronic obstructive pulmonary disease; ASA PS, American Society of Anesthesiologists physical status.

Dashed lines represent failed univariate analysis due to perfect correlation (complete separation).

*p < 0.05, statistically significant differences.
Risk Factors of Restenosis After Full Endoscopic Foraminotomy for Lumbar Foraminal Stenosis: Case-Control Study

Jong Hun Seo, Chang Il Ju, Seok Won Kim, Seung Myung Lee, Pius Kim
Department of Neurosurgery, College of Medicine, Chosun University, Gwangju, Korea

Objective: To investigate risk factors associated with postoperative restenosis after full endoscopic lumbar foraminotomy (FELF) in patients with lumbar foraminal stenosis (LFS).

Methods: A single-center, retrospective case-control study was conducted on patients diagnosed with foraminal stenosis who underwent FELF between August 2019 and April 2022. The study included 56 patients, comprising 18 cases and 38 controls. Clinical data, radiologic assessments, and surgical types were compared between the groups. The cutoff values of radiologic parameters that differentiate the 2 groups were investigated.

Results: No significant difference in age, sex distribution, or presence of adjacent segment disease or grade I spondylolisthesis was observed between the groups. Cases had a higher degree of disc wedging angle (DWA) (3.0° ± 1.1° vs. 0.5° ± 1.4°, p < 0.001), larger coronal Cobb angle (CCA) (8.8° ± 5.1° vs. 4.7° ± 2.5°, p = 0.004), and smaller segmental lumbar lordosis (SLL) than controls (11.0 ± 7.4 vs. 18.0 ± 5.4, p = 0.001). Optimal cutoff values for DWA, CCA, and SLL were estimated as 1.8°, 7.9°, and 17.1°, respectively. A significant difference in surgical types was observed between cases and controls (p = 0.004), with the case group having a higher distribution of patients undergoing discectomy in addition to TELF.

Conclusion: The study identified potential risk factors for restenosis after FELF in patients with LFS, including higher DWA, larger CCA, smaller SLL angle. We believe that discectomy should be performed with caution during FELF, as it can lead to subsequent restenosis.

Keywords: Lumbar foraminal stenosis, Endoscopic spine surgery, Transforaminal endoscopic lumbar foraminotomy, Restenosis

INTRODUCTION

Lumbar foraminal stenosis (LFS) is responsible for approximately 8% to 11% of degenerative lumbar spine diseases. As the clinical characteristics of this condition have become more widely recognized, the importance of surgical intervention has grown. Surgical treatments for LFS can generally be categorized into neural decompression and fusion procedures. Fusion is often necessary due to the frequent association of intervertebral foraminal stenosis with various degenerative changes. However, elderly patients or those with chronic diseases face a higher risk of postoperative complications related to general anesthesia and blood loss, leading to an increased preference for minimally invasive treatment methods in recent years.

Consequently, endoscopic surgery, a form of minimally invasive spine surgery, has undergone significant advancements over the past 2 decades, providing a beneficial treatment option for elderly patients at high risk for complications related to general anesthesia. Historically, the use of endoscopic spine surgery was limited to the lumbar spine, but through the efforts of various researchers, its applicability has expanded to include the cervical and thoracic spine as well as a broader range of patho-
logical conditions, such as spinal stenosis, intervertebral foraminal stenosis, and complex lesions. Recent studies have even reported successful endoscopic surgical outcomes for tumor lesions, comparable to traditional surgery. One of the most significant achievements of endoscopic surgery is its ability to largely replace fusion procedures in the treatment of intervertebral foraminal stenosis.

Nonetheless, it is uncertain whether the duration and durability of symptom relief and the risk of stenosis recurrence with endoscopic decompression alone of the intervertebral foramen can be compared to the fusion technique, which offers both neural decompression and structural stabilization. This represents a key challenge that the endoscopic approach needs to address. Therefore, this study aims to examine the risk factors associated with postoperative restenosis, a primary reason for reoperation following full endoscopic lumbar foraminotomy (FELF) in patients with LFS. To the best of our knowledge, this is the first study to compare restenosis cases after FELF to a control group.

MATERIALS AND METHODS

1. Study Populations

Prior to the start of this study, the Institutional Review Board of Chosun University Hospital approved for the research design (CHOSUN 2023-04-029). This retrospective study was conducted in a single center on patients diagnosed with foraminal stenosis who underwent full FELF for foraminal stenosis from August 2019 to April 2022. Participants were selected based on the following inclusion criteria: (1) 18 years of age and older with a diagnosis of symptomatic moderate or severe intervertebral foraminal stenosis, (2) clear evidence of foraminal stenosis observed on lumbar magnetic resonance imaging (MRI) with corresponding lower extremity radicular pain, (3) symptom not improving after at least 3 months of nonsurgical treatment.

Exclusion criteria were as follows: (1) inconsistency between MRI findings and symptoms, (2) patients where low back pain is the main symptom rather than lower extremity radicular pain, (3) presence of spondylolytic spondylolisthesis of grade 2 or higher, (4) presence of segmental instability, (5) coexistence of severe grades 3–4 central spinal canal stenosis, (6) coexistence of other pathological conditions such as infection, trauma, or tumors, (7) cases of lumbar disc extrusion or sequestration.

2. Selection of Cases and Control Group

The definition of restenosis after FELF in this study, which served as the criteria for selecting the patient group, was as follows: (1) improvement in lower extremity radicular pain for at least one month after FELF surgery, (2) recurrence of lower extremity radicular pain in the same location within 1 year after surgery, (3) radiologic confirmation of foraminal stenosis recurrence at the same site as the initial surgery. The control group criteria were set as not having any clinical symptom recurrence and no radiological evidence of restenosis for at least one year after FELF surgery. To increase the statistical power of the independent variables, a control group twice the size of the case group was collected.

3. Clinical Data Collection

Basic clinical indicators of all selected patients, including age, sex, surgical level, and follow-up period, were collected. Clinical outcomes were assessed using the visual analogue scale (VAS), preoperatively, postoperatively and at 6-month follow-up. In terms of surgical technique, whether the basic TELF procedure was performed and whether additional discectomy was performed were investigated.

4. Radiologic Assessment

To evaluate the relationship between imaging findings and restenosis, a range of baseline radiologic parameters were obtained from preoperative static and dynamic simple radiograph of all study participants in both the case and control groups. The differences between the groups were then analyzed using statistical methods. Parameters that showed significant differences between groups were analyzed to calculate receiver operating characteristic curve, area under curve (AUC), optimal cutoff value, sensitivity, and specificity using statistical software. Their respective measurement methods are as follows (Fig. 1): (1) Total lumbar lordotic angle: angle measured between the upper endplate of L1 and the upper endplate of S1, (2) Segmental lordotic angle (SLA): angle measured between the upper endplate of upper vertebra and the lower endplate of lower vertebra, (3) Coronal Cobb angle (CCA): angle measured between the most tilted top vertebrae and the most tilted bottom vertebrae, (4) Disc height (DH): half the sum of the anterior and posterior heights of disc, (5) Foraminal height (FH): distance between the pedicles, (6) Disc wedging angle (DWA): angle between the inferior endplate of the upper vertebra and superior endplate of the lower vertebra. A positive value indicates disc wedging towards the side of the lesion, while a negative value indicates disc wedging on the side opposite the lesion. In case of L5/S1 level, angle between the upper endplate of L5 and the line connecting the top of bilateral sacral ala, (7) Dynamic SLA: differ-
ence of SLA between flexion and extension posture.

5. Statistical Analysis

Statistical evaluations were conducted using R ver. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All variables underwent descriptive statistical analysis, and appropriate statistical methods were used for comparisons between groups when necessary. For continuous variables, the normality of values was assessed for each variable, and either Welch T-test or Wilcoxon rank-sum test was used for analysis, depending on the appropriate method. Categorical variables were analyzed using either Pearson chi-square test or Fisher exact test, after checking the expected frequencies in the contingency table cells. A statistical significance level of 0.05 was set for evaluating significance.

6. Surgical Procedure

Intramuscular midazolam (0.05 mg/kg) and intravenous fentanyl (0.8 μg/kg) were administered as preoperative treatments, and the patient was conscious and underwent surgery with local anesthesia and a transforaminal epidural block. All patient was placed in the prone position on a radiolucent operating table, with the knees and hips slightly flexed to reduce the lumbar lordotic curve. All procedures were performed via a full endoscopic transforaminal approach, and an out-in technique was used to minimize exiting nerve root (ENR) irritation of the narrowed intervertebral foramen and facilitate resolution of the circumferential stenosis. For sufficient decompression of the ENR, the extent of bone work was planned through preoperative MRI, computed tomography, and x-ray evaluation, and the need for bone work in the superior articular process as well as the isthmus, lower pedicle of upper body, and upper endplate

Fig. 1. Measurement of radiologic parameters. (A) Coronal Cobb angle (CCA), disc wedging angle (DWA). (B) Total lumbar lordotic angle (TLA). (C) Disc height (DH), foraminal height (FH), segmental lordotic angle (SLA). (D, E) Dynamic segmental lordotic angle.
of lower body was determined preoperatively. If preoperative examination revealed a vertical or circumferential foraminal stenosis, removal of the protruding disc and osteophyte was planned. After removing the protruding disc and osteophytes, if the possibility of disc reprotrusion was expected, interbody discectomy was performed (Fig. 2). So, surgical procedures were classified into 2 types as follows: (a) TELF without discectomy, (b) TELF with discectomy.

(a) TELF without discectomy: Exposure of the ENR has been confirmed by sufficient bone resection and soft tissue removal such as ligamentum flavum, foraminal ligament, and fatty tissue. And then, the ENR was retracted to remove the protruding disc and osteophyte, if deemed necessary by the preoperative imaging evaluation. (b) TELF with discectomy: After the (a) procedure, interbody disc removal was performed.

7. Illustrative Case

A 62-year-old male patient presented with left leg radiating pain from the lateral thigh down to the anterolateral leg, with no history of previous back surgery. Preoperative MRI revealed narrowing of the left L3/4 intervertebral foramen (Fig. 3A), preoperative x-ray showed increased CCA and decreased total and SLA, and disc wedging to the lesion side (positive DWA) with overall DH reduction at L3/4 (Fig. 3D, E). Postoperative MRI showed dilatation of the L3/4 foramen (Fig. 3B), but approximately 6 months later, due to recurrent left lower extremity radicular pain, an MRI scan was performed and the L3/4 foramen was found to be narrowed again (Fig. 3C).

RESULTS

1. Patient Characteristics

A total of 56 patients were included in this case-control study, comprising 18 cases and 38 controls. The average age was 68.9 years for cases and 65.6 years for controls, with no significant difference in age (p = 0.3384) or sex distribution (p = 1.000) between the 2 groups. In the case group, the most common surgical level was L4–5 and L5–S1 and followed by L3–4. While in the control group, the most common surgical level was L5–S1, followed by L4–5 and L3–4. There was no significant difference in the presence of adjacent segment disease or grade I spondylolisthesis between the groups. Preoperative and postoperative VAS scores were comparable between the 2 groups. However, VAS scores at 6 months follow-up were significantly higher in
cases compared to controls (5.8 ± 1.1 vs. 2.2 ± 0.9, p < 0.001). The follow-up period was longer for cases than controls (22.3 ± 6.8 months vs. 17.2 ± 3.5 months, p = 0.007). The mean time to recurrence for cases was 7.4 ± 2.4 months. Complications were rare, with only 1 case each of dysesthesia and motor weakness. In the control group, dysesthesia occurred in 2 patients, and no motor weakness was reported. Other than that, there were no other major complications. These findings are summarized in Table 1.

2. Radiologic Parameters

Baseline radiologic parameters were compared between case and control groups (Table 2). There were no significant differences between the groups in DH, FH, total lumbar lordosis angle and dynamic segmental angle. However, cases had a higher degree of DWA (3.0° ± 1.1° vs. 0.5° ± 1.4°, p < 0.001) and larger CCA (8.8° ± 5.1° vs. 4.7° ± 2.5°, p = 0.004) than controls. SLA was

Fig. 3. An illustrative case of 62-year-old male patient. (A) Preoperative magnetic resonance imaging (MRI) showing foraminal stenosis at the L3/L4 level (arrow). (B) Postoperative MRI illustrating foraminal decompression following resection of the superior articular process, lower endplate, removal of ligamentum flavum, protruding disc, bony spur, and interbody disc (arrow). (C) Postoperative 6-month MRI revealing recurred foraminal restenosis at the L3/L4 level (arrow). (D, E) Preoperative simple radiograph demonstrating increased coronal Cobb angle, decreased lumbar lordotic angle (total lumbar lordotic angle, segmental lordotic angle), and increased disc wedging angle on the lesion side. (F, G) Intraoperative endoscopic view presenting the decompressed exiting nerve root.

Fig. 4. Boxplot illustrating the distribution of disc wedging angle, coronal Cobb angle, and segmental lordotic angle by groups.
Risk Factors of Restenosis After Endoscopic Lumbar Foraminotomy

Seo JH, et al.

Risk Factors of Restenosis After Endoscopic Lumbar Foraminotomy

Table 1. Demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 18)</th>
<th>Controls (n = 38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68.9 ± 7.5</td>
<td>65.6 ± 9.8</td>
<td>0.338</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (44.4)</td>
<td>17 (45)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (55.6)</td>
<td>23 (55)</td>
<td>1.000</td>
</tr>
<tr>
<td>Surgical level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3–4</td>
<td>2 (11.1)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>L4–5</td>
<td>8 (44.4)</td>
<td>17 (44.7)</td>
<td></td>
</tr>
<tr>
<td>L5–S1</td>
<td>8 (44.4)</td>
<td>20 (52.6)</td>
<td>0.377</td>
</tr>
<tr>
<td>ASD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1 (5.6)</td>
<td>1 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>17 (94.4)</td>
<td>37 (97.4)</td>
<td>0.544</td>
</tr>
<tr>
<td>Spondylolisthesis, grade I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3 (16.7)</td>
<td>1 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>15 (83.3)</td>
<td>37 (97.4)</td>
<td>0.093</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>8 ± 1.4</td>
<td>7.8 ± 1.4</td>
<td>0.602</td>
</tr>
<tr>
<td>Postoperative</td>
<td>3.4 ± 1.5</td>
<td>2.8 ± 1.5</td>
<td>0.166</td>
</tr>
<tr>
<td>F/U 6 months</td>
<td>5.8 ± 1.1</td>
<td>2.2 ± 0.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Time to recurrence (mo)</td>
<td>7.4 ± 2.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>F/U period (mo)</td>
<td>22.3 ± 6.8</td>
<td>17.2 ± 3.5</td>
<td>0.007*</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>1 (5.6)</td>
<td>2 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Motor weakness</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as means ± standard deviation or number (%). ASD, adjacent segment degeneration; VAS, visual analogue scale; F/U, follow-up. *p < 0.05, statistically significant differences.

Table 2. Comparisons of baseline radiologic parameters between case and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 18)</th>
<th>Controls (n = 38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc height</td>
<td>7.5 ± 2.5</td>
<td>8.3 ± 2.0</td>
<td>0.246</td>
</tr>
<tr>
<td>Foraminal height</td>
<td>15.6 ± 2.5</td>
<td>15.4 ± 2.2</td>
<td>0.798</td>
</tr>
<tr>
<td>Disc wedging angle (°)</td>
<td>3.0 ± 1.1</td>
<td>0.5 ± 1.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Coronal Cobb angle (°)</td>
<td>8.8 ± 5.1</td>
<td>4.7 ± 2.5</td>
<td>0.004*</td>
</tr>
<tr>
<td>Total lumbar lordosis angle (°)</td>
<td>33.2 ± 10.8</td>
<td>35.9 ± 10.2</td>
<td>0.395</td>
</tr>
<tr>
<td>Segmental lordotic angle (°)</td>
<td>11.0 ± 7.4</td>
<td>18.0 ± 5.4</td>
<td>0.001*</td>
</tr>
<tr>
<td>Dynamic segmental angle (°)</td>
<td>9.4 ± 4.9</td>
<td>7.6 ± 3.7</td>
<td>0.123</td>
</tr>
</tbody>
</table>

Values are presented as means ± standard deviation. *p < 0.05, statistically significant differences.

Table 3. Recommended cutoff values of radiologic parameters significantly associated with restenosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>Cutoff value (°)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc wedging angle</td>
<td>0.969</td>
<td>1.8</td>
<td>94.4</td>
<td>92.1</td>
</tr>
<tr>
<td>Coronal Cobb angle</td>
<td>0.757</td>
<td>7.9</td>
<td>55.6</td>
<td>92.1</td>
</tr>
<tr>
<td>Segmental lordotic angle</td>
<td>0.775</td>
<td>17.1</td>
<td>83.3</td>
<td>60.5</td>
</tr>
</tbody>
</table>

Values are presented as area under curve.

3. Surgical Types

Table 4 shows the comparison of surgical types between case and control groups in detail. In the case group, the distribution of surgical types was as follows: TELF without discectomy (12 patients, 66.7%) and TELF with discectomy (6 patients, 33.3%). In the control group, the distribution was: TELF without discectomy (36 patients, 94.8%), TELF with discectomy (2 patients, 5.2%).

Table 4. Comparison of surgical types between case and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 18)</th>
<th>Controls (n = 38)</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical type</td>
<td></td>
<td></td>
<td>0.12</td>
<td>0.01–0.63</td>
<td>0.017*</td>
</tr>
<tr>
<td>TELF without discectomy</td>
<td>12 (66.7)</td>
<td>36 (94.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TELF with discectomy</td>
<td>6 (33.3)</td>
<td>2 (5.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%). OR, odds ratio; CI, confidence interval; TELF, transforminal endoscopic lumbar foraminotomy. *p < 0.05, statistically significant differences.
The case group had a higher rate of patients undergoing discectomy in addition to TELF rather than the control group. In the control group, most patients underwent TELF without discectomy. With an odds ratio of 0.12, not performing discectomy was found to be more favorable for the development of restenosis. This difference was statistically significant (p = 0.017), indicating an association between surgical types and the risk of restenosis after endoscopic foraminotomy for LFS.

DISCUSSION

Apart from foraminal lesions, simple central stenosis, disc herniation, and other lesions without accompanying instability can typically be treated initially using nonfusion techniques. Unstable LFS with segmental instability, however, is commonly addressed with fusion techniques as the gold standard. In contrast, stable LFS without segmental instability has traditionally been treated with fusion techniques, which are the primary target subset in minimally invasive spine surgery to be replaced by nonfusion surgery. Consequently, numerous authors have sought to perform foraminotomy without fusion using both microscopic and endoscopic methods, achieving significant results. Long-established microscopic approaches have been introduced by Ozeki et al.\textsuperscript{14} and Park et al.\textsuperscript{15} Now, with the development of equipment such as endoscopic drills, lasers, and radiofrequency probes, the applicability and therapeutic effects of full endoscopic foraminotomy have been demonstrated by various authors.\textsuperscript{12,16-21}

Foraminotomy for LFS offers the benefits of motion preservation and reduced concern about adjacent segment degeneration, but it also appears to have disadvantages compared to fusion. According to the review of Ju and Lee,\textsuperscript{22} for complications following foraminotomy, the primary complications include recurrent stenosis with incidental durotomy, motor weakness, and dysesthesia. Technical issues, such as the surgeon's level of experience, may cause complications other than recurrent stenosis, but recurrent stenosis can occur even with complete nerve decompression achieved during surgery. This complication should be treated as a problem inherent in the surgical method called FELF, relating to its reliability and durability. It has been a significant concern for endoscopic surgeons due to limitations like the inability to entirely replace fusion surgery in cases of restenosis, resulting in the need for additional revision fusion surgery. Thus, identifying the risk factors for restenosis is a crucial first step in refining FELF into a more reliable and robust surgical technique.

In our study, preoperative baseline radiologic parameters indicated that DH was lower and FH was higher in the case group compared to the control group, DWA and CCA at the surgical level were angled towards the lesion, total lumbar lordosis angle and SLA were reduced, and dynamic segmental angle was high. Among these parameters, DWA, CCA, and SLA were found to be statistically significant risk factors, with DWA being the strongest. Additionally, SLA showed a more significant difference between the groups than total lumbar lordosis angle, suggesting that local alignment deserves more attention than global alignment. Data published by Haimoto et al.\textsuperscript{23} studying risk factors for restenosis after microscopic foraminotomy reported similar findings, with DWA being the most statistically significant risk factor. Some differences in statistical significance between the 2 studies may be due to the difference in power related to the number of samples. The data of Yamada et al.\textsuperscript{24} on recurrence after microscopic decompression for LFS identified degenerative lumbar scoliosis as a significant risk factor, suggesting that coronal alignment significantly affects restenosis. These findings are similar to those of this study. However, we found no other significant differences in risk factors attributable to technical differences between microscopic and endoscopic techniques for LFS.

When performing TELF, the rationale for conducting additional discectomy in the interbody space alongside TELF for protruded discs is to prevent the potential risk of postoperative disc material leakage and symptom recurrence. However, our data showed that the rate of TELF without discectomy in the control group was significantly higher, and the rate of TELF with discectomy in the case group was higher than the control group, with an odds ratio of 0.12, with a statistically significant difference. This result suggests that additional discectomy of the interbody space, which has been performed based on surgeon preference to prevent postoperative recurrence of foraminal disc herniation, is a risk factor for recurrence. While preemptively performing discectomy can remove the nucleus pulposus that may herniate later, it can also lower the DH on the ipsilateral side. Therefore, from the pathophysiologic perspective of foraminal stenosis, it may develop the vertical or circumferential stenosis and cause symptoms to recur.\textsuperscript{1} As a result, it is essential to achieve neural decompression through proper bone work, soft tissue removal, and careful resection of protruding disc and bony spur. However, it is recommended to avoid performing discectomy in the interbody space.

This study is a retrospective case-control investigation with a limited sample size, which implies that the evidence is relatively weak. To obtain stronger evidence, it would be essential to vali-
The study findings indicate that greater DWA toward the lesion, larger CCA, smaller SLA as a baseline radiologic parameter, and the inclusion of discectomy as part of the surgical procedure may be associated with a higher likelihood of restenosis after FELF for LFS. As a result, it is recommended that surgeons exercise caution when planning FELF surgery, taking care to avoid unnecessary discectomy during the procedure. By adopting these measures, it is anticipated that the risk of restenosis can be minimized, thereby optimizing patient outcomes, and reducing the need for further interventions.

NOTES

Conflict of Interest: The authors declare no conflicts of interest.
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Author Contribution: Conceptualization: JHS, CJJ, SWK, SML; Data curation: JHS; Formal analysis: PK; Funding acquisition: PK; Methodology: CJJ, SWK, SML; Project administration: SML; Visualization: CJJ, PK; Writing - original draft: JHS, PK; Writing - review & editing: JHS.

ORCID
Jong Hun Seo: 0009-0006-6802-3403
Chang Il Ju: 0000-0001-9123-2808
Seok Won Kim: 0000-0002-1910-0242
Seok Myung Lee: 0000-0003-1548-8435
Pius Kim: 0000-0001-5514-9257

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raminal lumbar disc herniations—operative technique. World Neurosurg 2019;130:244-53.
The Morphological Evaluation of the Cervical Muscle in Patients With Basilar Invagination: A Magnetic Resonance Imaging-Based Study

Junyu Lin1,2,*, Panjie Xu1,*, Jianying Zheng1, Zhang Zefan1, Jingwen Tan1, Hang Xiao1, Siyan Yu3, Qingan Zhu1, Wei Ji1

1 Division of Spinal Surgery, Department of Orthopaedics, Nanfang Hospital, Southern Medical University, Guangzhou, China
2 Department of Orthopaedics and Traumatology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
3 Department of Clinical Nutrition, Affiliated Cancer Hospital and Institute of Guangzhou Medical University, Guangzhou, China

Objective: To investigate the characteristics of functional muscle and muscle size in patients with basilar invagination (BI) and explore the effects of atlantoaxial dislocation.

Methods: Eighty BI patients (BI group) and 80 age- and sex-matched asymptomatic people (control group) were included. Axial T2 magnetic resonance imaging image was used to measure the cross-sectional area (CSA) and functional CSA (FCSA). The sternocleidomastoid (SCM), longus capitis and longus colli (LCap & LC), trapezius (Trap), splenius capitis (SpCap), splenius cervicis (SpC), semispinalis capitis (SSCap), semispinalis cervicis (SSC), multifidus (MS), levator scapulae (LS) and posterior deep layer muscles (PDLM) were evaluated. Correlations between age, atlantodental interval (ADI), Chamberlain distance and muscles were observed.

Results: BI group (39.4 ± 18.4 years; 33 males/47 females) exhibited significantly lower FCSA/CSA ratios than the control group in all extensor and flexor muscles, and presented smaller CSAs on the right and left Trap, SSC, LS, SCM, and left LCap & LC. FCSA/CSA ratios were significantly lower in BI patients with dislocation on the right Trap, SpCap, SpC, SSCap, MS, LS, LCap & LC, and PDLM, and the left SSCap, MS, and LCap & LC than in patients without deformity. Additionally, functional muscles of all parameters decreased with age in BI patients. Excluding children, the Trap, SpC, MS, and LS muscle sizes of BI patients tended to increase with age. ADI and Chamberlain distance tended to correlate negatively with FCSA/CSA ratio.

Conclusion: The BI patients, especially those with atlantoaxial dislocation, had less functional muscles compared with the control group. Moreover, their functional muscles decreased with age more obviously.

Keywords: Cross-sectional area, Functional cross-sectional area, Basilar invagination, Cervical muscle, Magnetic resonance imaging

INTRODUCTION

Basilar invagination (BI) is known as deformity of the cranio-cervical junction (CVJ) region with or without clinical neural symptoms.1-3 Our team conducted a series of research, focused on the changes in skeletal anatomy in BI patients and reported the characteristics of CVJ structures.4-6 We previously found that the BI patients presented stiffer cervical alignment than the asymptomatic population.6 It was deduced that the cervical muscles might contribute to the consequences. However, to the best
of our knowledge, paraspinal muscle morphology has not been reported in BI patients.

The musculoskeletal function plays an important role in spinal stability. The paraspinal muscles have been widely studied in cervical spine-related diseases. Patients who had lost cervical lordosis had smaller muscle size in semispinalis capitis and cervical extensor muscles than normal people. Individuals with chronic idiopathic neck pain had larger muscle volumes of the sternocleidomastoid (SCM). The fatty infiltration and asymmetry of cervical muscles were associated with clinical outcomes in patients with degenerative cervical myelopathy or cervical spondylotic myelopathy. The fatty infiltration of muscles was also studied in cervical deformity patients and was found to be alleviated after surgical correction and the achievement of lordotic curvature.

Since the physiotherapy and rehabilitation of BI patients commonly focus on the management of cervical musculoskeletal function after surgery or conservative treatments, understanding the morphology and features of cervical muscle in BI patients could guide medical workers to better treat patients and promote clinical efficiency. Therefore, this study aimed to investigate the characteristics of functional muscle and muscle size in BI patients and explore the effects of atlantoaxial dislocation in the cervical musculoskeletal system.

MATERIALS AND METHODS

1. Study Participants

This is a retrospective study, involving 80 BI patients (BI group) in our hospital in the past decade. Another 80 asymptomatic people (control group) were included by matching the age and sex of the BI group. Due to the skewed distribution of age of BI patients, we roughly divided all subjects into 4 age groups as following: (1) children group with age <18 years old; (2) young adults with age between 18 and 40 years old; (3) middle-aged adults with age between 41 and 55 years old; (4) old adults with age >55 years old. The Ethic Committee of Nanfang Hospital approved this study (NFEC-BPE-120) and waived the procedure of informed consent.

The inclusive criteria were: (1) For BI group, although BI may be caused by multifactors, the inclusion of BI patients is mainly based on gold standard in radiological image: the odontoid process 5 mm (at least) above the Chamberlain line for BI group; Patients met with the above criteria will be included, regardless of other kinds of accompanied malformation such as congenital Chiari malformation, syringomyelia, occipitalization of the atlas, atlantoaxial dislocation and extensive cervical vertebral fusions; (2) For control group, subjects should have no congenital malformation at the cervical spine; (3) For both groups, all subjects should have clear T2-weighted magnetic resonance imaging (MRI) images on cervical spine with at least one image on axial view at the intervertebral disc. Images on sagittal view were used to confirm the disc levels. The exclusive criteria were: (1) only T1-weighted MRI image was available, or T2-weighted MRI image with low quality; (2) surgical history with implants on divus, occipital, or cervical spine; (3) inflammation, tumors, or obvious space-occupying lesions on cervical muscles or bone structure; (4) diagnosis of cervical spondylotic, intervertebral disc herniation, or other severe degenerative diseases which were known to affect the cervical muscles.


Ten pairs of muscles, including the superficial and deep layers and anterior and posterior muscles, were selected in this study (Figs. 1, 2). To be specific, the anterior muscles were SCM, longus capitis (LCap), and longus colli (LC). Since it was difficult to identify the boundary between LCap and LC in upper cervical spine on MRI images, they were measured as a union muscle. The posterior muscles were trapezius (Trap), splenius capitis (SpCap), splenius cervicis (SpC), semispinalis capitis (SSCap), semispinalis cervicis (SSC), multifidus (MS) and levator scapulae (LS). Furthermore, the muscles posterior to the vertebra in deep layers, excluding the Trap, were also measured as a union muscle, and defined as posterior deep layer muscles (PDLM).

The preoperative T2-weighted MRI images (Fig. 2) were captured and reconstructed via a 3.0T MRI scanner (Siemens Medical Solutions, Erlangen, Germany). Axial MRI images were aligned parallel to the inferior endplate of the vertebral body. Images on axial view at cervical disc level were used. Image on midsagittal view was used to determine the disc level. The muscle boundary was identified by referring to the cervical muscle atlas of healthy person. The ImageJ software ver. 1.48 (National Institute Health, Bethesda, MD, USA) was used to measure the muscle size and functional muscle. Details have been reported elsewhere. Briefly, the axial image was imported into the software, converted to 8-bit type, and reset at the proper scale. Then 4 to 6 ellipses were drawn on lean muscle as sample regions of interest (ROIs), carefully avoiding any visible pixel of fat. The maximum and minimum signal intensity values of sample ROIs were regarded as the highest and lowest thresholds of lean muscle, respectively. This calibration procedure was conducted for
every cervical disc level of each subject to minimize measurement error. The cross-sectional area (CSA) of muscle was measured, and then the determined thresholds were applied to measure the lean muscle as functional cross-sectional area (FCSA). The ratio of FCSA to CSA (FCSA/CSA ratio) was further calculated. The mean CSA and FCSA/CSA ratio of all disc levels were calculated, respectively, for statistical analyses.

Additionally, the axial computed tomography (CT) image of BI patients were used to measure the atlantodental interval (ADI), distance between the posterior margin of anterior arch of C1 and the anterior margin of C2. The BI patients will be diagnosed with atlantoaxial dislocation if the ADI was greater than 3 mm in adults and greater than 5 mm in children. The distance from the odontoid to Chamberlain line (line between hard palate and posterior margin of foramen magnum) in BI patients was also measured on sagittal CT image.

3. Statistical Analyses
IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA) was used to conduct statistical analyses. Student t-test or Mann-Whitney U-test was used to compare the differences between groups. Pearson correlation test was used to analyze the correlations. The results were presented as mean ± standard deviation and p < 0.05 indicated statistical difference.

4. Reliability Analyses
Regarding the cervical muscular CSA and FCSA/CSA ratio, both the intraobserver and interobserver reliability results showed good agreements (intraclass correlation coefficient [ICC] > 0.8).

RESULTS

1. Demography
Both BI and control groups contained 80 subjects (33 males,
47 females), with a mean age of 39.4 ± 18.4 years and 38.9 ± 17.4 years, respectively. Moreover, both BI and control groups consisted of 14 children, 26 young adults, 26 middle-aged adults and 14 older adults, respectively. In the BI group, there were 43 subjects with atlantoaxial dislocation (46.7 ± 14.6 years, 10 males, 33 females) and 37 subjects without (30.8 ± 18.9 years, 23 males, 14 females). Regarding the dislocation rate, the females (70.2%, 33 of 47) had a higher rate than males (30.3%, 10 of 33), while the adults (62.1%, 41 of 66) showed a higher rate than children (14.3%, 2 of 14).

2. Muscular Morphology in BI and Control Groups

Overall, the BI group exhibited significantly lower FCSA/CSA ratios than the control group, all p = 0.000 (Table 1). In children, only the FCSA/CSA ratios on the right SpCap and the left Trap were higher in the BI group than in the control group. In young adults, except for the FCSA/CSA ratio on the left SpC, the rest of the indicators were lower in the BI group than in the control group. In middle-aged and older adults, the FCSA/CSA ratios of all the muscles were lower in the BI group than in the control group.

As shown in Table 2, the BI group had smaller muscle sizes than the control group on the right and left Trap, SSC, LS, SCM, and left LCap & LC. However, the BI group had larger muscle sizes on the right SpCap and SSCap. In children, muscle size of the right MS was larger in BI group than in control group. In young adults, the BI group presented smaller muscle size on the right Trap, SpC, LS, SCM, and LCap & LC, left Trap, LS, SCM, and LCap & LC. In middle-aged adults, the BI group presented smaller muscle sizes on the right Trap, SSC, LS, and LCap, left Trap, SSC, and LS, but larger muscle sizes on the right SpCap. In older adults, the BI group presented smaller muscle sizes on the right Trap and LS, but larger muscle sizes on the right and left MS.

3. Muscular Morphology in BI Patients With and Without Atlantoaxial Dislocation

As shown in Table 3, the BI patients with atlantoaxial dislocation had significant lower FCSA/CSA ratios on the right Trap, SpCap, SpC, SSCap, MS, LS, LCap & LC, and PDLM, and on the left SSCap, MS, and LCap & LC than the BI patients without dislocation. The dislocation population also tended to present lower FCSA/CSA ratios on the right SSC and SCM and the left Trap, SpCap, SpC, SSC, LS, SCM, and PDLM, without statistical significance.

The BI patients with atlantoaxial dislocation had significant smaller muscle sizes on the right and left PDLM. The dislocation population tended to present larger muscle sizes on the right and left Trap, SCM, and LCap & LC, but smaller muscle sizes on the right and left SpCap, SpC, SSCap, SSC, MS, and LS without significant difference.

4. Correlation Between Age and Muscular Morphology

For functional muscle, in control group, the age correlated negatively with FCSA/CSA ratios on the right SSCap, left SpC, SSCap, and SCM, but positively with FCSA/CSA ratios on the right Trap and SSC, left Trap and SSC. In BI group, the age correlated negatively with FCSA/CSA ratios on the right Trap, SpCap, SpC, SSCap, MS, LS, and LCap & LC, as well as on the left Trap, SpCap, SpC, SSCap, LS, SCM, and PDLM (Table 4; Fig. 3A, B).

For muscle size, in control group, the age correlated positively with muscle sizes on the right Trap, SpC, LS, and PDLM, and the left Trap, SpC, LS, and SCM, but negatively with muscle sizes on the right MS and the left MS. In BI group, the age corre-
Table 1. Comparisons of functional muscle between basilar invagination (BI) and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects</th>
<th>Children</th>
<th>Young adults</th>
<th>Middle adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (%)</td>
<td>BI (%)</td>
<td>p-value</td>
<td>Control (%)</td>
<td>BI (%)</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trap</td>
<td>73.9 ± 14.2</td>
<td>57.9 ± 22.0</td>
<td>0.000*</td>
<td>71.7 ± 15.2</td>
<td>82.1 ± 14.7</td>
</tr>
<tr>
<td>SpCap</td>
<td>79.8 ± 9.4</td>
<td>64.9 ± 19.4</td>
<td>0.000*</td>
<td>77.6 ± 11.1</td>
<td>86.4 ± 10.4</td>
</tr>
<tr>
<td>SpC</td>
<td>80.0 ± 12.2</td>
<td>63.2 ± 21.3</td>
<td>0.000*</td>
<td>87.0 ± 10.2</td>
<td>85.8 ± 11.1</td>
</tr>
<tr>
<td>SSCap</td>
<td>73.9 ± 10.3</td>
<td>55.9 ± 18.0</td>
<td>0.000*</td>
<td>82.0 ± 6.9</td>
<td>78.5 ± 13.0</td>
</tr>
<tr>
<td>SSC</td>
<td>79.3 ± 12.2</td>
<td>60.7 ± 14.6</td>
<td>0.000*</td>
<td>74.0 ± 18.3</td>
<td>75.5 ± 13.9</td>
</tr>
<tr>
<td>MS</td>
<td>61.8 ± 13.8</td>
<td>44.2 ± 18.1</td>
<td>0.000*</td>
<td>55.1 ± 10.4</td>
<td>50.2 ± 18.9</td>
</tr>
<tr>
<td>LS</td>
<td>86.0 ± 6.6</td>
<td>76.0 ± 12.5</td>
<td>0.000*</td>
<td>88.0 ± 7.6</td>
<td>88.5 ± 8.4</td>
</tr>
<tr>
<td>SCM</td>
<td>85.3 ± 7.3</td>
<td>74.9 ± 13.3</td>
<td>0.000*</td>
<td>88.9 ± 7.0</td>
<td>86.4 ± 10.9</td>
</tr>
<tr>
<td>LCap &amp; LC</td>
<td>82.6 ± 9.9</td>
<td>70.2 ± 18.9</td>
<td>0.000*</td>
<td>88.1 ± 6.3</td>
<td>88.8 ± 8.1</td>
</tr>
<tr>
<td>PDLM</td>
<td>67.3 ± 8.9</td>
<td>50.4 ± 12.3</td>
<td>0.000*</td>
<td>63.5 ± 7.4</td>
<td>55.8 ± 13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trap</td>
<td>74.5 ± 12.7</td>
<td>62.3 ± 19.2</td>
<td>0.000*</td>
<td>74.4 ± 12.6</td>
<td>84.8 ± 12.3</td>
</tr>
<tr>
<td>SpCap</td>
<td>81.5 ± 8.3</td>
<td>71.4 ± 17.7</td>
<td>0.000*</td>
<td>83.2 ± 6.2</td>
<td>84.9 ± 21.3</td>
</tr>
<tr>
<td>SpC</td>
<td>81.2 ± 11.0</td>
<td>71.1 ± 19.2</td>
<td>0.000*</td>
<td>87.8 ± 6.0</td>
<td>91.0 ± 8.6</td>
</tr>
<tr>
<td>SSCap</td>
<td>74.2 ± 9.7</td>
<td>58.7 ± 17.6</td>
<td>0.000*</td>
<td>84.8 ± 4.8</td>
<td>84.1 ± 10.0</td>
</tr>
<tr>
<td>SSC</td>
<td>78.9 ± 11.8</td>
<td>60.4 ± 17.5</td>
<td>0.000*</td>
<td>74.5 ± 19.4</td>
<td>69.5 ± 29.0</td>
</tr>
<tr>
<td>MS</td>
<td>60.4 ± 13.2</td>
<td>42.5 ± 17.5</td>
<td>0.000*</td>
<td>55.4 ± 10.5</td>
<td>51.6 ± 20.4</td>
</tr>
<tr>
<td>LS</td>
<td>80.6 ± 6.5</td>
<td>79.2 ± 11.1</td>
<td>0.000*</td>
<td>87.8 ± 4.2</td>
<td>90.0 ± 4.8</td>
</tr>
<tr>
<td>SCM</td>
<td>84.6 ± 7.9</td>
<td>77.2 ± 11.7</td>
<td>0.000*</td>
<td>90.7 ± 3.4</td>
<td>87.5 ± 9.1</td>
</tr>
<tr>
<td>LCap &amp; LC</td>
<td>83.1 ± 9.6</td>
<td>72.7 ± 16.5</td>
<td>0.000*</td>
<td>87.1 ± 8.4</td>
<td>89.8 ± 10.3</td>
</tr>
<tr>
<td>PDLM</td>
<td>67.3 ± 8.3</td>
<td>54.1 ± 11.3</td>
<td>0.000*</td>
<td>65.0 ± 6.5</td>
<td>59.9 ± 14.2</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

* p < 0.05, statistically significant differences. † These parameters were analyzed with Student t-test, while the rest of the parameters used Mann-Whitney U-test.
Table 2. Comparisons of muscle size between basilar invagination (BI) and control groups

| Variable | All subjects | Control (mm²) | BI (mm²) | P-value | Children | Control (mm²) | BI (mm²) | P-value | Young adults | Control (mm²) | BI (mm²) | P-value | Middle adults | Control (mm²) | BI (mm²) | P-value | Elderly | Control (mm²) | BI (mm²) | P-value |
|----------|--------------|---------------|----------|---------|----------|---------------|----------|---------|--------------|---------------|----------|---------|--------------|---------------|----------|---------|---------|----------|---------------|----------|---------|
| Trap     | 342.0 ± 197.2 | 232.0 ± 213.9 | 0.000*  | 118.7 ± 110.7 | 87.6 ± 48.3 | 0.581†  | 323.8 ± 169.8 | 258.1 ± 269.4 | 0.017*  | 398.3 ± 156.0 | 246.2 ± 201.8 | 0.001*  | 494.4 ± 190.0 | 302.5 ± 167.1 | 0.009*†  |
| SpCap    | 195.4 ± 69.8  | 225.0 ± 81.8  | 0.011*  | 155.6 ± 56.9  | 189.7 ± 81.2 | 0.232†  | 225.2 ± 67.2  | 232.8 ± 87.9  | 0.942†  | 189.9 ± 52.8  | 234.3 ± 79.5  | 0.013*  | 190.2 ± 93.6  | 228.6 ± 73.2  | 0.118†  |
| SpC      | 54.3 ± 23.2   | 49.3 ± 23.1   | 0.106†  | 28.0 ± 15.4   | 35.7 ± 29.2  | 0.598†  | 58.9 ± 22.7   | 46.8 ± 23.4  | 0.032*  | 65.9 ± 19.1   | 57.0 ± 21.4   | 0.086†  | 50.7 ± 16.7   | 50.1 ± 16.9   | 0.923†  |
| SSCap    | 237.5 ± 89.2  | 266.9 ± 101.4 | 0.046†  | 192.1 ± 80.4  | 216.9 ± 99.6 | 0.481†  | 279.1 ± 89.3  | 293.9 ± 104.7 | 0.812†  | 235.3 ± 84.2  | 270.7 ± 95.6  | 0.124†  | 209.6 ± 80.2  | 256.3 ± 98.9  | 0.129†  |
| SSC      | 132.1 ± 40.4  | 153.7 ± 47.4  | 0.003*  | 107.1 ± 29.3  | 130.4 ± 92.3 | 0.782†  | 143.2 ± 52.9  | 119.7 ± 41.4  | 0.838†  | 129.3 ± 31.9  | 102.8 ± 38.7  | 0.002†  | 139.7 ± 27.1  | 124.2 ± 39.7  | 0.09†   |
| MS       | 125.7 ± 37.5  | 134.0 ± 60.9  | 0.631†  | 140.0 ± 39.4  | 183.7 ± 28.9 | 0.007**†  | 139.7 ± 29.4  | 126.1 ± 60.5  | 0.318†  | 105.7 ± 36.3  | 106.2 ± 61.2  | 0.366†  | 122.5 ± 37.2  | 162.1 ± 46.8  | 0.020**† |
| LS       | 236.9 ± 96.7  | 153.7 ± 65.6  | 0.004*  | 143.8 ± 83.2  | 110.8 ± 53.3 | 0.412†  | 243.5 ± 77.3  | 152.6 ± 70.4  | 0.000*  | 261.6 ± 69.9  | 161.8 ± 69.6  | 0.000*  | 272.0 ± 130.5 | 174.2 ± 44.9  | 0.004*† |
| SCM      | 305.8 ± 109.1 | 262.7 ± 92.8  | 0.027*  | 207.0 ± 86.2  | 176.8 ± 113.5 | 0.232†  | 351.2 ± 97.5  | 290.6 ± 73.9  | 0.015**†  | 315.7 ± 95.6  | 272.9 ± 77.1  | 0.137†  | 302.2 ± 119.2 | 278.7 ± 85.7  | 0.556†   |
| LCap & LC | 97.8 ± 35.6  | 85.0 ± 31.9   | 0.068†  | 68.0 ± 26.5   | 50.8 ± 29.8  | 0.119†  | 120.9 ± 37.6  | 101.0 ± 32.2  | 0.046**†  | 91.0 ± 22.2  | 86.6 ± 21.4  | 0.470†  | 97.5 ± 35.2  | 86.5 ± 25.2  | 0.679†   |
| PDLM     | 1,304.7 ± 350.4 | 1,286.9 ± 343.4 | 0.599†  | 1,042.9 ± 402.1 | 1,188.3 ± 413.9 | 0.355†  | 1,394.6 ± 317.0 | 1,306.8 ± 335.6 | 0.337†  | 1,361.1 ± 280.7 | 1,303.7 ± 329.3 | 0.22†  | 1,294.9 ± 378.6 | 1,317.3 ± 325.1 | 0.748†   |

Value is presented as mean ± standard deviation. Traps, Trapezius; SpCap, splenius capitis; SpC, splenius cervicis; SSCap, semispinalis capitis; SSC, semispinalis cervicis; MS, multifidus; LS, levator scapulae; SCM, sternocleidomastoid; LCap and LC, longus capitis and Longus colli; PDLM, posterior deep layer muscles.

*P < 0.05, statistically significant differences. These parameters were analyzed with Student t-test, while the rest of the parameters used Mann-Whitney U-test.
Table 3. Comparisons of functional muscle and muscle size between basilar invagination (BI) patients with and without atlantoaxial dislocation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Functional muscle (%)</th>
<th>p-value</th>
<th>Muscle size (mm²)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BI without dislocation</td>
<td>BI with dislocation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trap</td>
<td>63.7 ± 23.8</td>
<td>53.0 ± 19.3</td>
<td>0.030*†</td>
<td>184.4 ± 146.8</td>
</tr>
<tr>
<td>SpCap</td>
<td>71.4 ± 17.7</td>
<td>59.2 ± 19.3</td>
<td>0.007*</td>
<td>229.8 ± 93.0</td>
</tr>
<tr>
<td>SpC</td>
<td>70.0 ± 23.2</td>
<td>58.1 ± 18.5</td>
<td>0.019*</td>
<td>51.8 ± 28.2</td>
</tr>
<tr>
<td>SSCap</td>
<td>62.3 ± 17.9</td>
<td>50.5 ± 16.3</td>
<td>0.003*ª</td>
<td>291.8 ± 123.0</td>
</tr>
<tr>
<td>SSC</td>
<td>65.4 ± 13.7</td>
<td>56.8 ± 14.4</td>
<td>0.06</td>
<td>118.9 ± 55.1</td>
</tr>
<tr>
<td>MS</td>
<td>49.9 ± 18.8</td>
<td>39.5 ± 16.3</td>
<td>0.013*ª</td>
<td>149.1 ± 65.4</td>
</tr>
<tr>
<td>LS</td>
<td>79.4 ± 13.6</td>
<td>73.3 ± 10.9</td>
<td>0.007*</td>
<td>159.2 ± 70.8</td>
</tr>
<tr>
<td>SCM</td>
<td>76.4 ± 15.0</td>
<td>73.5 ± 11.7</td>
<td>0.171</td>
<td>261.9 ± 110.8</td>
</tr>
<tr>
<td>LCap &amp; LC</td>
<td>75.9 ± 15.8</td>
<td>65.2 ± 20.1</td>
<td>0.014*</td>
<td>82.3 ± 37.4</td>
</tr>
<tr>
<td>PDLM</td>
<td>53.9 ± 12.9</td>
<td>47.3 ± 10.9</td>
<td>0.034*</td>
<td>1382.5 ± 389.9</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trap</td>
<td>64.1 ± 23.3</td>
<td>60.8 ± 15.1</td>
<td>0.503</td>
<td>176.4 ± 133.9</td>
</tr>
<tr>
<td>SpCap</td>
<td>74.1 ± 18.1</td>
<td>69.0 ± 17.2</td>
<td>0.181</td>
<td>209.3 ± 75.0</td>
</tr>
<tr>
<td>SpC</td>
<td>76.0 ± 20.0</td>
<td>67.3 ± 17.9</td>
<td>0.095</td>
<td>55.4 ± 28.6</td>
</tr>
<tr>
<td>SSCap</td>
<td>64.1 ± 18.7</td>
<td>54.1 ± 15.5</td>
<td>0.011*ª</td>
<td>291.8 ± 134.1</td>
</tr>
<tr>
<td>SSC</td>
<td>63.3 ± 19.9</td>
<td>58.1 ± 15.2</td>
<td>0.219¹</td>
<td>119.0 ± 41.2</td>
</tr>
<tr>
<td>MS</td>
<td>48.6 ± 19.1</td>
<td>37.7 ± 16.6</td>
<td>0.011*ª</td>
<td>148.6 ± 56.3</td>
</tr>
<tr>
<td>LS</td>
<td>81.0 ± 11.3</td>
<td>77.7 ± 10.9</td>
<td>0.109</td>
<td>172.7 ± 70.1</td>
</tr>
<tr>
<td>SCM</td>
<td>79.0 ± 12.9</td>
<td>75.7 ± 10.6</td>
<td>0.19</td>
<td>261.9 ± 106.6</td>
</tr>
<tr>
<td>LCap &amp; LC</td>
<td>78.2 ± 14.5</td>
<td>67.9 ± 16.9</td>
<td>0.006*</td>
<td>84.6 ± 37.3</td>
</tr>
<tr>
<td>PDLM</td>
<td>56.2 ± 12.6</td>
<td>52.2 ± 9.9</td>
<td>0.157</td>
<td>1377.6 ± 389.3</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
Traps, trapezius; SpCap, splenius capitis; SpC, splenius cervicis; SSCap, semispinalis capitis; SSC, semispinalis cervicis; MS, multifidus; LS, levator scapulae; SCM, sternocleidomastoid; LCap & LC, longus capitis and Longus colli; PDLM, posterior deep layer muscles.
* p < 0.05, statistically significant differences.
† These parameters were analyzed with Student t-test, while the rest of the parameters used Mann-Whitney U-test.

lated positively with muscle sizes on the right Trap, SpC, LS, SCM, and LCap & LC, the left Trap, SpC, and SCM (Table 4; Fig. 3C, D).

Excluding children, correlation between age and muscle sizes in adults alone are shown in Supplementary Table 1.

5. Correlation Between ADI, Chamberlain Distance, and Muscles in BI Patients

The ADI tended to correlate negatively with FCSA/CSA ratios on most of the target muscles without significant difference. The ADI also tended to correlate negatively with muscle sizes on most of the target muscles, especially on the right and left SSCap and PDLM.

The Chamberlain distance tended to present negative correlation with the FCSA/CSA ratios but tended to show positive correlation with the muscle sizes on most of the target muscles. However, no significant difference was observed.

Details are shown in Supplementary Tables 2 and 3.

DISCUSSION

This is the first research to investigate the cervical muscle morphology in BI patients by comparing with the age- and sex-matched asymptomatic people. The effects of atlantoaxial dislocation on muscles were also firstly explored in this study.

To summarize, less functional muscles were presented in all
Table 4. Correlations between age and muscular morphology in basilar invagination (BI) and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Functional muscle</th>
<th>Muscle size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>BI</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trap</td>
<td>0.347</td>
<td>0.002*</td>
</tr>
<tr>
<td>SpCap</td>
<td>0.142</td>
<td>0.208</td>
</tr>
<tr>
<td>SpC</td>
<td>-0.161</td>
<td>0.155</td>
</tr>
<tr>
<td>SSCap</td>
<td>-0.285</td>
<td>0.011*</td>
</tr>
<tr>
<td>SSC</td>
<td>0.31</td>
<td>0.005*</td>
</tr>
<tr>
<td>MS</td>
<td>0.112</td>
<td>0.322</td>
</tr>
<tr>
<td>LS</td>
<td>-0.004</td>
<td>0.972</td>
</tr>
<tr>
<td>SCM</td>
<td>-0.13</td>
<td>0.251</td>
</tr>
<tr>
<td>LCap &amp; LC</td>
<td>-0.175</td>
<td>0.121</td>
</tr>
<tr>
<td>PDLM</td>
<td>0.031</td>
<td>0.787</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trap</td>
<td>0.288</td>
<td>0.009*</td>
</tr>
<tr>
<td>SpCap</td>
<td>-0.052</td>
<td>0.644</td>
</tr>
<tr>
<td>SpC</td>
<td>-0.269</td>
<td>0.016*</td>
</tr>
<tr>
<td>SSCap</td>
<td>-0.424</td>
<td>0.000*</td>
</tr>
<tr>
<td>SSC</td>
<td>0.309</td>
<td>0.006*</td>
</tr>
<tr>
<td>MS</td>
<td>0.06</td>
<td>0.594</td>
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<tr>
<td>LS</td>
<td>-0.074</td>
<td>0.514</td>
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<tr>
<td>SCM</td>
<td>-0.296</td>
<td>0.008*</td>
</tr>
<tr>
<td>LCap &amp; LC</td>
<td>-0.153</td>
<td>0.176</td>
</tr>
<tr>
<td>PDLM</td>
<td>-0.06</td>
<td>0.596</td>
</tr>
</tbody>
</table>

r, Pearson correlation; Trap, trapezius; SpCap, splenius capitis; SpC, splenius cervicis; SSCap, semispinalis capitis; SSC, semispinalis cervicis; MS, multifidus; LS, levator scapulae; SCM, sternocleidomastoid; LCap & LC, longus capitis and Longus colli; PDLM, posterior deep layer muscles.

*p < 0.05, statistically significant differences.

anterior and posterior and superficial and deep layer muscles in young adults, middle-aged adults and the elderly with BI, but not in children. Additionally, the BI patients mainly presented smaller muscles sizes on the Trap, SSC, LS, SCM, and LCap & LC, but larger muscle sizes on the SpCap and SSCap. Moreover, BI patients with atlantoaxial dislocation tended to have less functional muscles in all parameters, especially on the Trap, SpCap, SpC, SSCap, MS, LS, LCap & LC, and PDLM, than those without dislocation. The muscle sizes of parameters were similar between BI patients with and without dislocation, but the muscle size of PDLM was smaller in dislocation population. Furthermore, the functional muscles of all target muscles decreased with age in BI patients, which was more obvious than in the control group. Interestingly, the ADI tended to correlate negatively with both FCSA/CSA ratio and CSA of most parameters, while the Chamberlain distance tended to correlate negatively with FCSA/CSA ratio but positively with CSA of most parameters.

1. Excessive Use Caused Muscle Fatigue and Dysfunction

One of the biomechanical roles of cervical musculoskeletal function is to maintain the stability of head and cervical spine. The excessive use of muscle would cause muscle fatigue and even dysfunction. Due to the prolapse of odontoid into the foramen magnum, the medulla oblongata and spinal cord are compressed which result in neural symptoms in BI patients. The BI patient was found to present a stiffer neck. We deduced that the BI patient needed to maintain their cervical spine in a certain posture to reduce discomfort. Therefore, compared to control group, BI patients’ muscle function was extensively affected,

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Fig. 3. Panels A and B demonstrated the linear regression between age and FCSA/CSA ratio in right and left sides, respectively. Panels C and D demonstrated the linear regression between age and CSA in right and left sides, respectively. Blue circle and line indicated control group; green circle and line indicated BI group. CSA, cross-sectional area; FCSA, functional cross-sectional area; ratio, FCSA/CSA; L, right; R, right; Trap, trapezius; SpCap, splenius capitis; SpC, splenius cervicis; SSCap, semispinalis capitis; SSC, semispinalis cervicis; MS, multifidus; LS, levator scapulae; SCM, sternocleidomastoid; LCap_LC, longus capitis and longus colli; PDLM, posterior deep layer muscles.
involved all cervical muscle groups, after long-term intensive posture. Meanwhile, such change was progressive, as the FCSA/C CSA ratio decreased with age but was not obvious in children.

In addition, on the one hand, the BI patients with atlantoaxial dislocation had more severe cervical instability than those without dislocation, so that they needed to make more effort to maintain the CVJ region at neutral and relatively normal position and their muscular malfunction was more obvious. On the other hand, larger ADI and Chamberlain distance indicated more severe malformation in CVJ region, accompanied with more severe compression. Thus, to resist against the compression, muscular overuse might be more common in BI patients with larger ADI and Chamberlain distance. The ADI and Chamberlain distance represented the degree of compression and thus correlated negatively with functional muscle.

As an adaptive organ, muscle might initially develop compensatory hypertrophy to partially compensate for loss of muscle function. It explained the lack of obvious differences in both muscle function and size between BI and control groups in children. Additionally, the muscle size also positively correlated with Chamberlain distance, suggesting that it was a compensatory change to offset the loss of function.

2. Muscle Size and Function decreased in Patients With Malformation

To the best of our knowledge, the muscle morphology in BI patients had been rarely reported so far. Thakar et al. investigated the cervical paraspinal muscles in 25 patients with Chiari I malformation, a common complication of BI, and found that the dimension of cervical paraspinal muscles including superficial, deep flexor and extensor were smaller than that of the control group. The authors calibrated the muscle CSA with vertebra body CSA to eliminate biases in body size so that we could not directly compare our muscle CAS results with theirs. However, we observed the same tendency that the CSA of Trap, SSC, LS, SCM, and LCap & LC were smaller in BI patients. Moreover, we supposed that the FCSA/CSA ratio was more meaningful than muscle size, but it was absent in the study of Thakar et al.

BI is a kind of bony malformation in CVJ region. There are few studies about muscle function in patients with cervical deformity. Passias et al. measured the cervical extensor muscle, which consisted of 5 separate muscles, in patients with cervical deformity. The mean FCSA/TCSA ratio were 0.58 at baseline and 0.67 at first year post-operation in their study, while the FCSA/CSA ratio of PDLM were 52.22% in BI group and 67.32% in control group (average right and left sides) in ours. Their baseline data were similar to those of BI patients in our study. Meanwhile, although they did not measure muscle parameters in normal people, and the data of FCSA/TCSA ratio at first year post-operation were quite similar to those of control group in our study. This indicated a good agreement of muscle morphology between cervical deformity and BI patients. Passias et al. included both alignment and clinical symptoms in their study, and well associated these factors with muscle function. However, the sample size was too small (only 22 cases) comparing to ours (160 cases). Moreover, we identified the main extensor and flexor muscles and quantified each result, respectively, while Passias et al. measured 5 main extensor muscles as a union. Our research was the first study that measure the muscles separately as many as possible.

Another study from Passias et al. showed that patients with cervical deformity illustrated apparent fatty infiltration alterations in the posterior extensor musculature of the cervical spine, especially in the upper cervical spine. They also recommended that fatty infiltration as a predictor of postoperative sagittal alignment. The FCSA/TCSA ratio was 0.65 in the patients with cervical deformity, higher than that of PDLM in BI group (52.22%) but lower than the control group (67.32%) in our study. The difference may be due to different bone abnormality.

3. BI Is Not the Only Factors That Cause Abnormal Muscular Morphology

The abnormal morphology of muscle in BI patients could be resulted from various factors, such as age, muscular or bony malformation, or degenerative diseases. However, we believe that BI itself is the primary bony malformation and intrinsic cause of changes in muscular morphology.

A control group with age- and sex-matched subjects was used as comparison to BI group in this study. And for both groups, we excluded subjects with cervical spondylosis intervertebral disc herniation, or other severe degenerative diseases that were known to affect muscle size or function. These factors which might cause bias were eliminated as best as we could. Hence, although the degenerative changes etc. were not listed as independent variables, our data well supported the conclusion in this study.

Moreover, the present study mainly aimed to demonstrated the differences in muscle size and functional muscle between BI patients and control subjects basing radiological data. We agree that BI itself and related deformities on CVJ region are contributing factors. We did not systematically analyze the po-
Potential causes in current work. This is an interesting theme and we will collect more detailed patient data for further analyses in future study.

4. BI Patients Were Recommended to Take Early Exercise on Muscle

So far, most studies reported that the cervical/lumbar muscle were correlated with cervical/lumbar alignment (e.g., sagittal vertical axis) and clinical outcomes, such as visual analogue score and Neck Disability Index scores. Yoon et al.8 investigated the ratio of flexor to extensor muscle CSAs and found that it positively correlated with the cervical lordotic angle, recommending exercise programs to strengthen the extensor muscles. A randomized controlled trial proved that, in addition to conventional exercises, specific training of deep cervical flexor muscles could help subjects improve muscle endurance, pain, and disability.21 A pilot study reported that after 10-week systematic training on cervical muscles, the chronic whiplash patients presented significant increase in muscle size (MS and LCap & LC) and decrease in fatty infiltration (MS), with recovery of muscle strength and reduction of neck disability.22

The literature affirms the effect of cervical muscle training on cervical spine stability and muscle function. In the present study, the results indicated that functional muscles were less in BI patients and decreased with age with more obvious trends than control group. Furthermore, our previous study also revealed that BI patients presented the loss of cervical curvature. Therefore, early exercise on both cervical extensor and flexor muscles is necessary to alleviate fatty infiltration and strengthen muscle function. The cervical muscle training may even prevent BI patients from the exacerbation of clinical symptom as aging, because early intervention would provide BI patients better muscle strength, prevent the occurrence of atlantoaxial dislocation, and stop the progression of neural compression. With efficient muscle training, the BI patients may not require surgical treatment in the future.

5. Thresholding Technique to Qualify Muscle Function on MRI Images

The thresholding technique to measure the functional muscle by detecting the lean muscle has been well validated in the Fortin and Battie study in many published papers. The ICCs of ImageJ software varied between 0.78 and 0.99 in most muscular indicators, and excellent agreement was shown between muscle composition measurements using ImageJ and another software (inter-software ICCs: 0.81–0.99). Furthermore, a study investigated the inter- and intrarater reliability of a novice and an experienced rater, finding that (1) the intrarater ICCs varied between 0.84 and 0.99 for the novice rater, and varied between 0.94 and 0.99 for the experienced rater in all measurements of CSA and FCSA, (2) the interrater ICCs varied between 0.75 and 0.98 in CSA measurements, and varied between 0.60 and 0.77 in FCSA measurements. This method has been applied to assess the association between cervical muscle morphology and clinical outcomes in patients with degenerative cervical myelopathy. Hence, we believe the thresholding technique method is reliable and repeatable.

Some researchers indirectly estimated the muscle function by measuring the area of fat infiltration (FIA) and then calculating the FIA/CSA ratio, or further calculating FCSA/CSA ratio = 1–FIA/CSA ratio, in which they set up a threshold for fat and used this value for all measurements. However, this method lacked a calibration step. In this study, we measured the functional muscle directly, and the procedure contained a step of calibration for each slice and each subject. It helped to reduce the inter-individual and inter-slice difference, so that we believed our results were more reliable.

There are limitations in this study. Firstly, we did not include clinical outcome indicators. This was a retrospective study, and many BI patients were outpatients. It was difficult to collect all the information. It would be better to design a prospective study in the future. Secondly, it is preferable to normalize the muscle size with the CSA of intervertebral disc. However, we found that it was hard to recognize the margin of disc in some cases, which made it difficult to accurately measure the CSA of disc. Hence, we had to dismiss these data and skip the normalization.

CONCLUSION

The BI patients, especially those with atlantoaxial dislocation, had less functional muscles compared with the control group. Moreover, the functional muscles of most parameters decreased with age and tended to negatively correlate with ADI and Chamberlain distance. It would benefit the BI patients to take early muscle exercise. Our findings may have important implications for developing the knowledge of the association between cervical muscle and BI.

NOTES

Supplementary Material: Supplementary Tables 1-3 can be found via https://doi.org/10.14245/ns.2346302.151.
Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: JL, WJ; Data curation: JL, PX, JZ, ZZ, JT, HX, WJ; Formal analysis: JL, PX, SY; Funding acquisition: QZ, WJ; Methodology: JL, PX, JZ, ZZ, JT, HX; Project administration: QZ, WJ; Writing - original draft: JL, PX; Writing - review & editing: WJ.

ORCID
Junyu Lin: 0000-0002-1530-4408
Jianying Zheng: 0000-0003-3810-465X
Hang Xiao: 0009-0007-7440-5640
Siyan Yu: 0000-0002-6004-5409
Wei Ji: 0000-0001-8271-9411

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### Supplementary Table 1. Correlations between age and muscle size (CSA) in BI and control groups (adults only)

<table>
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CSA, cross-sectional area; BI, basilar invagination; r, Pearson correlation; Trap, trapezius; SpCap, splenius capitis; SpC, splenius cervicis; SSCap, semispinalis capitis; SSC, semispinalis cervicis; MS, multifidus; LS, levator scapulae; SCM, sternocleidomastoid; LCap & LC, longus capitis and Longus colli; PDLM, posterior deep layer muscles.

*p < 0.05, statistically significant differences.
### Supplementary Table 2. Correlations between ADI and parameters in BI groups

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BI, basilar invagination; ADI, atlantodental interval; r, Pearson correlation; Trap, trapezius; SpCap, splenius capitis; SpC, splenius cervicis; SSCap, semispinalis capitis; SSC, semispinalis cervicis; MS, multifidus; LS, levator scapulae; SCM, sternocleidomastoid; LCap & LC, longus capitis and Longus colli; PDLM, posterior deep layer muscles. *p < 0.05, statistically significant differences.
### Supplementary Table 3. Correlations between Chamberlain distance and parameters in BI groups

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BI, basilar invagination; r, Pearson correlation; Trap, trapezius; SpCap, splenius capitis; SpC, splenius cervicis; SSCap, semispinalis capitis; SSC, semispinalis cervicis; MS, multifidus; LS, levator scapulae; SCM, sternocleidomastoid; LCap & LC, longus capitis and Longus colli; PDLM, posterior deep layer muscles.
Correlation Between the Severity of Multifidus Fatty Degeneration and the Size of Ossification of Posterior Longitudinal Ligament at Each Spinal Level

Jinyoung Park1, Yong Eun Cho2, Kyung Hyun Kim2, Sanghoon Shin1, Sungjun Kim1, Chae Hwan Lim1, Seok Young Chung1, Yoon Ghil Park1

1Department of Rehabilitation Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
2Department of Neurosurgery, Spine and Spinal Cord Institute, Gangnam Severance Spine Hospital, Yonsei University College of Medicine, Seoul, Korea
3Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Objective: This study aimed to investigate the correlation between ossification of the posterior longitudinal ligament (OPLL) size and multifidus fatty degeneration (MFD), hypothesizing that larger OPLL sizes are associated with worse MFD.

Methods: One hundred four patients with cervical OPLL who underwent surgery were screened. OPLL occupying diameter and area ratios, the severity of MFD using the Goutallier classification, and range of motion (ROM) of cervical flexion-extension (ΔCobb) were measured. Correlation analyses between OPLL size, MFD severity, and ΔCobb were conducted. MFD severity was compared for each OPLL type using one-way analysis of variance.

Results: The final clinical data from 100 patients were analyzed. The average Goutallier grade of C2–7 significantly correlated with the average OPLL diameter and area occupying ratios, and OPLL involved vertebral level (r = 0.58, p < 0.01; r = 0.40, p < 0.01; r = 0.47, p < 0.01, respectively). The OPLL size at each cervical level significantly correlated with MFD of the same or 1–3 adjacent levels. ΔCobb angle was negatively correlated with the average Goutallier grade (r = -0.31, p < 0.01) and average OPLL occupying diameter and area ratios (r = -0.31, p < 0.01; r = -0.35, p < 0.01, respectively). Patients with continuous OPLL exhibited worse MFD than those with segmental OPLL (p < 0.01).

Conclusion: OPLL size is clinically correlated with MFD and cervical ROM. OPLL at one spinal level affects MFD at the same and 1–3 adjacent spinal levels. The worsening severity of MFD is associated with the longitudinal continuity of OPLL.

Keywords: Cervical spine, Multifidus, Ossification of posterior longitudinal ligament, Paraspinal muscles, Range of motion, Spinal canal

INTRODUCTION

Ossification of the posterior longitudinal ligament (OPLL) is a pathological process of ectopic ossification at the posterior longitudinal ligament of spine.1 Axially enlarged ossification can compress the spinal cord or mechanically irritate the spinal roots, thereby causing myeloradiculopathy. Severe neurological symptoms are sometimes accompanied by paralysis or gait disturbances that may require surgical treatment. Therefore, identifying prognostic factors in patients with OPLL can aid in determining the optimal clinical strategy for patients. OPLL has been suggested to have a multifactorial etiology owing to its...
poorly identified pathophysiology. Its genetic background has been identified, as presenting susceptible genes as follows: BMP2, BMP4, BMP 9, COL6A1, COL11A2, ESR1, IL-1β, IL-15RA, RUNX2, RXRB, TLR5, TGFβ1, TFG3, VDR, and HLA haplotype, etc. However, gene therapy for OPLL has not yet been implemented. Thus, identifying modifiable factors that influence the manifestation or progression of OPLL is more important.

Several hormones, including growth hormone, insulin-like growth factor, insulin, leptin, 1,25-dihydroxyvitamin D, parathyroid hormone, transforming growth factor-β, and bone morphogenetic protein, are correlated with the ossification of the spinal ligaments. Metabolic syndromes, such as diabetes mellitus, impaired glucose tolerance, and obesity, are also related to the prevalence of spinal hyperostosis.

However, little clinical evidence on the relationship between paraspinal muscle quality and OPLL severity currently exists. Among the paraspinal muscles, the important role of the multifidus in stabilising the spine and modulating spinal motion has been elucidated. Thus, multifidus dysfunction causes several clinical symptoms and signs contributing to spinal degeneration. The multifidus fatty degeneration (MFD) has been studied as a risk factor for spinal degeneration, including spinal stenosis and intervertebral disc degeneration. However, research on the correlation between OPLL and MFD is scarce, and as a consequence, there has been no study that includes MFD as an independent variable in analyzing the factors affecting the prognosis after OPLL surgery.

Thereby, the present study is designed to investigate the correlation between OPLL size and the severity of MFD, under the hypothesis that larger OPLL would be correlated with worse MFD, and is first to analyse the correlation by each cervical spinal level. As MFD was expected to be correlated with a decreased cervical range of motion (ROM); therefore, additional analyses of the dynamic radiographs were conducted.

MATERIALS AND METHODS

1. Study Design and Population

In the present cross-sectional study, 104 patients with cervical OPLL who underwent surgery between February 2015 and November 2017 at a tertiary hospital were screened. Prior to the operation, all patients underwent plain cervical spinal radiography of the anteroposterior (AP) and lateral views, as well as dynamography of the full flexion and extension positions and computed tomography (CT) of the cervical spine in the supine position. The CT images were acquired at 2-mm intervals, and reformatted to make sure that they were perpendicular to each vertebral axis also at 2-mm intervals. Patients’ data that met the following criteria were excluded: (1) a history of cervical spinal surgery, (2) combined thoracic OPLL, (3) inflammatory spondylitis (ankylosing spondylitis), and (4) insufficient medical records. The collected demographic data were age, sex, and height.

The study protocol was approved by the relevant Institutional Review Board (3-2021-0206) and complied with the principles of Good Clinical Practice and the Declaration of the World Medical Association. Informed consent was waived, because it was retrospective study and does not expose patient-identifiable information.

2. Radiologic Measurements

Two physiatrists participated in the radiologic measurements by reviewing the CT images and dynamograms. If the measured values differed from one another, a consensus was reached through discussion between these researchers. The OPLL sizes and Cobb angles were measured using the Picture Archiving and Communication System (Centricity PACS Radiology RA1000 Workstation, GE Healthcare, Barrington, IL, USA), which enables the display, manipulation, and editing of radiologic images.

1) OPLL size

Based on the axial section of preoperative CT, the AP diameter and area of the spinal canal and OPLL were measured at the maximal OPLL occupying axial image of each C2–7 level. The OPLL occupying diameter and area ratios were calculated as follows:

OPLL occupying diameter ratio = OPLL AP diameter/spinal canal AP diameter.
OPLL occupying area ratio = OPLL occupying area/spinal canal area.

2) Cervical ROM

To investigate the preoperative ROM in the sagittal plane of the cervical spine, Cobb angles were measured between C2–7 using preoperative dynamography performed with the patient in the standing position with full anterior flexion and posterior extension of the neck. The ΔCobb was calculated as the difference between Cobb angles of C2–7 when the cervical spine was fully flexed and extended.

3) K-line and OPLL involvement

As kyphosis line (K-line) has been utilized in making surgical
decisions in OPLL patients, patients in this study were categorized into K-line (+) group and K-line (-) group. The plane lateral view of the cervical spine in the neutral position was used in measurement. The K-line was drawn connecting the midpoints of the spinal canal at C2 and C7. Patients with OPLL that exceeded the K-line were labeled as K-line (-), whereas those who did not exceed the K-line were labeled as K-line (+).

4) Classification of MFD
The MFD at each C2–7 level was graded using the Goutallier classification on axial CT. The Goutallier classification is as follows: grade 0, normal muscle; grade 1, muscle contains fatty streaks; grade 2, fatty infiltration but more muscle than fat remains; grade 3, equal amounts of fat and muscle; grade 4, amount of fatty infiltration is greater than that of muscle. Among the multiple axial CT images of each spinal level, the one with the most severe MFD was selected and graded. Because the multifidus muscle supports the spine bilaterally, the higher Goutallier grade between those of the right and left multifidus was selected and used in the analysis. The average Goutallier grade of MFD at C2–7 and the grade of each spinal level were used in the analyses.

5) OPLL type
OPLL is divided into the following types according to the continuity of the ossified lesions: continuous, segmental, mixed, and localized.

3. Statistical Analysis
1) Data analysis
The baseline demographic characteristics were analysed using a t-test. Spearman correlation analyses were conducted between OPLL size (either the OPLL AP diameter or area occupying ratios), MFD, and cervical ROM, as these variables did not follow a normal distribution. One-way analysis of variance (ANOVA) was conducted to determine the severity of MFD for each OPLL type. The independent t-test was used to find the difference in OPLL size and the severity MFD between K-line (+) group and K-line (-) group. IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA) was used to perform all the analyses. A p-value of < 0.05 was considered statistically significant.

2) Sample size calculation
For correlation analyses, at least 76 samples were needed to adjust for an effect size of 0.55, an alpha value of 0.05, and 1-β (power) of 0.95, and more than 25 samples were needed for each OPLL type to enable 1-way ANOVA for 4 different OPLL types, adjusting for an effect size of 0.75, an alpha value of 0.2, and 1-β

Table 1. Clinical characteristics of cervical ossification of posterior longitudinal ligament patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristic</td>
<td></td>
</tr>
<tr>
<td>Age (yr), mean (range)</td>
<td>55.98 (32–83)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (69.0)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (31.0)</td>
</tr>
<tr>
<td>Height (cm), mean ± SD</td>
<td>166.47 ± 9.50</td>
</tr>
<tr>
<td>OPLL Topography of OPLL at the C2–7, mean ± SE</td>
<td></td>
</tr>
<tr>
<td>OPLL diameter occupying ratio</td>
<td>0.31 ± 0.01</td>
</tr>
<tr>
<td>OPLL area occupying ratio</td>
<td>0.19 ± 0.02</td>
</tr>
<tr>
<td>OPLL AP diameter (mm)</td>
<td>4.08 ± 0.17</td>
</tr>
<tr>
<td>Spinal canal diameter (mm)</td>
<td>13.42 ± 0.11</td>
</tr>
<tr>
<td>OPLL area (mm²)</td>
<td>40.91 ± 2.31</td>
</tr>
<tr>
<td>Spinal canal area (mm²)</td>
<td>245.7 ± 2.67</td>
</tr>
<tr>
<td>OPLL involved vertebral level</td>
<td>4.81 ± 1.18</td>
</tr>
<tr>
<td>Type of OPLL, n (%)</td>
<td></td>
</tr>
<tr>
<td>Continuous type</td>
<td>33/100 (33.0)</td>
</tr>
<tr>
<td>Segmental type</td>
<td>28/100 (28.0)</td>
</tr>
<tr>
<td>Mixed type</td>
<td>37/100 (37.0)</td>
</tr>
<tr>
<td>Localized type</td>
<td>2/100 (2.0)</td>
</tr>
<tr>
<td>Cervical range of motion (˚), mean ± SE</td>
<td></td>
</tr>
<tr>
<td>C2–7 Cobb angle of full flexion</td>
<td>-9.27 ± 1.08</td>
</tr>
<tr>
<td>C2–7 Cobb angle of full extension</td>
<td>18.16 ± 0.82</td>
</tr>
<tr>
<td>ΔCobb</td>
<td>27.43 ± 1.16</td>
</tr>
<tr>
<td>Multifidus fatty degeneration</td>
<td></td>
</tr>
<tr>
<td>Goutallier grade at the C2–7, mean ± SE</td>
<td>1.97 ± 0.38</td>
</tr>
<tr>
<td>Goutallier grade, n (%)</td>
<td>n = 600 spinal levels</td>
</tr>
<tr>
<td>Grade 0</td>
<td>19/600 (3.2)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>125/600 (20.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>345/600 (57.5)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>76/600 (12.7)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>35/600 (5.8)</td>
</tr>
<tr>
<td>Most degenerated level</td>
<td>C3</td>
</tr>
<tr>
<td>Least degenerated level</td>
<td>C2</td>
</tr>
</tbody>
</table>

SD, standard deviation; OPLL, ossification of posterior longitudinal ligament; AP, anteroposterior; SE, standard error; ΔCobb, C2–7 range of motion between full flexion-extension between. Goutallier classification system: grade 0, normal muscle; grade 1, some fatty streaks; grade 2, less than 50% fatty muscle atrophy; grade 3, 50% fatty muscle atrophy; grade 4, greater than 50% fatty muscle atrophy.
RESULTS

The clinical data of 100 patients in total were used in the analyses after 4 patients who had undergone previous spinal surgery were excluded.

1. Baseline Characteristics

The patients’ clinical characteristics are listed in Table 1. The average OPLL diameter and area occupying ratios of 6 cervical levels (C2–7) were 0.31 and 0.19, respectively. OPLL was frequent in the order of mixed, continuous, segmental, and localized types. The average Goutallier grade of the multifidus at the C2–7 level was 1.97. The mean AP ROM was 27.43°. C3 exhibited the most degeneration, whereas C2 exhibited the least (Tables 1 and 2, Fig. 1).

2. OPLL Size and MFD

The OPLL size was largest at the C4 level, followed by C5, C3, C6, C7, and C2 (Table 2, Fig. 1), and this result is correspondent to that of a previous study. The average Goutallier grades from C2–7 were significantly correlated with the average OPLL occupying diameter and area ratios of C2–7 (r = 0.58, p < 0.01, Fig. 2A; r = 0.40, p < 0.01, Fig. 2B, respectively). The OPLL size at each level of the cervical spine was significantly correlated with OPLL occupying ratio (%)

![Fig. 1. OPLL size and MFD of each spinal level from C2–7.](image)

Table 2. Characteristics of ossification of posterior longitudinal ligament and multifidus fatty degeneration by cervical levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cervical level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C2–7</td>
</tr>
<tr>
<td>OPLL size</td>
<td></td>
</tr>
<tr>
<td>OPLL diameter occupying ratio</td>
<td>0.31 ± 0.01</td>
</tr>
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</tr>
<tr>
<td>Multifidus fatty degeneration</td>
<td></td>
</tr>
<tr>
<td>Goutallier grade</td>
<td></td>
</tr>
<tr>
<td>Goutallier grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard error or number (%).
OPLL, ossification of posterior longitudinal ligament; AP, anteroposterior.
Goutallier classification system: grade 0, normal muscle; grade 1, some fatty streaks; grade 2, less than 50% fatty muscle atrophy; grade 3, 50% fatty muscle atrophy; grade 4, greater than 50% fatty muscle atrophy.
the MFD of the same level (Table 2). It also exhibited a significant correlation with the MFD of the 1–3 adjacent cervical spinal levels (Table 2, Fig. 3). In addition, OPLL involved vertebral level was positively correlated with the average Goutallier grades from C2–7 (r = 0.47, p < 0.01) by Pearson correlation analysis.

3. OPLL Size and Cervical ROM
The average OPLL occupying diameter ratio of C2–7 was negatively correlated with ΔCobb (r = -0.31, p = 0.02) (Fig. 2C) as was the average OPLL occupying area ratio of C2–7 (r = -0.35, p < 0.01) (Fig. 2D).

4. Cervical ROM and MFD
ΔCobb angle was negatively correlated with the average Goutallier grade of C2–7 (r = -0.31, p < 0.01) (Fig. 2E).

5. OPLL Size and MFD Severity According to OPLL’s K-Line Invasion
The K-line (−) group had higher OPLL diameter occupying ratio (p = 0.002) and OPLL area occupying ratio (p = 0.001), as well as a more OPLL involved vertebral level (p = 0.021) than K-line (+) group. The MFD in K-line (−) group was more than in the K-line (+) group (p = 0.005) (Supplementary Table 1).

6. MFD by OPLL Type
Prior analysis was conducted to examine the variation in age among subgroups of OPLL types, with the objective of validating the degree of severity of MFD specific to each OPLL type, while eliminating for the potential confounding influence of age on MFD measurements. Welch’s robust 1-way ANOVA and post hoc analysis were employed since the subgroups follow normality by Kolmogorov-Smirnov or Shapiro-Wilk analysis, with the exception of the localized type, which was observed in only

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Fig. 2. Correlation of average OPLL size, cervical range of motion, and average multifidus fatty degeneration of C2–7. The multifidus fatty degeneration (average Goutallier grade of C2–7) was significantly correlated with the average OPLL occupying diameter and area ratios of C2–7 (A: r = 0.58, p < 0.01; B: r = 0.40, p < 0.01, respectively). The anteroposterior cervical range of motion (ΔCobb) was significantly correlated with the average OPLL occupying diameter and area ratios of C2–7 (C: r = -0.31, p = 0.02; D: r = -0.35, p < 0.01, respectively). Multifidus fatty degeneration was significantly correlated with cervical range of motion (E; r = -0.31, p < 0.01). OPLL, ossification of posterior longitudinal ligament; ΔCobb, C2–7 range of motion between full flexion-extension between.
Multifidus Degeneration in Patients With Ligament Ossification

Fig. 3. Correlation of OPLL size and multifidus fatty degeneration of each cervical level of C2–7. The OPLL occupying diameter ratio (A) and area ratio (B) at each level of the cervical spine was significantly correlated with the multifidus fatty degeneration of the same level and 1–3 adjacent cervical spinal levels. OPLL, ossification of posterior longitudinal ligament. *p < 0.05. **p < 0.001.

Fig. 4. The severity of multifidus fatty degeneration for each OPLL type. The Goutallier classification was as follows: grade 0, normal muscle; grade 1, muscle contains fatty streaks; grade 2, fatty infiltration but more muscle than fat remains; grade 3, equal amounts of fat and muscle; grade 4, amount of fatty infiltration is greater than that of muscle. OPLL, ossification of posterior longitudinal ligament. *p < 0.05.

DISCUSSION

To the best of our knowledge, this is the first study to directly investigate the relationship between the severity of OPLL and MFD at each cervical spinal level. Clinical interest in the multifidus muscle in chronic spinal disease has been increasing, as it is an important stabiliser and mover of the spine. The multifidus, a pinnate muscle, attaches to the spinous process of the spine, stabilises the adjacent posterior side of the spine, and holds 2–3 spinal levels to allow the creation of higher torque, even with a small contractile force.

The pathogenesis of OPLL is thought to be multifactorial, and obtaining a clear explanation remains difficult. A significant correlation between the severity of MFD and OPLL size will play a significant role in elucidating the pathogenesis of OPLL. Some possible mechanisms are as follow: denervation, chronic inflammation, mechanotransduction, and disuse-induced muscular degeneration.

1. Denervation

Denervation of the peripheral nerve causes fatty degeneration of the target muscle. It has been studied at the molecular signalling level, revealing that denervation-activated fibro-ad-
ipogenic progenitors activate signal transducer and activator of transcription 3 (STAT3) and interleukin-6 (IL-6) and promote muscle atrophy and fibrosis. A study group demonstrated that inhibition of IL-6, Janus kinase, and STAT3 pathway suppresses the protein degradation pathway, thereby attenuating skeletal muscle atrophy. If OPLL invaded the neural foramen of the vertebra, the posterior rami of the spinal nerve, which innervates the multifidus muscle, would be irritated, causing radiculopathy, and may cause MFD pathohistologically.

2. Chronic Inflammation

Considering that the action of proinflammatory cytokines, such as IL-6, tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor-BB (PDGF-BB), are involved in the pathophysiology of ossifying spinal ligaments, inflammatory response is suggested to related to OPLL. A recent study revealed that IL-6 is more highly presented in continuous type OPLL than in segmental type OPLL. This result implies that inflammation may also be the reason why MFD is more severe in continuous compared to the segmental type in this present study. In addition, Nuclear factor-kB (NF-kB) activation was studied to positively correlate with the content of TGF-β1 and PDGF-BB in spinal ligament cells, which would contributes to osteoblastic differentiation. Considering NF-kB is associated with skeletal muscle atrophy or degeneration along with TNF-α or IL-6, an overall inflammatory condition in ligament and adjacent skeletal muscles are suspected in patients with OPLL presenting MFD. A study group elucidated that TNF expression in the multifidus muscle was greater in high levels of fat-infiltrated multifidus rather than low levels of fat infiltration. Moreover, as well as the aforementioned tissue-derived cytokines, the serum erythrocyte sedimentation rate was higher in OPLL patients than in non-OPLL controls, and patients with OPLL in progress exhibited elevated highly-sensitive C-reactive protein levels than those with OPLL in nonprogress. Therefore, it can be reasonably suspected that this inflammatory condition may also related to the degeneration of the spinal muscles.

3. Mechanotransduction

Mechanical stress, such as tensile strain, induces the osteogenic differentiation of posterior longitudinal ligament fibroblasts through the upregulation of several molecules, such as osteocalcin, alkaline phosphatase, or type I collagen. Bone morphogenetic protein-2, which is the most mentioned gene contributing to OPLL, is activated via mechanotransduction and plays a role in ossification. When the stabiliser muscles are weakened, nonphysiological and unnecessary mobility develops in the spine, and microfriction occurs more frequently in the spinal ligaments or facet joints. This pathological process causes abnormal ossification of ligaments in accordance with the forementioned mechanotransduction-related processes. Noncoding ribonucleic acids (RNA), which do not translate into protein, have been increasingly recognized for their involvement in various biological processes, including bone metabolism and muscle atrophy. For instance, long noncoding RNA H19, closely associate with BMP9-induced osteogenic differentiation in mesenchymal stem cells in OPLL, is also related to muscle atrophy process. Moreover, mechanosensitive micro RNAs, such as miR-103, which has been revealed to increase osteoblastic activity, is also associated with muscle atrophy. The shared genetic processes between bone metabolism and muscle atrophy at both the protein and RNA levels provide a potential genetic background for understanding the correlation between OPLL size and MFD severity.

4. Disuse-Induced Muscular Degeneration

Disuse-induced atrophy or dysfunction of these muscles would promote the degeneration of long bones and their related joints. Numerous studies have demonstrated the relationship between deconditioning of the paralumbar axial muscles and low back pain. Most of the early studies used the volume, cross-sectional area, or power as the parameters to estimate the condition of the axial muscles. Muscle density and fatty streak proportion within a muscle were considered to reflect the skeletal muscle condition. A study revealed that reduced multifidus density was associated with more severe osteoarthritis of the facet joint. Another study group recently analysed fatty infiltration of the paracervical muscle at 2 spinal levels, C4/5 and C5/6, with the maximum occupancy ratio of OPLL, yielding a significant correlation between OPLL size and MFD at the C5/6 level. However, this study is limited in that not all spinal levels were examined. Similarly, in patients with ankylosing spondylitis, more fatty degeneration is observed in the multifidus muscles of the lumbar spine than in those without this condition. Considering that fatty infiltration occurs in the late stage of muscular degeneration, long-term disuse or deconditioning can be expected to play a role in MFD. In addition, because the invasion of OPLL concerning the K-line is classified in the axial plane, the significant decrease in cervical ROM (ΔCobb angle) observed in the K-line (-) group (Supplementary Table 1) indicates that not only longitudinal involvement of OPLL but also axial involve-
ment may impact the restriction of ROM, potentially leading to disuse-related MFD. Although the effect of physical exercise on MFD in patients with OPLL could not be directly analysed in this study, a case-control study revealed that regular and moderate amounts of physical exercise are associated with a decreased risk of OPLL. However, no specific guidelines on exercise in patients with OPLL are available, even in the clinical practice guidelines on the management of ossification of the spinal ligament.

This study has several limitations. As this study did not compare the severity of MFD between OPLL group and non-OPLL controls, it was difficult to investigate the extent of which OPLL itself affects the severity of MFD. However, even if a comparison is conducted between the OPLL group and non-OPLL group, it will be challenging to draw straightforward conclusions because it is difficult to control each patient’s lifestyle or genetic background. In addition, it may be limited in scope because only patients who underwent surgery were included, may resulting in a bias in the correlation coefficient; nonetheless, it was designed to focus on OPLL severe enough to necessitate mechanical decompression. More quantitative image processing techniques can be utilized to quantify the severity of MFD based on magnetic resonance imaging, however this method is difficult to employ in a busy clinical setting, hence simple classification was used.

CONCLUSION

The OPLL occupying diameter and area ratios are clinically correlated with the severity of MFD and cervical ROM. The OPLL at one spinal level affects the MFD at the same and 1–3 adjacent spinal levels. The worsening severity of MFD is associated with the longitudinal continuity of OPLL. Clinicians need to pay attention to these relationships, since MFD does not immediately resolve after decompression surgery. This study will be useful not only in identifying the factors significantly associated with postoperative pain or function, but also in establishing a personalized postoperative exercise program for muscular reeducation in consideration of the severity of patients’ MFD.

NOTES

Supplementary Material: Supplementary Tables 1-2 can be found via https://doi.org/10.14245/ns.2346506.253.

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: JP, YGP; Data acquisition: SS, CHL, SYC, YEC; Data curation: JP; Methodology: JP, KHK, SK; Project administration: JP, YEC; Visualization: JP; Writing – Original Draft: JP; Writing – Review & Editing: JP, SS, YGP.

ORCID
Jinyoung Park: 0000-0003-4042-9779
Yong Eun Cho: 0000-0001-9815-2720
Kyung Hyun Kim: 0000-0002-1338-5523
Sanghoon Shin: 0000-0001-7333-6515
Sungjun Kim: 0000-0002-7876-7901
Chae Hwan Lim: 0000-0002-1496-3866
Seok Young Chung: 0000-0003-1484-6771
Yoon Ghil Park: 0000-0001-9054-5300

REFERENCES


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**Supplementary Table 1.** OPLL size and MFD according to OPLL's K-line invasion

<table>
<thead>
<tr>
<th>Variable</th>
<th>K-line (+) (N = 80)</th>
<th>K-line (-) (N = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55.8 ± 9.5</td>
<td>56.9 ± 9.5</td>
<td>0.65</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<td>0.60</td>
</tr>
<tr>
<td>Male</td>
<td>54 (67.5)</td>
<td>15 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (32.5)</td>
<td>5 (25.0)</td>
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</tr>
<tr>
<td>OPLL size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPLL diameter occupying ratio</td>
<td>0.29 ± 0.12</td>
<td>0.38 ± 0.11</td>
<td>0.002</td>
</tr>
<tr>
<td>OPLL area occupying ratio</td>
<td>0.16 ± 0.08</td>
<td>0.23 ± 0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Involved vertebral level</td>
<td>4.68 ± 1.18</td>
<td>5.35 ± 1.04</td>
<td>0.021</td>
</tr>
<tr>
<td>ΔCobb</td>
<td>28.8 ± 10.8</td>
<td>22.1 ± 13.3</td>
<td>0.021</td>
</tr>
<tr>
<td>Multifidus fatty degeneration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goutallier grade</td>
<td>1.92 ± 0.38</td>
<td>2.19 ± 0.31</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

OPLL, ossification of posterior longitudinal ligament; MFD, multifidus fatty degeneration; OPLL, ossification of posterior longitudinal ligament; ΔCobb, C2–7 range of motion between full flexion-extension between; K-line, kyphosis line.

Goutallier classification system: grade 0, normal muscle; grade 1, some fatty streaks; grade 2, less than 50% fatty muscle atrophy; grade 3, 50% fatty muscle atrophy; grade 4, greater than 50% fatty muscle atrophy.
### Supplementary Table 2. Average age by OPLL type

<table>
<thead>
<tr>
<th>OPLL type</th>
<th>No.</th>
<th>Age (yr), mean ± SD</th>
<th>Intergroup differences</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>33</td>
<td>56.0 ± 8.5</td>
<td>Continuous vs. segmental</td>
<td>0.998</td>
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<td>Continuous vs. mixed</td>
<td>1.000</td>
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<td></td>
<td></td>
<td></td>
<td>Continuous vs. localized</td>
<td>0.973</td>
</tr>
<tr>
<td>Segmental</td>
<td>28</td>
<td>55.6 ± 10.1</td>
<td>Segmental vs. mixed</td>
<td>0.996</td>
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<td>Segmental vs. localized</td>
<td>0.961</td>
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<tr>
<td>Mixed</td>
<td>37</td>
<td>56.1 ± 9.8</td>
<td>Mixed vs. localized</td>
<td>0.976</td>
</tr>
<tr>
<td>Localized</td>
<td>2</td>
<td>59.0 ± 17.0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

OPLL, ossification of posterior longitudinal ligament; SD, standard deviation.
Saving Stabilizing Structure Treatment With Bilateral-Contralateral Decompression for Spinal Stenosis in Degenerative Spondylolisthesis Using Unilateral Biportal Endoscopy

Dong Hyun Lee¹, Dong-Geun Lee¹, Choon Keun Park¹, Jae-Won Jang¹, Jin Sub Hwang¹, Jun Yong Kim¹, Yong-Eun Cho¹, Sang Won Lee¹, Dong Chan Lee², Bang Sang Han¹, Sang Yeop Han¹

¹Department of Neurosurgery, Spine Center, The Leon Wiltse Memorial Hospital, Suwon, Korea
²Department of Neurosurgery, Spine Center, The Leon Wiltse Memorial Hospital, Anyang, Korea

Objective: This study aimed to evaluate the treatment of spinal stenosis with spondylolisthesis using bilateral-contralateral unilateral biportal endoscopic (UBE) decompression to minimize facet joint damage.

Methods: We retrospectively evaluated 42 patients with grade 1 spondylolisthesis who underwent bilateral-contralateral UBE decompression between July 2018 and September 2019. To identify segmental instability, static and dynamic images from preoperative and postoperative procedures and final follow-up radiographs were reviewed. Lateral radiograph slippage ratio, sagittal motion, and facet joint preservation were evaluated. Clinical assessments were conducted using the visual analogue scale (VAS), Oswestry Disability Index (ODI), and modified MacNab criteria.

Results: The average final follow-up period was 26.5 ± 1.3 months. The average preoperative slip percentage was 15.70% ± 5.25%, which worsened to 18.80% ± 5.41% at the final follow-up (p < 0.005). The facet joint preservation rate was 95.6% ± 4.1% on the contralateral side. Improvements in the VAS scores (leg pain: from 7.9 ± 2.2 to 3.1 ± 0.7; p < 0.005; back pain: from 7.2 ± 3.0 to 2.8 ± 1.0; p < 0.005) were observed at the final follow-up. The mean preoperative ODI was 26.19 ± 3.42, which improved to 9.6 ± 1.0 (p < 0.005). Thirteen patients exhibited delayed focal segmental instability following decompression. Despite the absence of symptoms or improvement with conservative treatment in the majority of patients with delayed instability, two patients required fusion surgery to address the instability. Additionally, 2 patients developed facet synovial cysts, while 2 experienced spinous process fractures.

Conclusion: Bilateral decompression with a contralateral UBE approach could be an effective and alternative treatment method to reduce instability in spinal stenosis with grade 1 spondylolisthesis.

Keywords: UBE, Contralateral, Zygapophyseal joint, Spinal stenosis, Spondylolisthesis

INTRODUCTION

Patients with degenerative spondylolisthesis, a condition that greatly influences older people and most commonly affects the lower lumbar spine, generally have symptoms of back and/or lower extremity pain and neurological deficits. Although conservative treatments, such as anti-inflammatory drug use and physical therapy, can help alleviate the pain caused by degener-
ative spondylolisthesis, back and/or leg pain persists in many patients and may require surgical treatment to ameliorate it, stabilize the spine, and improve body function. Spinal fusion remains the gold standard for the surgical care of degenerative spondylolisthesis, particularly in the presence of spinal instability.

Dynamic radiographic research has proven that most patients with degenerative spondylolisthesis do not have spinal instability, and that their symptoms are primarily due to spinal nerve root compression or stimulation of inflamed nerve root. Open spinal decompression, with or without fusion, is generally performed in these patients. In particular, surgical processes involving fusion are traumatic, require general anesthesia, have a long recovery period, and are frequently associated with a high incidence complications and elevated costs.2

Minimally invasive surgical methods, such as unilateral biportal endoscopic (UBE) decompression that targets the pain-generating area, have recently been revised with the goal of reducing fusion, resulting in improved clinical outcomes and increased patient satisfaction.3,7 Nevertheless, despite the continuous development of surgical processes using spinal endoscopic and related equipment, issues such as iatrogenic instability caused by facet joint involvement remain.8

In the ipsilateral approach, the medial facet joint is unavoidably exposed at the surgical site. The facet joint is less involved on the contralateral side than on the ipsilateral side when unilateral laminotomy bilateral lumbar decompression is performed.9,10 In particular, invasion of the facet structure is minimized during contralateral decompression when using endoscopic decompression (Fig. 1A, B).11,12 However, there have been no reports on bilateral-contralateral decompression in patients with spinal stenosis in degenerative spondylolisthesis who require minimal facet joint damage. In such cases, the operator approaches the left side to decompress the right side and vice versa. Thus, we performed bilateral-contralateral decompressions on both sides to minimize damage to the facet joint for the treatment of spinal stenosis with spondylolisthesis via UBE (Fig. 1C).

A key consideration is that the safety and effectiveness of this method in the treatment of patients with degenerative spondylolisthesis has not been completely established. This retrospective study aimed to describe in detail how this approach can be applied safely and effectively to treat patients with grade 1 degenerative spondylolisthesis, summarize our experiences, identify technical obstacles, and present the surgical outcomes of spondylolisthesis treatment.

MATERIALS AND METHODS

1. Patient Selection

This retrospective study included 42 consecutive patients who were treated using bilateral-contralateral UBE techniques between July 2018 and September 2019. All patients were diagnosed with grade 1 lumbar spondylolisthesis according to the Meyerding classification system,13 and had lumbar stenosis and neurogenic claudication with or without lumbar radiculopathy.14 Diagnosis was made using standard lumbar anteroposterior and lateral radiographs (degree of spondylolisthesis of ≥ 3 mm).

Symptoms such as lasting radicular leg pain, neurological deficits, or neurogenic intermittent claudication refractory to preservation treatment for ≥ 6 months caused by moderate-to-severe spinal canal stenosis with lateral recess stenosis were considered indications for surgery. Based on the magnetic resonance imaging (MRI) grading system for lumbar foraminal stenosis,15 patients with grade 3 severe foraminal stenosis and complete loss of fat and/or neuromuscular morphological changes were excluded. Patients with pre-existing degenerative scoliosis with a Cobb angle of > 20°, degenerative spondylolisthesis greater than or equal to grade 2 in the Meyerding classification system, segmental instability (i.e., translation of angular movement of > 4 mm or 10° between flexion and extension on upright lateral radiographs), a history of prior lumbar spine surgery, or < 20 or > 80 years of age were excluded from the study. During the same period, fusion was performed on 26 patients with spondylolisthesis who required surgery that did not correspond to the bilateral-contralateral UBE decompression indication. Three neurosurgeons centrally examined each patient’s radiographic and MRI findings to confirm degenerative lumbar canal stenosis with spondylolisthesis without disc herniation.

All the included patients underwent bilateral-contralateral UBE decompression. A facet-sparing procedure was performed in all cases. Data access and use were approved by the Institution
tional Review Board (IRB No. 2022-W04) of the Leon Wiltse Memorial Hospital, Suwon. Preapproval was not necessary for the use of the data in this study as it included anonymous secondary data published for research purposes.

2. Surgical Technique

After placing the patients under general anesthesia, they were positioned with their abdomen free on the radiolucent Relton-Hall framework. The skin and surgical field were arranged using the standard method. Bilateral-contralateral UBE decompression was performed with ongoing general saline irrigation, a waterproof final layer of draping, and a smooth drainage system for saline outflow.

These preservation techniques were necessary to protect patients from hypothermia caused by immersion in the cold saline solution. The fluoroscope was arranged parallel to the disc space to obtain accurate anteroposterior images. The spinal levels of interest were indicated on the skin using a biplanar fluoroscope. Four small incisions penetrating the deep fascia were required for bilateral-contralateral UBE decompression. Two

Fig. 2. The circle indicates the initial targeting area: the spinolaminar junction. Skin incisions are made along the medial pedicle line, separated by 2–3 cm. Lt., left; Rt., right.

Fig. 3. (A) Decompressing the right side by approaching through the left side. (B) Decompressing the left side by approaching through the right. Dual monitors allow the operator to go to the contralateral side and immediately start decompression.

Fig. 4. Unilateral biportal endoscopic decompression is performed with left-side access using a 0° arthroscope. (A) The spinolaminar junction is the starting point for decompression. (B) The origin of the ligamentum flavum is detached (*), and the base of the spinous process is removed using a high-speed diamond bur. (C) Decompression of the contralateral lateral recess (right decompression via left-side approach). (D) Decompression of the contralateral lateral recess (left decompression via right-side approach). Lt, left; Rt, right.
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Skin incisions are generally made along the medial pedicle line, separated by 2–3 cm, using the left approach (Figs. 2, 3A). Serial dilators (≤ 10 mm) are used to divide the paraspinal muscles, enlarge the instrument portal, and gently remove the soft tissues from the interlaminar space. A narrow gap was created by the inflow of normal saline. The overall surgical process was conducted in a precise and expanded surgical field using meticulous hemostasis (Fig. 4). By modifying the inflow of hydrostatic pressure and managing the outflow, hemostatic disruptions such as bleeding from small epidural veins and oozing from bones could be observed. A radiofrequency wand was used for proper cauterization of bleeding from soft tissues and larger epidural veins (ArthroCare, Austin, TX, USA). Bone wax was also used to prevent severe bleeding. Decompression from the spinolaminar junction was performed using an electric high-speed diamond bur, 3 or 4 mm in diameter (Primado 2; NSK, Fukushima, Japan). 

The decompression steps were as follows (Fig. 4):

1. The ipsilateral lamina was drilled, starting cranially at its lower edge; the origin of the ligamentum flavum and underlying epidural fat became visible, as shown in Fig. 4A.
2. The underside of the contralateral lamina was drilled to approach the lateral recess. The ligamentum flavum was preserved to protect the underlying neural tissues. Hypertrrophic and deformed facets of joints are usually observed during severe stenosis. More bone was removed from the base of the spinous process to widen the laminotomy window and provide easier access to the contralateral lateral recess (Fig. 4B).
3. Extract the contralateral half of the ligamentum flavum and decompress the lower side of the contralateral facet joint to release the contralateral traversing nerve root (Fig. 4C).
4. To facilitate reentry from the right side, move the UBE tower to the opposite side. The surgeon should also position themselves on the right side of the patient and perform contralateral left decompression using the right approach. By utilizing dual monitors (Fig. 3B), the surgeon can switch to the other side without relocating the instruments and begin the contralateral approach, thereby reducing time. It is advisable to approach the right side approximately 5 mm lower than the conventional approach to prevent excessive laminectomy of the lamina caused by the right hand getting caught on the lamina (Fig. 2).
5. The Freer Elevator (Endovision, Seoul, Korea) can be used to locate the pre-existing left laminectomy site and access the epidural area. Perform laminectomy only on the portion trapped in the right lamina and conduct contralateral decompression using the same method as before (Fig. 4D).
6. Supplementary Fig. 1 shows pre- and postoperative image.

3. Radiographic Measurements

To identify segmental instability, static and dynamic images from the preoperative and postoperative procedures and final follow-up radiographs were reviewed. The Taillard method was used to measure the slippage ratio of lateral radiographs, and the sagittal motion in spondylolisthesis was estimated based on the difference in the slippage of the flexion-extension points. Preoperative computed tomography (CT) images were used to measure disc height, facet angle, and Pathria grading scales, as previously demonstrated. Supplementary Fig. 2 shows how the measurements were performed. MRI studies of the lumbar spine were conducted over 2 days during the preoperative and postoperative periods. The method described by Dozhono et al. was used to evaluate facet joint preservation; however, MRI was performed instead of CT (Supplementary Fig. 3). For the mean value, each measurement was repeated 3 times by the 3 spine surgeons.

4. Clinical Outcomes

Clinical results were assessed based on the visual analogue scale (VAS) for back pain and leg symptom, while the Oswestry Disability Index (ODI) and MacNab criteria were used to evaluate the degree of disability and medical care results, respectively. Assessments were conducted during the preoperative, postoperative, and final follow-up periods. In the case of complications, medical charts were carefully examined. Operation time and length of hospital stay were also included.

5. Statistical Analyses

IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA) was used for all statistical analyses. Medical outcomes and radiological changes after surgery were assessed using Wilcoxon signed-rank tests. The Mann-Whitney U-test was used to compare changes in the slippage ratio at the final follow-up between patients with and without spinal instability. Statistical significance was set at p < 0.05. Intraclass correlation coefficient analysis was used to assess the interobserver reliability to validate the assessed data.
RESULTS

A total of 42 patients (9 men and 33 women) were included in the study. All patients underwent single-level decompression with grade 1 spondylolisthesis, with L4–5 affected in 28 patients and L3–4 in 14 patients. The patients' average age was 60 years (range, 48–76 years), and the clinical and radiological final follow-up period was 26.5 ± 1.3 months (range, 24–29 months). The average slip percentage before surgery was 15.70% ± 5.25%, which worsened and increased to 18.80% ± 5.41% at the final follow-up (p < 0.005; Supplementary Fig. 4). Thirteen patients showed delayed instability and increased slip percentage from 12.75% ± 2.34% to 18.98% ± 2.77% (p < 0.005). Slip percentage increased from 17.09% ± 5.78% to 18.83 ± 6.44% in the stable group of 29 patients (p < 0.005). There was a statistically significant increase in slipping in the delayed instability group (p < 0.005). The percentage of facet joint preservation was 95.6% ± 4.1% on the contralateral approach. There was no statistically significant difference in the facet Pathria grade.

The operation time was 108.8 ± 32.2 minutes (range, 92–150 minutes). The average volume of blood loss during surgery and on postoperative day 1 was 60.1 ± 20.2 mL. The average duration of hospital stay was 3.4 ± 2.4 days (range, 3–6 days). On postoperative day 1, most patients were able to ambulate. The demographic data are presented in Table 1. Multivariate forward selection stepwise logistic regression analysis of the factors that could cause instability after decompression in spondylolisthesis (disc height, facet angle, and spondylolisthesis movement) revealed p = 0.312, p = 0.932, and p = 0.137, respectively (Table 2). After surgery, the patients showed a significant improvement in their symptoms. The VAS scores for leg and back pain decreased from 7.9 ± 2.2 to 3.1 ± 0.7 (p < 0.005) and from 7.2 ± 3.0 to 2.8 ± 1.0 (p < 0.005), respectively, at the final follow-up. The mean preoperative ODI was 26.19 ± 3.42, which improved to 9.6 ± 1.0 (p < 0.005) at the final follow-up.

According to the modified MacNab criteria, the final results were excellent in 26 patients (61.9%), good in 12 (28.6%), fair in 2 (4.8%), and poor in 2 (4.8%). Overall, 90.0% of patients had good or excellent outcomes. A few surgical complications were identified, including delayed focal segmental instability after decompression in 13 patients. Although no symptoms or relief with conservative treatment was noted, 2 patients underwent fusion surgery due to instability. A facet synovial cyst developed in 2 patients, although it was asymptomatic and disappeared within the follow-up period. Two patients had a spinous process fracture. No complications associated with infections or wounds were observed. Mild complications were reported, although none of the patients experienced worsening of symptoms.

DISCUSSION

The pathological prevalence of degenerative spondylolisthesis varies depending on the population and measurement method used to evaluate it. A large population-based study of patients aged > 65 years in China revealed that degenerative spondylolisthesis showed a higher preponderance in female patients, with a prevalence of 25.0% in women and 19.1% in men. Despite improvements in spinal endoscopic surgical steps owing to the development of relevant equipment in recent decades, certain problems, such as iatrogenic instability caused by the violation of the facet joints, remain to be solved. For sufficient exposure...
of the surgical field using the ipsilateral method, the encroachment of the facet is unavoidable. According to a previous report, the facet joints on the contralateral part were violated to a lesser degree than those on the ipsilateral section in unilateral laminotomy bilateral lumbar decompression, and the percentage reduction of the joint area undergoing the ipsilateral method was 22.6%. Based on that report, fractures in the inferior articular process accounted for 6% of cases treated using the ipsilateral approach. A high risk of facet joint damage in decompression has been reported for patients with an upper lumbar level lesion, a narrow lamina, and sagittal plane joint morphology. A contralateral endoscopic method developed to reduce iatrogenic instability caused by laminectomy with violation of the facet joints has shown good medical and surgical results. Based on this, we performed bilateral-contralateral UBE decompression in spinal stenosis with grade 1 spondylolisthesis and obtained good clinical results.

Our radiological outcomes showed that the percentage reduction of the facet joint plane was 4.4% after using the contralateral method, which was lower than the previously reported percentages of facet joint decrease when using the ipsilateral method. This finding demonstrates the efficacy of the contralateral method for decompression with facet joint preservation. Although less than one-third of the affected facet joints can tolerate vertebral shear forces in cadaveric study and facet joint destruction does not lead to acute instability due to alternative pathways to support the spine, reducing the involvement of the facet joint is one of the final goals of preventing progressing instability in minimally invasive endoscopic surgery, and the bi-contralateral approach we implemented may minimize the destruction of the facet joint, potentially reducing the risk of instability.

Although randomized (level I) and prospective (level II) evidence has shown the benefits of the addition of fusion for spondylolisthesis surgery, other evidence indicates that fusion provides no distinct benefits in spinal stenosis with spondylolisthesis. Försth et al. randomly selected 247 patients in a study that examined decompression alone and decompression with fusion. The findings showed that the application of fusion did not result in superior results, with similar ODI scores, 6-minute walk test scores, and reoperation percentages between the 2 groups at 2 years. However, the fusion group had a longer length of hospital stay, longer operative time, and greater volume of blood loss. More recently, Inose et al. found that random participants with low-grade (< 30%) L4–5 spondylolisthesis who underwent decompression alone, decompression and fusion, or decompression and stabilization, had no significant differences in the VAS score for low back or leg pain or the Japanese Orthopedic Association score among the 3 groups.

Although minimally invasive fusion is being introduced, minimally invasive simple decompression has been reported to have medical outcomes equivalent to those of open fusion, with a lower cost, shorter operating time, reduced volume of blood loss, and shorter length of hospital stay than open fusion. Some experts particularly prefer decompression only for treating older patients with “stable spondylolisthesis,” owing to the relatively lower morbidity and mortality rates associated with the procedure.

Jang et al. retrospectively examined 21 patients who underwent minimally invasive lumbar laminoplasty such as microsurgical bilateral decompression via a unilateral approach for lumbar stenosis associated with grade I degenerative spondylolisthesis. In patients with preoperative evidence of sagittal motion on dynamic radiographs, a significant increase in slippage was noted, explaining why decompression was performed in rigorously selected stable spondylolisthesis with minimal sagittal motion. Kelleher et al. examined data from 25 participants with grade I degenerative spondylolisthesis diagnosed with leg-dominant signs without noteworthy back pain or obvious dynamic instability. Surgical intervention consisted of minimally invasive bilateral decompression using a unilateral approach. In Kelleher’s study, the mean slip progression was 8.4%, which differs from our average slip percentage of 3.10% ± 3.39%, despite the lack of a relationship between the degree of olisthesis or radiographic slip development and the need for revision surgery. It is necessary to observe increased slipping with a longer follow-up period.

We performed bilateral-contralateral decompression using UBE to protect the facet and overcome the shortcomings of a typical unilateral laminectomy bilateral decompression. In contrast to reports citing a cumulative reoperation rate as high as 34%, our study reported only 2 reoperation fusions among 42 cases (4.8%). Increases in the percentage of asymptomatic slippage and facet cysts were also reported in our study. Two patients had spinous fractures, although their conditions demonstrated sufficient improvement with conservative treatment. It is generally accepted that instability in the lumbar spine is caused by mobile degenerative spondylolisthesis with mechanical low back pain and that the recommended treatment is decompression with fusion. According to a Washington State administrative data report, the rate of reoperation after laminectomy is close to 28% for spondylolisthesis. Compared to other reports in which at least one-third of patients with degenerative spon-
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To reduce both the -

However, global sagittal parameters -

Since the bilateral-contralateral approach using UBE invades the multifidus muscles on both sides, it may reduce the advantages of the existing minimally invasive surgery when compared to the conventional one-sided approach. However, the injury to the multifidus muscle after UBE surgery has been previously reported to be minimal, showing no difference from that before surgery within several months. The invasion of the facet structure is minimized during contralateral decompression through endoscopic surgery. We performed bilateral-contralateral UBE decompression to minimize the involvement of both facet joints in grade 1 spondylolisthesis. This approach can minimize the destruction of both facet joints and potentially minimize the delayed risk of instability that may occur after decompression of the spondylolisthesis. Although it is impossible to compare the impact of instability between bilateral-contralateral decompression and unilateral laminectomy with unilateral decompression using UBE in patients with spondylolisthesis due to the lack of literature.

To the best of our knowledge, this is the first report to provide clinical and radiological results on the extensive use of bilateral-contralateral decompression via UBE for spinal stenosis in low-grade spondylolisthesis. The use of our bilateral-contralateral approach resulted in only minor complications. Although reoperation was needed in 2 patients with olisthesis due to increased delayed instability after decompression, this method is very promising, as it was associated with a low reoperation rate. Two patients had spinous process fractures, although these occurred due to inexperience in the early period performing bilateral-contralateral decompression. Conservative treatment was sufficient for back pain. Spinous fractures can occur when inexperienced surgeons perform the bilateral-contralateral approach. Although this can be alleviated with conservative treatment, it can also reduce the patients’ postoperative satisfaction. To prevent spinous process fractures, when performing left decompression through the right approach after completing right decompression through the left approach, the right approach rather than the left approach should go to the caudal side. It is possible to prevent additional laminectomy in the existing laminectomy, thereby minimizing the invasion of the spinous process base. Although not essential, using dual monitors was effective in reducing the operation time because the operator could move to the opposite side and initiate contralateral access without moving the UBE deck and monitor.

This study had a relatively small sample size (42 patients); thus, further studies with larger sample sizes are required to verify these results.

In this case series, we encountered a lack of consensus regarding the definition of lumbar instability in the literature, including wide thresholds of 2–5 mm on flexion-extension radiographs. In this study, a threshold of 3-mm sagittal translation and 10° sagittal rotation was used, based on flexion-extension imaging. The actual percentage of patients with postoperative instability may be higher, as asymptomatic patients may have missed follow-up after 2 years. We performed the final radiography a minimum of 24 months after surgery. However, the final follow-up duration differed for each patient, which may have affected the outcomes. The error in the results could have been reduced if the follow-up time after surgery had been uniform for all patients.

Previous reports have shown that patients with lumbar degenerative spondylolisthesis tend to have a propensity for sagittal imbalance and a higher pelvic incidence than patients with degenerative spinal stenosis, and that sagittal imbalance in patients with degenerative spondylolisthesis is correlated with the loss of lumbar lordosis. However, global sagittal parameters could not make pre- and postoperative comparisons. There are limitations to discovering an association between global sagittal parameters and slippage in spondylolisthesis after bilateral-contralateral UBE decompression.

Excellent results were obtained for the preservation of the facet joint in our study. However, although the rate of reoperation was lower than that after decompression, as reported in previous studies, no patient in the control group was treated with unilateral laminectomy bilateral decompression for specific
comparisons. Therefore, whether unilateral laminectomy with bilateral decompression has clinical significance remains unclear. Further studies, particularly randomized controlled experiments and studies with control groups, are necessary to explore this subject further.

CONCLUSION

In our study, applying bilateral-contralateral UBE decompression in patients with lumbar spinal stenosis and grade 1 degenerative spondylolisthesis provided good clinical mid-term medical results with a low reoperation rate, despite a slight increase in slippage. We believe that bilateral-contralateral UBE decompression for lumbar spinal stenosis with grade 1 degenerative spondylolisthesis may be a good surgical option for lowering the rate of postoperative instability.

NOTES

Supplementary Materials: Supplementary Figs. 1-4 can be found via https://doi.org/10.14245/ns.2346504.252.

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ORCID

Dong Hyun Lee: 0000-0002-8252-622X
Dong-Geun Lee: 0000-0002-9668-9134
Jae-Won Jang: 0000-0001-5555-4359
Young-Eun Cho: 0000-0001-9815-2720
Dong Chan Lee: 0000-0001-5614-4490

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Supplementary Fig. 1. (A) Preoperative axial T2-weighted magnetic resonance imaging (MRI) demonstrating lumbar spinal stenosis at the level of L4–5 in spondylolisthesis. (B) Postoperative axial MRI image shows decompression after the bilateral-contralateral decompression. (C) Preoperative computed tomography (CT) scan images demonstrating lumbar spinal stenosis at the level of L4–5 in spondylolisthesis. (D) Postoperative CT scan image with minimal facet resection.
Supplementary Fig. 2. Flexion (A) and extension (B). Digital plain radiographic images are used to determine the movement at the level of spondylolisthesis (3.76° motion in this case). (C) Disc height was gauged based on preoperative lumbar computed tomography scans by applying a midsagittal image and identifying the gap from the midpoint of the endplate at the level of the spondylolisthesis. (D) The facet angle was measured by calculating the angle generated by linking the 2 endpoints of each facet on a preoperative axial lumbar computed tomography (midcut through the disc) and a line linking the 2 dorsal points of each facet joint. When the facet angles were different (right side vs. left side), the average value was applied (69.5° in this example).
**Supplementary Fig. 3.** Measurement of facet joint preservation on preoperative (A) and final follow-up (B) via magnetic resonance imaging. The dashed lines highlight the extent of the laminotomy. The percentage of facet preservation = \( \frac{y}{x} \times 100\% \).
Supplementary Fig. 4. Progression of anterior slippage. The average overall slip percentage was 15.70% ± 5.25% preoperatively, which increased to 18.80% ± 5.41% at the last follow-up. PreOp, preoperation; PostOp, postoperation.
Anterior Transarticular Crossing Screw Fixation for Atlantoaxial Joint Instability: A Biomechanical Study

Hang Xiao1, Zhiping Huang1, Panjie Xu1, Junyu Lin1,2, Qingan Zhu1, Wei Ji1,3

1Division of Spinal Surgery, Department of Orthopaedics, Nanfang Hospital, Southern Medical University, Guangzhou, China
2Department of Orthopaedics and Traumatology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
3Department of Orthopaedics, Yunfu People’s Hospital, Yunfu, China

Objective: To evaluate the biomechanical stability of anterior transarticular crossing screw (ATCS) and compare it with anterior transarticular screw (ATS) which may provide basic evidence for clinical application.

Methods: Eight human fresh cadaveric specimens (occiput-C4) were tested with 5 conditions including the intact status, the injury status (type II odontoid fracture), the injury+ATS fixation status (traditional bilateral ATS fixation); the injury+unilateral ATCS fixation status; and the injury+bilateral ATCS fixation status. Specimens were applied to a pure moment of 1.5 Nm in flexion-extension, lateral bending, and axial rotation, respectively. The range of motions (ROMs) and the neutral zones (NZs) of C1 to C2 segment were calculated and compared between 5 status.

Results: ATS and ATCS fixations significantly reduced the motions in all directions when compared with the intact and injury statues (p < 0.05). In flexion-extension, the ROMs of ATS, unilateral ATCS, and bilateral ATCS were 4.7° ± 2.5°, 4.1° ± 1.9°, and 3.2° ± 1.2°, respectively. Bilateral ATCS resulted in a significant decrease in ROM in flexion-extension when compared with ATS and unilateral ATCS (p = 0.035 and p = 0.023). In lateral bending and axial rotation, there was no significant difference in ROM between the 3 fixations (p > 0.05). Three fixations resulted in similar NZs in all directions (p > 0.05).

Conclusion: ATCS is a biomechanically effective alternative or supplemental method for atlantoaxial instability.

Keywords: Cervical spine, Atlantoaxial joint, Joint instability, Biomechanics, Cadaver, Internal fixators

INTRODUCTION

Atlantoaxial instability can arise from numerous conditions, such as trauma, malignancy, rheumatoid arthritis, congenital anomalies, inflammation, degenerative joint disease, or infectious disease. Due to the intricate and vital structures in the vicinity, surgical fixation is necessary to provide robust stability and security in this region. The anterior transarticular screw (ATS) fixation for atlantoaxial instability is a classic technique that Barbour1 first described in 1971 and was anatomically studied by Lu et al.2 in 1998. Afterward, no further relevant studies were published until 2003 when Reindl et al.3 reported a case of traumatic instability using the classic retropharyngeal Smith-Robinson approach. Two years later, they conducted a biomechanical study to demonstrate the effectiveness and feasibility of this technique in atlantoaxial stabilization.4 Subsequently, this technique was used to treat various atlantoaxial disorders with satisfactory postoperative outcomes, and now ATS fixation is widely used.5-10

However, in some unique clinical cases, such as atlantoaxial facet splitting, atlantoaxial lateral mass loss, screw cut-out at the atlantoaxial facet, fracture of the anterior rim of the C2 articu-
lar, or high-riding vertebral artery, traditional fixation techniques may not be feasible.\textsuperscript{11,12} This may be due to fewer landmarks for safe and effective repositioning of ATS.\textsuperscript{4,11} We have previously proposed anterior transarticular crossing screw (ATCS) fixation through anatomical and morphometric studies in adults and children, demonstrating the safety and feasibility of this technique.\textsuperscript{11,14} The results showed that ATCS has a longer screw purchase and can achieve significantly stronger screw holding capability. ATCS may provide a useful supplement or salvage procedure for ATS. However, it has not been evaluated from a biomechanical perspective. Therefore, the present study aims to evaluate the biomechanical stability of ATCS and compare it with conventional ATS.

**MATERIALS AND METHODS**

1. **Specimen Preparation**

Eight specimens (Occiput-C4) were collected from fresh-frozen human cadavers. The sex and age of the donors were unknown, and specimens with osteoporosis (T value < 2.5) were excluded by bone mineral density examination. Routine anteroposterior and lateral x-ray examinations were performed to exclude obvious deformities, fractures, tuberculosis, tumors, and other pathological conditions in the specimens.

All specimens were stored at -20°C and thawed at room temperature overnight before the experiment. Muscle tissue was removed, and the joint capsule and ligaments were carefully preserved. The partial occipital bone and C4 vertebrae were embedded in dental stone to maintain C1–2 levels during testing. The specimens were regularly sprayed with normal saline to keep them moist.

This study was approved by the Ethic Committee of Nanfang Hospital (NFEC-2022-197).

2. **Surgical Procedures**

Odontoid process was cutoff with an electric drill, a 2.5-mm diameter drill splinter, a rongeur forceps and an osteotome after testing in the intact status, resulting in a type II odontoid fracture. For ATS, the entry point was located at the midpoint of the C2 body, which is in the medial third of the C1–2 facet joint, below the sulcus on the anterior body of the C2.\textsuperscript{4,14} For ATCS, the entry point was set 5 mm lateral to the C2 body from the midline to the contralateral side in the coronal plane, to ensure a sufficient gap between the screw head and the C2–3 intervertebral disc, thereby mitigating the risk of adjacent level ossification.\textsuperscript{14} In the sagittal plane, the entry point was set at the anteroinferior level of the C2 body.

The ideal direction for ATS and ATCS was toward the superolateral corner of the superior articular process of C1 on anteroposterior radiograph, leaving 2–3 mm clearance from lateral margin of the lateral mass, as shown in Figs. 1 and 2. On lateral radiographs, all screws are aimed at the superoposterior corner of C1 superior articular process.\textsuperscript{15}

During the procedure, a 1.0-mm K-wire was used to drill in...
a specific direction under x-ray fluoroscopy. Once the needle was inserted into the subcortical area in the atlas mass, a 2.5-mm electric drill bit was used to drill along the K-wire, and a 4-mm diameter hollow tension screw was inserted. The same procedure was then performed on the contralateral side to complete bilateral ATCS fixation for the specimen. The type of screw used in this procedure was peak summit from DePuy Spine, Johnson. The radiography of the embedded specimen after implantation verified that the fixation was satisfactory, as illustrated in Fig. 3. To minimize damage to the specimens, ATCS and ATS were randomly performed on the left or right side of each specimen.

3. Biomechanical Testing

Fig. 4 shows a custom-designed spinal testing machine that applied a pure couple moment to the specimens under 5 conditions, in flexion-extension, lateral bending, and axial rotation. Each specimen was subjected to a continuous pure moment of 1.5 Nm for 3 cycle loading, with a displacement rate of 2°/sec. Data from the third cycle was used in the testing. Two optoelectronic camera systems (Certus; Northern Digital, Waterloo, ON, Canada) were used to measure the motion of the cervical spine. With an accuracy of 0.1°, this is currently the most accurate motion measurement system. The 2 cameras were angled +/- 45° toward the posterior view of the specimen to ensure that no markers were missed during motion, particularly in axial rotation. The marker carriers with 4 infrared light-emitting diodes were attached to the C1, C2, and C3. The Optotrak 3-dimensional motion measurement system was used to continuously calculate the motion of the markers, with a sampling frequency of 20 Hz. Range of motions (ROMs) and neutral zones (NZs) between C1 and C2 in flexion-extension, lateral bending, and axial rotation were calculated, respectively. To reduce the influence of the test order, the sequence of the 2 fixation procedures and the order of the 3 directions were randomized.

Each specimen was tested with following 5 configurations: (1) the intact status; (2) the injury status (type II odontoid fracture); (3) the injury+ATS fixation status (traditional bilateral ATS fixation); (4) the injury+unilateral ATCS fixation status; and (5) the injury+bilateral ATCS fixation status.

4. Statistical Analysis

The left lateral bending and axial rotation movements were observed to be statistically similar to those on the right side (p > 0.05); therefore, an average value was calculated for both directions. To determine the differences in ROMs and NZs between the intact, injury, ATS fixation, and ATCS fixation groups in all directions, we employed 1-way analysis of variance with a
Tukey post hoc test. The data were presented as mean ± standard deviation, and statistical significance was set at p < 0.05. All statistical analyses were performed using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA).

5. Observation Indicators

ROM refers to the degree of displacement between the maximum range of motion and the neutral position when a pure couple moment is applied. The neutral position is the state in which the spinal column experiences the least amount of stress and requires minimal force to maintain proper posture.

NZ is the section of the ROM where the load on the spine is nearly zero, and the ligaments are most relaxed, enabling a broad range of spinal motion with minimal force.

RESULTS

Table 1 shows the ROMs and NZs of the C1–2 segments in 5 different conditions, with a comparison between ATS, unilateral ATCS, and bilateral ATCS represented in Figs. 5 and 6. In intact status, the ROMs in flexion-extension, lateral bending, and axial rotation were 12.4° ± 6.7°, 3.3° ± 1.6°, and 63.7° ± 28.8°, respectively. Compared with the intact state, the ROMs of the C1–2 segments in the injury state were significantly increased in the flexion-extension, lateral bending, and axial rotation directions (26.2° ± 8.9°, 11.0° ± 3.3°, and 78.3° ± 10.3°, respectively) (p < 0.05). After ATCS and ATS fixation, the ROMs and NZs of the fixed segments were significantly reduced compared to the intact and injured states (p < 0.05). The ROMs for ATS, unilateral ATCS, and bilateral ATCS in flexion-extension were 4.7° ± 2.5°, 4.1° ± 1.9°, and 3.2° ± 1.2°, respectively. Significant differ-
ences were found between bilateral ATCS and the other 2 methods (p < 0.05). No significant differences were found between the 3 fixations in lateral bending or in axial rotation (p > 0.05).

The NZs for the intact state were 3.2° ± 3.6°, 0.8° ± 0.8°, and 25.8° ± 12.5° in flexion-extension, lateral bending, and axial rotation, respectively. In all directions, the injury state increased the NZs, whereas the 3 fixation states decreased the NZs significantly when compared with the intact state (p < 0.05). After ATS fixation and bilateral ATCS fixation, the NZs reduced to 0.6° ± 0.5°, 0.5° ± 0.3° in flexion-extension, 0.3° ± 0.3°, 0.3° ± 0.5° in lateral bending, and 2.1° ± 4.1°, 0.8° ± 0.6° in axial rotation, respectively. Similarly, after unilateral ATCS fixation, the NZs were 0.4° ± 0.3°, 0.3° ± 0.5°, and 0.6° ± 0.5° in the respective directions. Except in direction of axial rotation (p < 0.05), no significant differences were observed in NZs between the 3 conditions (p > 0.05).

DISCUSSION

Atlantoaxial instability can be caused by several factors, such as trauma, tumors, rheumatoid arthritis, and infectious diseases, which often lead to severe spinal cord injury and nerve root-related abnormal manifestations. The key to relieving these symptoms is to surgically stabilize the atlantoaxial complex. However, surgical treatment of the C1–2 segment has always been a challenge in spine surgery due to the complexity of the atlantoaxial joint. The atlantoaxial posterior approach, first proposed by Gallie et al. in 1939, has become the mainstream posterior fixation technique after continuous development and innovation. Nonetheless, in cases with contraindications such as abnormal vertebral artery, posterior atlantoaxial structural fractures, lateral mass fractures, or patients who need a cervical operation in supine position with cardiovascular and respiratory disease, the posterior approach may not be feasible.

The use of ATS for patients with atlantoaxial instability was first reported in 1971 by Barbour, and its anatomic parameters were studied by Lu et al. using 30 dried human cervical spines to confirm its feasibility. However, traditional ATS fixation techniques may not be possible or may fail in some unique clinical cases, such as atlantoaxial facet splitting, atlantoaxial lateral mass loss, screw cut-out the atlantoaxial facet, fracture of the anterior rim of the C2 articular, or high-riding vertebral artery. Kim et al. found that traditional ATS lacks biomechanical stability in flexion and extension in specific cases. Therefore, we proposed a novel ATCS fixation technique and studied its anatomical characteristics. Our study demonstrated that ATCS has a significantly longer screw purchase, which is favorable for resisting screw pullout. ATCS appears to be feasible and may become an alternative option for atlantoaxial fixation techniques. Three years later, Lvov et al. performed ATCS in 2 patients and achieved good atlantoaxial joint stability in the postoperative evaluation, showing better long-term clinical outcomes. In 2020 and 2022, we designed a retrospective multiplanar computed tomography-based morphometric study to determine the morphometric characteristics and the potential trajectory of ATCS in adults and children. We comprehensively measured the range of screw lengths of ATCS, as well as screw lateral angles (LAs) and incline angles (IAs), which provide security guarantees for ATCS. Our study showed that the longer screw length of ATCS has larger pullout strength. However, there are no biomechanical stability tests of ATCS. Therefore, this current study aims to analyze the biomechanical characteristics, including ROMs and NZs of ATS, unilateral ATCS, and bilateral ATCS fixation, to provide basic evidence for clinical application.

The results of the biomechanical stability test revealed that the ROMs after each of the 3 procedures was less than the intact and injured states with statistically significant differences. This indicates that each procedure achieved great immediate stability and satisfactory clinical efficacy. However, the distant fusion effect in body has not been observed yet. Sen et al. found that the ROMs and NZs of ATS were 5.41° and 1.07° in flexion-extension, 0.97° and 0.36° in lateral bending, and 1.67° and 0.47° in axial rotation, respectively. Furthermore, the ROMs of ATS collected by Lapsiwala et al. were 4.89°, 0.98°, and 1.98° in the 3 directions, respectively. These data were comparable to the actual ROMs and NZs of ATS measured in this study, demonstrating the reliability of our findings. On the other hand, the ROMs of unilateral ATCS performed in this study were 4.11°, 0.82°, and 1.87° in flexion-extension, lateral bending, and axial rotation, respectively. The ROMs of bilateral ATCS were 3.20°, 0.81°, and 1.43° in flexion-extension, lateral bending, and axial rotation, respectively, indicating better stability than ATS. According to our previous anatomical findings on fresh cadaveric specimens, we found that the ATCS screw length (40.4 mm) was significantly longer than ATS (26.4 mm) (p < 0.001). The ATCS screw length of C1 purchase was 14.8 mm, similar to ATS (14.9 mm), while the ATCS length of C2 purchase was 25.6 mm, longer than ATS (11.4 mm) (p < 0.001). Besides, similar to our previous study, the large LAs and IAs of ATCS, up to 38.4° and 41.0°, respectively, providing more space for further bone graft on the facet surface, allowing for stronger fixation and an increased probability of bone fusion. Bianco et al. demonstrated...
that initial stiﬀnesses and peak pullout forces were larger in longer screws that those in shorter screws, thus it is expected that ATCS ﬁxation is more stable than ATS ﬁxation, consistent with our measurements.

The analysis of the ROMs for the 3 procedures demonstrated similar stability in lateral bending and axial rotation. However, we believe that unilateral ATCS is clinically advantageous for several reasons: (1) The ROM exhibits a sig-nificant decreasing trend, suggesting better stability; (2) Tian et al.22 found that high-risking vertebral artery may results in a significantly increased risk of injury during surgical procedures, the surgical strategy is using alternative ﬁxation methods instead of C2 pedicle screw. Unilateral ATCS allows for anterior soft tissue exposure from a unilateral incision to expose the axis. It is less invasive and utilizes the virtual space, reducing the the infection rate and the risk of contralateral soft tissue stripping and vertebral artery injury, which may accelerate postoperative rehabilitation; (3) Bilateral ATCS requires higher accuracy in screw placement, making the procedure more challenging.

ATCS is more stable than ATS in ﬂexion and extension, possibly because the atlantoaxial joint provides only 12% of the motion of the upper cervical spine in ﬂexion and extension, whereas it provides 50% in lateral bending and axial rotation, thus strong ﬁxation has a greater impact on stability in this direction.23 Moreover, the 4 mm diameter hollow tension screw used in ATCS can be tightly attached to the atlantoaxial facet, which is far from the center of rotation of the vertebral body and has a longer screw length and force arm, whereas the ATS screw is near the atlantoaxial facet and lateral mass, reducing its ability to resist ﬂexion and extension movements. However, the main structure of the axis is cancellous bone, and previous ﬁnite element analysis studies suggest that the longer screws used in ATCS may not withstand the greater stresses in the direction of lateral bending and axial rotation.24 Therefore, although ATCS ﬁxation can signiﬁcantly reduce the ROM of lateral bending and axial rotation of the atlantoaxial spine, excessive head and neck rotation should be avoided to prevent ﬁxation failure. A comprehensive ﬁnite element analysis of the ATCS is also needed to determine the stress and optimize the ATCS technique.

However, the present study has several limitations, which are common among studies on fresh cadaver specimens. Firstly, human cervical spine specimens are diﬃcult to obtain in large numbers, resulting in weak statistical power. The small sample size affects the representativeness of the measurement results, and more samples are needed to verify the reliability. Secondly, the age, gender, and other speciﬁc information of the cadaver specimens in this study are unknown, and there is bias in the selection of specimens. To minimize the inﬂuence of non-treatment factors, the biomechanical test design was based on a self-control study. Thirdly, the inﬂuence of individual muscles and ligaments on spinal motion after the atlantoaxial instability operation was not considered in this experiment. Fourthly, long-term biomechanical data are also unknown as this study only tested acute stability. Fifthly, ATCS ﬁxation technique is demanding and not every clinical surgeon can perform it accurately, which aﬀects its practicability.

CONCLUSION

In current cadaveric biomechanical study, ATCS ﬁxation can provide similar biomechanical stability in 3 directions compared with ATS ﬁxation, suggesting that ATCS ﬁxation may potentially serve as an alternative or supplemental method for treating atlantoaxial instability. Furthermore, though there is equivalent biomechanical stability between unilateral ATCS ﬁxation and bilateral ATCS ﬁxation, the former is more favorable due to its reliability and efficiency. Further clinical studies are needed to evaluate long-term biomechanical stability of ATCS ﬁxation.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: HX, WJ; Data curation: HX, ZH, PX, JL, WJ; Formal analysis: HX; Funding acquisition: QZ, WJ; Methodology: HX, ZH, PX, JL; Project administration: QZ, WJ; Writing - original draft: HX; Writing - review & editing: WJ.

ORCID
Hang Xiao: 0009-0007-7440-5640
Wei Ji: 0000-0001-8271-9411

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REFERENCES

Spatiotemporal Gait Parameters and Gait Asymmetry in Patients With Lumbar Disc Herniation, Treated With Microdiscectomy: A Prospective, Observational Study

Masoud Amir Rashedi Bonab¹, Suleyman Sener², Tugba Kuru Colak¹, Mahsa Amirrashedi¹⁵, Ipek Yelden⁶, Deniz Konya², Zafer Orkun Toktas⁷

¹Physiotherapy and Rehabilitation Department, Institute of Health Sciences, Marmara University, Istanbul, Turkey
²Department of Neurosurgery, GZA Sint-Augustinus, Wilrijk, Belgium
³Physiotherapy and Rehabilitation Department, Faculty of Health Sciences, Marmara University, Istanbul, Turkey
⁴Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kongens Lyngby, Denmark
⁵Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Amager and Hvidovre, Copenhagen, Denmark
⁶Physiotherapy and Rehabilitation Department, Faculty of Health Sciences, Istanbul University-Cerrahpaşa, Istanbul, Turkey
⁷Department of Neurosurgery, Faculty of Medicine, Bahçeşehir University, Istanbul, Turkey

Objective: The aim of this study was to emphasize on the interaction of spatial and temporal gait parameters and analyse the gait asymmetry in the patients with lumbar disc herniation (LDH) before and after microdiscectomy.

Methods: This was a prospective, observational study conducted on 59 cases of LDH planned for lumbar microdiscectomy, and healthy control group with 54 participants for analysis was performed prior to surgery and 15 days after surgery. The spatiotemporal gait parameters were measured using a “Win-Track” gait analysis platform system. All the participants walked barefoot for 10 times with their normal walking speed in the same day. The 3 flawless walking data were recorded and the arithmetic means were computed. The gait symmetry index was used to calculate the walking asymmetry. The pain intensity of the patients was recorded shortly before performing the analysis by a visual analogue scale.

Results: In the postoperative assessment LDH patients had significantly shorter temporal parameters, longer spatial parameters, faster walking speed, and more cadence than the preoperative assessment (p < 0.05). There were improvements in the asymmetry values of the postoperative gait parameters compared to the preoperative values, but these differences were not significant (p > 0.05). In addition, there was a significant difference in all parameters in terms of gait asymmetry between the postoperative assessment and the healthy controls (p < 0.05).

Conclusion: These results can guide the patient-specific evaluating and implementation of gait rehabilitation programs, and design protocols before or after surgery in the LDH patients.

Keywords: Intervertebral disc displacement, Gait analysis, Pain, Discectomy, Gait asymmetry
INTRODUCTION

Disc herniation leads to functional loss and disability in daily life activities and negatively affects the quality of life among lumbar disc herniation (LDH) patients. The most important clinical complaints in the LDH patients are lumbar and radiating lower extremity pain, weakness, paresthesia, and numbness. Depending on LDH in sprawling of pain to spine and legs, lower extremity functions, especially walking speed are adversely affected and usually walk slower than their healthy individuals. Although there are differences in symptoms and pain intensity of LDH patients, generally inadequate and abnormal gait patterns and thus deterioration in gait quality and capacity occur.

Gait analysis is a clinically important biomarker for evaluation and treatment planning of disease states. The gait parameters that obtained by gait analysis systems are important gait variables, because they can be easily evaluated and measured to obtain gait deviations and walking difficulties, make a diagnosis, determine appropriate therapy, monitor the patient’s progress, determine the prognosis, and they can help in understanding the functional limitations during gait. The most common parameters selected for gait analysis are the spatiotemporal parameters, which include step duration, swing duration, double support duration, step length, stride length, walking speed (velocity), and cadence. Gait symmetry is defined as a coordinated and consistent activity of the lower extremities during walking. In addition, gait asymmetry reflects a natural functional difference between the limbs due to pathology, and is clinically important in measuring gait pattern changes for observe alterations in gait and evaluate rehabilitative intervention effects. Studies supports existing recommendations that the gait symmetry index should be used as the most precision assessment of gait symmetry on the basis of spatiotemporal gait parameters.

Lumbar microdiscectomy is the most commonly performed minimally invasive spinal surgical procedure for the treatment of patients with LDH, and because it results in less tissue destruction, it minimizes the patient’s activity restriction period. After lumbar microdiscectomy, patients typically mobilize the surgical day and are discharged home the following day. It is known that increases in walking time in the days after lumbar surgery are one of several factors of major improvement in physical function. In the literature, some new research suggests that 2 weeks of activity restriction following lumbar microdiscectomy may be sufficient for most patients. However, there are no studies on the interactions in the spatiotemporal parameters of gait and the changes in gait asymmetry during this process.

Studies have identified the use of gait parameters as a relevant tool for the evaluation of patients with spinal problems and for objective measurement of outcome and recovery. Although it has been demonstrated that there is a strong relationship between gait parameters and functional disability, especially in patients with LDH, data on the evaluation and use of these parameters for postoperative recovery after microdiscectomy seem to be lacking.

The aim of this study was to emphasize on that the interaction of spatiotemporal gait parameters and changes occurring compared to the healthy control group is given importance in the patients with LDH. In addition, this study was planned to analyze the changes in spatiotemporal gait parameters and gait asymmetry in the LDH patients before and 15 days after microdiscectomy within the period of minimum activity restriction. We hypothesized that there would be changes in the spatiotemporal gait parameters and gait asymmetry during the period of minimal activity restriction with the reduction of pain after microdiscectomy.

MATERIALS AND METHODS

This study included the patients admitted to Bahçeşehir University Göztepe Medical Park Hospital, Brain and Spine Surgery Department, and were diagnosed with LDH between May 2016 and December 2017. This study and its procedures were approved by the ethical committee of the Bahçeşehir University Faculty of Medicine (Protocol No. 22481095-020-482, 2016-04/07), and it was performed in terms of the guidelines of the Declaration of Helsinki. All patients provided written informed consent.

Also, the following inclusion criteria were applied: (1) individuals who were diagnosed with LDH by a specialist; (2) the patients with LDH had a medical history and proven by MRI; (3) to be diagnosed with disc herniation at L4–5 and L5–S1 levels; (4) aged between 25–80 years old; (5) pain symptom on lumbar area or lower extremity for at least 1 month. Moreover, the exclusion criteria were as follows: (1) receiving any conservative treatment; (2) having congenital deformity in the spine or lower extremity; (3) history of spinal surgery or other diseases affecting gait; (4) pregnancy; (5) situations that may cause balance problems; (6) presence of nerve root damage symptoms; and (7) using assistive gait appliance.

In the present study, quantitative gait assessment was performed using a gait analysis platform system (Win-Track; Medicapteurs, Balma, France). The dimensions of this device are 1,610 mm × 652 mm × 30 mm (length × width × height), the thickness...
of the platform is 9 mm, which consists of 12,288 resistive type sensors. The dimensions of these sensors are 7.8 × 7.8 mm², and the acquisition frequency of the apparatus is up to 200 images/sec, which has the ability of digitally recording the pedobarographic and spatiotemporal information of subjects’ gait based on the center of foot pressure. The Win-Track platform device is equipped with sensitive sensors that detect all walks and convert them into numerical data, which are then transferred to the computer environment (Fig. 1). Since Win-Track provides fast and high reliability quantitative analysis, this platform was used in this study.20,21 The test-retest reliability of the “Win-Track” Platform walk analysis platform system was performed by Ramachandra et al.22 in 2012. As for the gait protocol used in our study, we adopted the 3-step protocol that has been previously shown to have good reliability, with intraclass correlation coefficient values ranging from 0.75 to 0.90.22

The sample size and power analysis were performed using the G*Power (v3.1.9.7, Axel Buchner, Universitat Kiel, Germany) program. The sample size for this study was predicted by calculating the differences of the mean values of back pain intensity (1.7) and leg pain intensity (3.5), as well as the average values of standard deviation for back pain intensity (2.7) and leg pain intensity (2.75) between presurgery and 3-month follow-up. These measurements were assessed by the visual ana-

![Fig. 1. A sample format of the spatiotemporal analysis.](https://doi.org/10.14245/ns.2346122.061)
logue scale (VAS) based on the study of Schulte et al.\textsuperscript{23} which yielded an effect size of \(d = 0.6605227\). With statistical power 95% and an alpha level of 0.05, it was determined that a minimum of 51 participants was needed for each group.

The participants were asked to continuously walk barefoot for 10 times in their normal walking speed as straight as possible without any gait assist device on the Win-Track platform within the same day, prior to and 15 days after surgery. The pain intensity of the patients was recorded shortly before performing the analysis. There was no change in the pain intensity of the patients during the analysis. Three flawless walking data analysis of spatiotemporal gait parameters were recorded and the arithmetic means were computed with 3 repetitions. In the gait chart transferred from the platform to the computer environment during walking, the 3 most perfect gait data, in which the gait cycle (3 steps) and foot pressure can be clearly seen, were selected for analysis. Whenever they were about to take a rest, the patients were allowed to sit down on a chair. The analysis of the spatiotemporal gait parameters was performed on the healthy control group’s participants by the same investigator using the same equipment and measurement protocol (Fig. 2). The patient provided written informed consent for the publication of her identifiable image included in Fig. 2.

The brief description of the gait parameters used in this article is as follows:

- **Step duration (sec):** the time elapsed in the right or left step length.
- **Gait cycle duration (sec):** the time elapsed in a gait cycle.
- **Double stance duration (sec):** the period of time when both heels are in contact with the ground.
- **Swing duration (sec):** the period of time when the foot under consideration is not in contact with the floor.
- **Step length (cm):** the distance between the heel contact of both feet during walking (Fig. 3).
- **Gait cycle length (cm):** the distance between the 2 heel contacts of the same foot (Fig. 3).
- **Walking speed (velocity) (cm/sec):** walking speed is obtained by multiplying step length by cadence.
- **Cadence (step/min):** the number of steps per unit time.

Pain intensity was obtained using a VAS. VAS is usually a horizontal line, containing a numerical range from 0 (no pain) to 10 (the strongest pain), anchored by word descriptors at each end with “no pain” (score of zero) on the left side and “most severe pain level” or “the worst pain imaginable” (score of 100 [100-mm scale]) on the right side. The patient was asked to mark the line point representing his or her current pain.\textsuperscript{24}

The gait symmetry index (Robinson formula) was used to calculate the asymmetry between the left and right extremities during walking as a percentage (X: gait parameter; L: parameter of left limb; R: parameter of right limb).\textsuperscript{25} The value of 0% indicates perfect symmetry, while increasing values indicates its asymmetry.

\[
\text{Symmetry Index} = 2 \times \frac{|X_R - X_L|}{(X_R + X_L)} \times 100\%
\]

The IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA), was used for the all statistical analysis (SPSS Inc., Chicago, IL, USA). Normality was analyzed using the Kolmogorov-Smirnov test. Chi-square test was used to compare the gender between surgical group and healthy controls. The Independent t-tests for parametric, or Mann-Whitney U-tests for non-parametric.
metric data was used to compare the means between surgical group and healthy controls for demographic characteristics, gait symmetry and all the spatiotemporal gait parameters. The paired sample t-test and Wilcoxon test were used to analyze the spatiotemporal gait values and gait symmetry in the patients with LDH before and 15 days after surgery. A p-value of < 0.05 was considered to indicate a statistically significant difference.

RESULTS

In total, 113 participants were included in this study as 59 patients with LDH (24 females, 35 males) and 54 healthy individuals in the control group (27 females, 27 males). The distribution of disc herniation level in the patients with LDH was as follows: 31 patients (52.5%) at the level of L4–5, and 28 (47.5%) patients at the level of L5–S1. There was no significant difference in the distribution of the disc herniation level in LDH (p = 0.696). The side of the disc herniation was distributed 32–27 (54.2%–45.8%) between right and left in LDH. There were also

Table 1. Demographic characteristics of the participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDH (n = 59)</th>
<th>Healthy controls (n = 54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.05 ± 14.21 (26–79)</td>
<td>47.91 ± 11.01 (25–75)</td>
<td>0.194</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.71 ± 0.1 (1.52–1.88)</td>
<td>1.70 ± 0.07 (1.55–1.85)</td>
<td>0.545</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.36 ± 10.22 (56–99)</td>
<td>74.44 ± 10.91 (52–98)</td>
<td>0.052</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.84 ± 3.47 (20.5–36.9)</td>
<td>25.74 ± 3.38 (18.7–34.7)</td>
<td>0.090</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.320</td>
</tr>
<tr>
<td>Female</td>
<td>24 (40.7)</td>
<td>27 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (59.3)</td>
<td>27 (50.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation (range) or number (%). LDH, lumbar disks herniation; BMI, body mass index.

Table 2. Pain intensity score of vertebral level before surgery

<table>
<thead>
<tr>
<th>No.</th>
<th>Pain intensity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L4–5</td>
<td>31</td>
<td>5.84 ± 1.51 (3–8)</td>
</tr>
<tr>
<td>L5–S1</td>
<td>28</td>
<td>5.86 ± 1.21 (4–8)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation (range).

Table 3. The distribution of the temporal and spatial gait parameters in LDH and healthy controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDH preop (n = 59)</th>
<th>Healthy controls (n = 54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L step duration (sec)</td>
<td>0.59 (0.57–0.61)</td>
<td>0.52 (0.50–0.56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>R step duration (sec)</td>
<td>0.58 (0.56–0.60)</td>
<td>0.52 (0.50–0.54)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>L gait cycle duration (sec)</td>
<td>1.19 (1.16–1.21)</td>
<td>1.05 (1.02–1.08)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>R gait cycle duration (sec)</td>
<td>1.17 (1.13–1.20)</td>
<td>1.05 (1.01–1.09)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>L double stance duration (sec)</td>
<td>0.35 (0.33–0.36)</td>
<td>0.29 (0.28–0.30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>R double stance duration (sec)</td>
<td>0.35 (0.33–0.36)</td>
<td>0.30 (0.28–0.31)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>L swing duration (sec)</td>
<td>1.35 (1.31–1.38)</td>
<td>1.18 (1.15–1.22)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>R swing duration (sec)</td>
<td>1.34 (1.31–1.37)</td>
<td>1.20 (1.17–1.23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>L step length (cm)</td>
<td>45.06 (43.57–46.65)</td>
<td>56.33 (55.68–57.02)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>R step length (cm)</td>
<td>45.65 (43.88–47.53)</td>
<td>56.58 (55.71–57.50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>L gait cycle length (cm)</td>
<td>93.23 (90.88–95.93)</td>
<td>112.70 (111.32–114.13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>R gait cycle length (cm)</td>
<td>90.69 (87.92–93.77)</td>
<td>111.75 (110.29–114.13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Velocity (cm/sec)</td>
<td>69.87 (67.23–72.87)</td>
<td>115.70 (113.87–117.38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cadence (step/min)</td>
<td>91.07 (88.57–93.54)</td>
<td>123.74 (122.30–125.08)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean (95% confidence interval). LDH, lumbar disks herniation; preop, preoperative; L, left; R, right. 1Independent t-test. 2Mann-Whitney U-test.
The demographic characteristics of the participants are presented in Table 1. There were no significant differences between the 2 groups in terms of age, height, weight, body mass index (BMI), and sex (p > 0.05).

no significant differences between right and left in terms of disc herniation side (p = 0.515).

Fig. 4. Box plot presentation of mean values for spatial and temporal gait parameters before (preoperative), 15 days after surgery (postoperative), and healthy controls group. (A) Step duration, (B) gait cycle duration, (C) double stance duration, (D) swing duration, (E) step length, (F) gait cycle length, (G) velocity, and (H) cadence. *p < 0.05. °p > 0.05. aPaired sample t-test. bWilcoxon test. cIndependent t-test. dMann-Whitney U-test.
Table 4. Comparison of spatial and temporal gait parameters between preoperative and postoperative, and between preoperative and healthy controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDH (n = 59)</th>
<th>Within-group change score</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Healthy controls (n = 54)</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L step duration (sec)</td>
<td>0.59 (0.57–0.61)</td>
<td>0.54 (0.52–0.55)</td>
<td>-0.05 (-0.08 to -0.03)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.52 (0.50–0.56)</td>
</tr>
<tr>
<td>R step duration (sec)</td>
<td>0.58 (0.56–0.60)</td>
<td>0.52 (0.51–0.54)</td>
<td>-0.06 (-0.09 to -0.04)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.52 (0.50–0.54)</td>
</tr>
<tr>
<td>L gait cycle duration (sec)</td>
<td>1.19 (1.16–1.21)</td>
<td>1.07 (1.05–1.09)</td>
<td>-0.11 (-0.15 to -0.09)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.05 (1.02–1.08)</td>
</tr>
<tr>
<td>R gait cycle duration (sec)</td>
<td>1.17 (1.13–1.20)</td>
<td>1.07 (1.05–1.10)</td>
<td>-0.1 (-0.14 to -0.06)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.05 (1.01–1.09)</td>
</tr>
<tr>
<td>L double stance duration (sec)</td>
<td>0.35 (0.33–0.36)</td>
<td>0.30 (0.28–0.31)</td>
<td>-0.05 (-0.07 to -0.03)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.29 (0.28–0.30)</td>
</tr>
<tr>
<td>R double stance duration (sec)</td>
<td>0.35 (0.33–0.36)</td>
<td>0.31 (0.30–0.32)</td>
<td>-0.04 (-0.06 to -0.02)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.30 (0.28–0.31)</td>
</tr>
<tr>
<td>L swing duration (sec)</td>
<td>1.35 (1.31–1.38)</td>
<td>1.22 (1.18–1.24)</td>
<td>-0.13 (-0.18 to -0.08)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.18 (1.15–1.22)</td>
</tr>
<tr>
<td>R swing duration (sec)</td>
<td>1.34 (1.31–1.37)</td>
<td>1.22 (1.19–1.25)</td>
<td>-0.12 (-0.16 to -0.08)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.20 (1.17–1.23)</td>
</tr>
<tr>
<td>L step length (cm)</td>
<td>45.06 (43.57–46.65)</td>
<td>52.53 (50.79–54.22)</td>
<td>7.50 (5.40–9.60)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>56.35 (55.68–57.02)</td>
</tr>
<tr>
<td>R step length (cm)</td>
<td>45.65 (43.88–47.53)</td>
<td>54.14 (52.68–55.35)</td>
<td>8.50 (6.50–10.50)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>56.58 (55.71–57.50)</td>
</tr>
<tr>
<td>L gait cycle length (cm)</td>
<td>93.23 (90.88–95.93)</td>
<td>106.13 (104.17–108.22)</td>
<td>13.00 (10.00–16.00)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>112.71 (111.32–114.13)</td>
</tr>
<tr>
<td>R gait cycle length (cm)</td>
<td>90.69 (87.92–93.77)</td>
<td>106.67 (104.73–108.65)</td>
<td>16.00 (12.30–19.30)</td>
<td>&lt;0.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>111.75 (110.29–114.13)</td>
</tr>
<tr>
<td>Velocity (cm/sec)</td>
<td>69.87 (67.23–72.87)</td>
<td>94.61 (92.39–96.90)</td>
<td>24.73 (21.87–27.51)</td>
<td>&lt;0.001&lt;sup&gt;§&lt;/sup&gt;</td>
<td>115.70 (113.87–117.38)</td>
</tr>
<tr>
<td>Cadence (step/min)</td>
<td>91.07 (88.57–93.54)</td>
<td>106.70 (104.73–108.54)</td>
<td>15.60 (13.14–18.09)</td>
<td>&lt;0.001&lt;sup&gt;§&lt;/sup&gt;</td>
<td>123.74 (122.30–125.08)</td>
</tr>
</tbody>
</table>

Values are presented as mean (95% confidence interval).
LDH, lumbar discs herniation; L, left; R, right.
<sup>†</sup>Paired sample t-test. <sup>‡</sup>Wilcoxon test. <sup>§</sup>Independent t-test. <sup>¶</sup>Mann–Whitney U-test. <sup>a</sup>p-value: comparison between preoperative and postoperative. <sup>b</sup>p-value: comparison between postoperative and healthy controls.
Table 5. Results of the gait symmetry in preoperative, postoperative and healthy controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDH (n = 59)</th>
<th>Healthy controls (n = 54)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step duration (sec)</td>
<td>13.34 (10.62–16.23)</td>
<td>10.63 (8.59–12.98)</td>
<td>0.135</td>
<td>2.22 (1.60–3.06)</td>
</tr>
<tr>
<td>Gait cycle duration (sec)</td>
<td>7.51 (5.84–9.12)</td>
<td>5.93 (4.59–7.24)</td>
<td>0.180</td>
<td>2.34 (1.57–3.26)</td>
</tr>
<tr>
<td>Double stance duration (sec)</td>
<td>6.74 (4.70–8.85)</td>
<td>8.64 (6.78–10.86)</td>
<td>0.236</td>
<td>3.31 (2.04–4.97)</td>
</tr>
<tr>
<td>Swing duration (sec)</td>
<td>6.32 (4.35–8.73)</td>
<td>6.68 (5.33–8.12)</td>
<td>0.784</td>
<td>2.42 (1.80–3.32)</td>
</tr>
<tr>
<td>Step length (cm)</td>
<td>12.22 (9.67–14.91)</td>
<td>9.15 (7.14–11.24)</td>
<td>0.085</td>
<td>3.81 (2.96–4.85)</td>
</tr>
<tr>
<td>Gait cycle length (cm)</td>
<td>7.01 (5.45–8.71)</td>
<td>4.49 (3.29–5.83)</td>
<td>0.061</td>
<td>3.34 (2.42–4.45)</td>
</tr>
</tbody>
</table>

Values are presented as mean (95% confidence interval).
LDH, lumbar discs herniation.
<sup>a</sup>p-value: comparison between preoperative and postoperative assessment (paired sample t-test).<sup>b</sup>p-value: comparison between postoperative and healthy controls (Mann-Whitney U-test).

The mean (standard deviation) of the pain intensity score was 5.85 (1.36) (range, 3–8) for the patients with LDH before surgery. LDH patients did not report any pain intensity on the 15th day after surgery. Table 2 shows the distribution of the pain intensity score of the disc herniation level in the patients with LDH before surgery. There was no significant difference in terms of VAS scores between the disc herniation levels in the LDH before surgery (p = 0.959).

The spatiotemporal gait parameters were compared with both extremities between the 2 groups. In the preoperative assessment LDH patients had significantly longer step duration, longer gait cycle duration, longer double stance duration, longer swing duration, shorter step length, shorter gait cycle length, slower velocity and less in cadence than the healthy controls. There were significant differences between the 2 groups in all terms of the spatiotemporal gait parameters (p < 0.05) (Table 3).

In the postoperative assessment LDH patients had significantly shorter temporal parameters and longer spatial parameters than the preoperative (Fig. 4). There were significant differences between preoperative and postoperative assessment in all terms of spatial and temporal gait parameters (p < 0.05) (Table 4).

In addition, boxplots in Fig. 4 show the differences in terms of spatial and temporal gait parameters compare between postoperative and healthy controls. In patients with LDH, the temporal parameters of gait at 15 days after surgery were similar to those of the healthy control, and there was no statistically significant difference between the 2 groups (p > 0.05). However, the difference between the postoperative and healthy control groups in terms of the spatial gait parameters were statistically significant (p < 0.05) (Table 4).

Table 5 shows the gait asymmetry values of the patients with LDH before and 15 days after surgery and the healthy control group. There were improvements in the asymmetry values of the postoperative gait parameters compared to the preoperative values, but these improvements were not statistically significant (p > 0.05). The LDH patients in postoperative assessment had significantly higher gait asymmetry than the healthy controls (p < 0.05).

DISCUSSION

This study was conducted to evaluate the interactions and alterations in spatiotemporal gait parameters and analyze the gait asymmetry pre- and postoperatively in the individuals with and without LDH. Also, the potential impacts of microdiscectomy on the LDH patients were quantitatively assessed by comparing the gait abnormalities before and after performing the surgical procedure. We observed an increase in the spatial and a decrease in temporal characteristics of the gait in the LDH patients compared to those in normal subjects.

The results of our study showed that there were significant differences in all spatiotemporal parameters of gait between LDH patients (preoperative) and healthy controls, and while improvements in all spatiotemporal gait parameters were significant on the 15th day after microdiscectomy compared to presurgery, these improvements were not achieved in gait asymmetry. Furthermore, our findings revealed that while microdiscectomy significantly improves the temporal parameters of gait, these improvements were not meaningful in terms of spatial parameters and gait asymmetry between LDH and healthy subjects.

As far as we know, the present study is the first to examine the gait symmetry of LDH patients before and 15 days after microdiscectomy, and compare with healthy controls. Although changes were obtained postoperative gait asymmetry scores than
the preoperative assessment in patients with LDH, differences were not significant. In addition to, it was determined that there was still more gait asymmetry after surgery currently compared to healthy controls.

Some investigators reported important findings regarding the consideration of psychological factors such as lumbar instability, impaired paraspinal muscle activity and quality, lower extremity muscle weakness, and fear assumptions about pain in addition to physiological factors and pain with walking, when studying spinal disorders. The presence of these factors leads to inefficient energy expenditure, fatigue and imbalance in spinal and adversely affects the patient's quality of life and daily activities such as walking.

In the literature, several investigators have found some differences in gait kinematics between normal and chronic low back pain (CLBP) cases in nonsurgical cases. For example, Barzilay et al. stated that, healthy controls had faster walking speed with longer step length and higher cadence compared to CLBP counterparts. Also, Bacchini et al. examined the gait behaviors in 9 patients with lumbar stenosis using a 3-dimensional (3D) opto-electronic system, and noticed an increase in the double stance duration and the decreased stride length in these patients. Al-Obaidi et al. studied the pain-related factors affecting gait performance in 31 CLBP and 24 normal cases. Conclusively, it has been demonstrated that, step length, single support time, and walking velocity differed between the 2 groups. CLBP patients tend to walk slowly with shorter step length and shorter single support time, which are mainly attributed to psychological factors such as pain-related fear beliefs, rather than physiological ones. Similarly, Hicks et al. studied gait performance in elderly adults (mean age, ~71.5) with CLBP, and demonstrated that, the patients with CLBP have significantly shorter step length, shorter stride length, greater stance times, and longer periods of double support time, which substantially declines the walking speed in these participants as compared to pain-free individuals.

In addition, most spatiotemporal parameters differed between the patients and control subjects. The patients with lumbar spinal stenosis (LSS) had the longer stride duration, shorter stride length, and at slower speed compared to the control group. More recently, Miscusi et al. demonstrated a decreased walking velocity and a shorter step length in the LDH group in comparison to control group, which may be resulted from back pain, lumbar instability, and impaired spinal muscle activity.

In line with our previous work, we found a significant difference in all the spatiotemporal gait parameters between the LDH and healthy control groups. LDH group's participants had significantly longer step duration, longer gait cycle duration, longer double stance duration, longer swing duration, shorter step length, shorter gait cycle length, slower walking speed, and less in cadence for both extremities as compared with healthy controls, which is attributed to the strong correlation between pain intensity and gait parameters. These results are consistent with previous findings reported by Papadakis et al. and Kim et al.

Regarding our results and clinical observations, the LDH patients often try to alter and adopt their gait patterns to alleviate the level of pain induced in different physical activities. They usually avoid wide trunk, pelvic and hip movements, restrict the relative knee range of motion, and refrain from weight transfer between left and right extremity to avoid exacerbation of the pain, to maintain their balance. This strategy can negatively affect their gait parameters resulting in a shorter step length of these extremities and casus deterioration in gait symmetry.

Several studies attempted to assess the improvements in gait pattern after surgical treatment. Accordingly, Suda et al. have assessed the gait performance in the patients with neurogenic intermittent claudication via a ground reaction force plate. They showed that, gait cycle length, velocity, and also the gait pattern markedly improved in these patients 6-month postsurgery. Loske et al. performed a pre-operation and postoperation gait analysis on the patients with LSS and observed notable improvements in gait variables in these group at 12-month follow-up tests. Meanwhile, faster walking speed, higher cadence, and longer gait cycle length were observed after surgery. In another study, Haddas et al. examined the spatiotemporal gait parameters before and 3 months after surgery in patients with degenerative lumbar spondylolisthesis, and they revealed that significant improvements were observed in terms of increased velocity, decreased step duration, and decreased double stance duration after surgery; However, the same was not current for spatial parameters. Moreover, they reported there was a significant difference in terms of spatiotemporal parameters between 12 weeks after surgery and controls, although most of the mean values returned to normal after surgery.

In the current study, we noticed that, gait profile is quite different in the LDH patients before and 15 days after microdiscectomy intervention, which is due to a reduction in lower limb pain, increase in the level of self-confidence and ability of walking, enhancement in the muscle strength and endurance, and in lumbar stability as well. Thanks to the short-term effects of surgical treatment and postoperative rehabilitation programs, which promote the self-confidence along with the functional...
ability in these patients, the spatial and temporal characteristics of the gait achieved the normal level only by passing 15 days postoperation given that. In addition, although the postoperative group had similar temporal parameters to the healthy control group, they had shorter step length, shorter gait cycle length, slower velocity, and less cadence than the healthy control. However, it should be noted that this period (15 days after surgery) is not sufficient to achieve full recovery in gait parameters. The difference in all parameters might be caused by presence of lower extremity insufficient muscle strength, abnormal gait pattern developed by the patient, and pain.

Although some researchers have been carried out on gait symmetry in other spinal disease, it seems that studies are lacking investigating changes in gait asymmetry before and after microdiscectomy surgery within the period of minimum activity restriction in LDH patients. Loske et al. indicated the LSS patients had higher gait asymmetry than the healthy control subjects, and while the spatiotemporal parameters reached normal values ~10th week after surgery, gait asymmetry reached levels of the healthy controls ~12th month after surgery. Moreover, they reported that improvements in gait asymmetry (less asymmetric) were highly associated with pain intensity (greater reduction).

Another study by Natarajan et al. evaluated the gait asymmetry clinically by using wearable devices with the new scoring algorithm they suggested and reported in LDH patients who underwent surgery the gait asymmetry index were higher than the control group, and there was a significant difference between the 2 groups. According to the results of this research, that although the mean values of gait asymmetry were different before and after surgery in patients with LDH, this difference was not significant between the 2 assessments. It also revealed that 15 days after surgery is not a sufficient period to achieve improvements in gait symmetry and regain normal values.

According to the authors clinical experiences there are possible reasons for differences of the gait asymmetry in the LDH patients after surgery compared with the control group. The weak proximal limb, decreased core muscle stability, lower extremity muscle weakness of the affected side and pain intensity and/or perception are among the major causes that are likely to persist. Overall, as it is known that the presence of a unilateral limp and the compensatory limb motions resulted in increased the gait asymmetry factors and reduced smoothness of limb motions in LDH patients.

This study has several strengths, and the most notable one was the sample size, which is large enough and uniform (e.g., similar age ranges and BMI, and use of one type of surgery) to guarantee and credit the reliability and applicability of our findings. Another strength of our research was that, repeated the measurements and gait asymmetry analysis, which is of paramount importance when the end goal is clinical application. Also, it has some limitations such as inaccessibility to 3D camera set and other forms of inquiry and inability to obtain kinetic and kinematic values. Evaluation of physical activity levels of the patients and the fact that the gait habits of everyday life were not evaluated, can be acceptable. We suggest that future studies should investigate when patients with LDH will regain normal gait patterns after the surgical treatment. In addition to, the WinTrack platform system offers distinct advantages over 3D camera systems used in clinics. Specifically, it provides a faster analysis and is more cost-effective. However, we acknowledge that access to this platform may not always be available. In such cases, an alternative approach would be to record the patient’s walking and have it analyzed by a specialist in the field. It is important to note, however, that the results obtained through this method may not be entirely objective.

CONCLUSION

Regarding the methodology pursued in our study and the objective analysis of the outcomes, it is feasible to achieve the best possible decision given in clinical applications without the need for performing any further analysis.

This paper attempted to assess the spatiotemporal gait and gait symmetry alterations in the LDH patients, then compared the results with healthy control group, and also compared with preoperative and postoperative results. Although the LDH patients develop a unique gait strategy to prevent pain intensity, it negatively affects normal gait parameters and this cause different problems in later periods. In LDH patients, eliminating or minimizing pain with microdiscectomy surgery can improve spatiotemporal gait parameters in the period of minimum activity restriction, but this period seems insufficient to achieve full recovery in gait and regain gait symmetry. For this reason, in order to eliminate deficiencies and provide full recovery, it is necessary to give importance to ambulatory gait training and treatment in rehabilitation programs in the period of minimum activity restriction. Our results can guide the patient-specific evaluating and implementation of gait rehabilitation programs, and design protocols before or after surgery in the LDH patients. The results of this study showed that it is possible to obtain better results in time and distance parameters of walking by reliev-
ing or eliminating pain in LDH patients with minimally invasive surgical methods such as microdiscectomy. However, it is important to note that factors such as impaired paraspinal muscle activity and quality, lower extremity muscle weakness and psychological factors that may affect walking, apart from pain, should be considered in the treatment.

NOTES

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ORCID
Masoud Amir Rashedi Bonab: 0000-0002-7875-0499
Suleyman Sener: 0000-0002-7990-4090
Tugba Kuru Colak: 0000-0002-3263-2278
Mahsa Amirrashedi: 0000-0002-3062-7641
Ipek Yeldan: 0000-0002-6344-4157
Deniz Konya: 0000-0002-4263-6096
Zafer Orkun Toktas: 0000-0002-5842-5891

REFERENCES


Relationships Between Skeletal Muscle Mass, Lumbar Lordosis, and Chronic Low Back Pain in the Elderly

Myung Woo Park1,*, Sang Jun Park2,*, Sun Gun Chung3

1Department of Rehabilitation Medicine, Chung-Ang University Hospital, Seoul, Korea
2Jun Rehabilitation Medicine Clinic, Seoul, Korea
3Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Objective: Loss of skeletal muscle mass is known to be associated with multiple morbidities. However, there is a dearth of reports on its association with lumbar lordosis and musculoskeletal pain. The aim of this study was to delineate the cross-sectional relationship between loss of skeletal muscle mass, lumbar lordosis, and chronic low back pain (CLBP).

Methods: A total of 721 medical records were reviewed, and data from 165 older subjects (over 65 years old; 81 men and 84 women) were retrospectively analyzed. Subjects were categorized into either the CLBP group (back pain for more than 6 months; 35 men and 36 women) or the control group (46 men and 48 women). The modified skeletal muscle mass index (MSMI, appendicular skeletal muscle mass \( \text{[kg]} / \text{weight \[kg]} \times 100 \)), assessed by bioelectrical impedance analysis, and lumbar lordotic angle (LLA) were measured and compared between the CLBP group and the control group. The correlation between MSMI and LLA was investigated.

Results: The LLA of men and women in the CLBP group was significantly lower than that of the control group (p < 0.05). The MSMI was decreased in the CLBP group compared to the control group (p < 0.05). For both sexes, positive correlations were observed between the MSMI and LLA.

Conclusion: A close cross-sectional relationship was observed between MSMI, LLA, and CLBP. This suggests a potential interaction between the reduction in skeletal muscle mass and altered lumbar spine sagittal alignment, which could lead to CLBP.

Keywords: Low back pain, Sarcopenia, Lordosis

INTRODUCTION

Chronic low back pain (CLBP) has become an important social issue in the era of aging as it can lead to increased medical costs, as well as, disabilities affecting the patient’s quality of life.1 While it is hard to pinpoint a specific cause of low back pain, approximately 97% of low back pain is believed to be related to mechanical causes.2 This has given rise to a growing body of research focusing on recovery or rehabilitation after surgical interventions for these causes,3,4 prognostic predictions for post-operative outcomes,5 and parameters associated with CLBP.6–9 To prevent or treat CLBP, maintaining sound mechanical integrity of low back would be crucial because stability of spine depends on passive spinal column, active spinal muscles, and neural controls.10

More recently, there has been a surge in studies investigating the various influences of sarcopenia on cardiovascular disease, metabolic disorders, and musculoskeletal disorders.7,11,12 Considering that muscle is vital for protecting the integrity of the musculoskeletal system, there must be meaningful associations between loss of skeletal muscle mass and painful musculoskeletal conditions. Previous studies examining the relationship between regional muscle mass and CLBP reported that the cross-sectional area of the trunk and back muscles, as assessed by com-
The importance of healthy muscular control on spinal column was evidenced that muscular activation or training helped to prevent CLBP by providing stability or postural correction. Also, altered sagittal alignment has been described as a substantially influencing factor for CLBP including symptomatic adjacent segment degeneration, and a meaningful relationship has been reported between CLBP and decreased lumbar lordotic angles (LLAs). Considering muscle integrity is important for maintaining normal LLA and adequate sagittal balance; there may be a significant association between loss of skeletal muscle mass and CLBP, probably through altered sagittal balance such as changes of LLA.

To examine the hypothesis that there might be close relationships between skeletal muscle mass, LLA, and CLBP, this study retrospectively analyzed health-screening data to investigate any differences in muscle mass and LLA between elderly subjects with and without CLBP, and to evaluate the relationship between skeletal muscle mass and LLA.

MATERIALS AND METHODS

1. Data Source

We performed a retrospective cross-sectional study based on health-screening data of subjects aged 65 and over who had routine medical check-up at the Gangnam Health-Care Center, Seoul National University Hospital between January 1, 2012 and June 30, 2014. The routine medical check-up program is a preventive health-screening program for normal population, comprising a basic anthropometric examination, serologic tests, tumor marker studies, head and neck examination, simple radiologic studies, abdominal ultrasonography, cardiologic work-ups, gastrointestinal endoscopic studies, and counseling with a physician. Additionally, all medical check-up recipients underwent BIA, standing lumbar lateral radiography, and an assessment of back pain history by a physician. All of the subjects were Koreans by ethnicity and citizenship.

Subjects who had been experiencing low back pain for more than 6 months were included in the CLBP group, while subjects who reported no back pain during the past 6 months were included as study controls. Medical data were excluded from the analysis if a subject had acute low back pain newly occurred within the past 6 months, spine cancer, spinal trauma, compression fracture, rheumatoid arthritis, history of spinal surgery, or if there was no written medical record about back pain history on review of system.

This study was approved by the institutional review board of Seoul National University Hospital (IRB No. H-1404-031-568).

2. Data Analysis

A lumbar spine lateral radiograph was taken, with focus on the lumbar region and at a distance of approximately 1 meter away from the subject. The subject was instructed to stand naturally while gripping a handle in front of them as lightly as possible to maintain balance. For measurements of LLA, 2 lines were drawn parallel to the upper endplate of the L1 vertebra and the lower endplate of the L5 vertebra. Perpendicular lines to each of the aforementioned lines were drawn so that their intersection formed the LLA (Fig. 1).

BIA with 8 tactile electrodes (MF-BIA8; InBody 720, Biospace, Seoul, Korea) was used to measure the impedances of 5 body segments (right arm, left arm, trunk, right leg, and left leg) separately, and using 6 different frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, 1,000 kHz). In the routine medical check-up, a trained nurse took the BIA measurements after at least 3
hours of fasting and voiding by the subject. For the measurements, subjects were instructed to be barefoot and stand upright with their feet placed on electrodes of the machine platform, and with their hands gripping on to the electrodes of the arm handles. The ASM was obtained by summing the 4 measurement values of both arms and legs, which were separately presented after calculation of muscle mass in each limb and the trunk. To compare muscle masses among subjects with different body habitus, ASM was normalized considering the body weight to generate the modified skeletal muscle mass index (MSMI), calculated as (ASM [kg]/weight [kg] × 100%).

3. Statistical Analysis

Age, weight, height, body mass index (BMI), MSMI, and LLA were compared between the CLBP and control groups by using an independent T-test. Correlation analysis was also performed between LLA and MSMI using Pearson correlation coefficients. All statistical analyses were performed separately for male and female subjects as normal ranges of MSMI and LLA are reported to differ significantly based on sex. In addition, a subgroup analysis was performed in which the total subject was divided into 2 age groups: those under 70 and those aged 70 or over.

RESULTS

1. Subject Profiles

Data of 308 subjects over the age of 65 were extracted from a dataset of 721 subjects who underwent BIA and lumbar spine radiography on the same day. Subjects who did not meet the study-specific inclusion criteria were excluded (n = 143). Subjects with a history of spine trauma (n = 41), no description for the presence or absence of back pain (n = 38), back pain occurrence within 6 months (n = 35), history of spine surgery (n = 12), compression fractures (n = 10), spine cancer (n = 6), and rheumatoid arthritis (n = 1) were excluded from the analysis. Data of the remaining 165 subjects were included in the final analysis. The final analysis included data of 81 men and 84 women categorized into either the CLBP or the control group (Fig. 2).

Table 1. Subject characteristics at the time of study entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 81)</th>
<th>Women (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLBP (n = 35)</td>
<td>Control (n = 46)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70 ± 3.9</td>
<td>69.6 ± 5.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.9 ± 7.4</td>
<td>68.4 ± 7.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.3 ± 4.7</td>
<td>168.1 ± 4.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 2.4</td>
<td>24.2 ± 2.2</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
CLBP, chronic low back pain; BMI, body mass index.
*p < 0.05, statistically significant differences.
Women with CLBP were significantly shorter than those in the control group (p = 0.02); however, there were no significant differences in age, weight, or BMI between the 2 study groups for men or women (Table 1).

2. Comparisons of the LLA Between the CLBP and Control Groups

Fig. 3A illustrates the differences in LLA between CLBP and control groups. A significantly lower LLA was observed in men from the CLBP group (29.8° ± 10.6°) compared to those in the control group (37.1° ± 8.5°, p = 0.001). Similarly, LLA was smaller in women with CLBP in comparison to their counterpart controls (32.1° ± 11.2° vs. 38.3° ± 9.2°, p = 0.006). In the subgroup analysis, participants were divided into 2 groups: those under 70 years of age and those aged 70 or over. For men under the age of 70, the CLBP group had a statistically significant lower LLA than the control group (29.4° ± 10.2° vs. 38.8° ± 8.7°, p = 0.002) (Fig. 3B). For women aged 70 or over, the CLBP group had a statistically significant lower LLA than the control group (30.3° ± 11.2° vs. 37.7° ± 8.8°, p = 0.046) (Fig. 3C) (see Supplementary Tables 1 and 2 for details).

3. Comparison of the MSMI Between the CLBP and Control Groups

Fig. 3D illustrates the difference in MSMI between CLBP and control groups. Male CLBP subjects had lower MSMI (31.2% ± 1.7%) than male control subjects (32.3% ± 1.9%, p = 0.008). Female subjects also showed similar results considering MSMI values (26.1% ± 1.9% vs. 27.1% ± 2.1%, p = 0.021) for the CLBP and control groups, respectively. In the subgroup analysis based on age into 2 groups (< 70 and ≥ 70), the MSMI value was significantly lower in the CLBP group compared to the control group for women under 70 (25.8% ± 1.9% vs. 27.5% ± 2.3%; p = 0.007) (Fig. 3E) (see Supplementary Tables 1 and 2 for details).

4. Relationship Between the MSMI and the LLA

Positive correlations were observed between the LLA and the MSMI both in the male (r = 0.220, p = 0.048) and female (r = 0.225, p = 0.040) subjects (Fig. 4A, D). In the age-stratified subgroup analysis, a significant positive correlation between LLA and MSMI was observed in women under the age of 70 (r = 0.336, p = 0.015) (Fig. 4E).
DISCUSSION

In the present study, retrospective analysis of routine medical check-up data of subjects older than 65 years revealed decreased LLA and MSMI in CLBP subjects. The LLA and MSMI of the CLBP group was significantly lower than that of the control group.

A significant positive relationship between LLA and MSMI were also observed.

1. Relationship Between Muscle Mass and CLBP

The results of this study, which showed significantly lower MSMI in the CLBP group, were in line with previous studies.

Fig. 4. Correlation between LLA and MSMI. The Pearson correlation coefficient between the LLA and the MSMI for men (A–C) and women (D–F). (A, D) Total subject population, (B, E) subjects aged 65 to less than 70, and (C, F) subjects aged 70 and above. LLA, lumbar lordotic angle; MSMI, modified skeletal muscle mass index; CLBP, chronic low back pain. *p < 0.05.

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that have demonstrated the relationship between CLBP and the quality and quantity of truncal and appendicular muscle. Danneels et al. reported that the cross-sectional areas of the psoas and multifidus muscles below the L4 endplate were decreased in patients with CLBP. Hicks et al. and Baek et al. also reported that increased fat infiltration of the trunk muscles was significantly associated with CLBP, although the area per se of the trunk muscles did not show a significant difference. Additionally, Eguchi et al. demonstrated that the severity of clinical symptoms, as assessed by the Roland-Morris Disability Questionnaire, was significantly correlated with ASM. Considering previous findings on the association between truncal muscle and ASM, which is used as a criterion for sarcopenia, the present results showing that the CLBP group had lower MSMI could be interpreted in 2 different ways.

Firstly, it may reflect the fact that the mechanical integrity of the lumbar spine is influenced, not only by the paraspinal and abdominal muscles, but also by whole body muscles including the proximal limb muscles. Leinonen et al. reported that activity of the gluteus muscles was reduced in patients with CLBP during flexion-extension cycle. Increase of fatigability in the gluteus maximus muscle was also noted in CLBP patients through an electromyography fatigue analysis. Furthermore, the evidence that multiple kinetic chains were involved in CLBP has also been supported by the study by Kim et al., which showed increased activity of contralateral latissimus dorsi, ipsilateral gluteus maximus, and ipsilateral biceps femoris in patients with CLBP during hip extension test. In addition, a previous study by Eguchi et al. demonstrated that ASM was associated with posterior pelvic tilt. This research also found a correlation between low back pain and both the ASM and posterior pelvic tilt. This suggests that decreased skeletal muscle mass may influence low back pain through its interactions with sagittal alignment. Based on this evidence, the lower MSMI in the CLBP group implicates that loss of muscle mass may predispose elderly people to CLBP.

Secondly, lower MSMI in the CLBP group may be consequential of chronic pain endured rather than a causative factor. It has been reported that chronic musculoskeletal conditions prevented patients from maintaining physical activities. However, de-conditioning effects of CLBP in our results might not have been substantial because the data were collected from a preventive health-screening program for normal population, indicating that the pain severity of CLBP in this study might not be severe enough to make the subjects seek medical service. It limits the interpretation of the results that the pain severity was not assessed in this study. While it is not possible to delineate causal relationships in this cross-sectional analysis, a relationship between CLBP and decreased muscle mass is intriguing.

2. Quantification of Muscle Mass and Sarcopenia

In the diagnosis of sarcopenia, skeletal muscle mass can be quantified by measuring ASM using dual-energy x-ray absorptiometry (DXA) or BIA. To appreciate variations in the body habitus of each person, European Working Group on Sarcopenia in Older People (EWGSOP) and Asian Working Group for Sarcopenia (AWGS) have presented cutoff values for the MSMI based on a height-adjusted (ASM [kg]/height [m]²) or weight-adjusted (ASM [kg]/weight [kg] × 100) method. Between the 2 methods, the weight-adjusted method is preferred in elderly people of Asian origin, as it has previously been reported that the height-adjusted method had a tendency to underestimate the prevalence of sarcopenic obesity and sarcopenia, and did not correspond well with measurements of physical function in elderly Asians. In this study, we measured MSMI using the weight-adjusted method.

As the medical check-up program did not include measurements of muscle strength or performance, we could not apply the criteria of sarcopenia advocated by EWGSOP or AWGS. Nevertheless, when we applied the cutoff values of MSMI for sarcopenia from a previous study to compare with the Korean population, it is intriguing that the CLBP group in the present study had a substantially higher prevalence of sarcopenia (17.1% for men and 13.9% for women) than the control group (2.2% for men and 0% for women). The prevalence of sarcopenia in subjects with CLBP in this study tended to be higher than normal age-matched population, in which it was 9.7% and 11.8%, respectively. This suggests a meaningful cross-sectional association between sarcopenia and CLBP.

It is of note that the prevalence of sarcopenia in our subjects was substantially low compared with those of other cohorts including the Fourth Korean National Health and Nutrition Examination Surveys (KNHANES IV) conducted in 2008–2009, which reported approximately 9.7% for men and 11.8% for women. The authors speculate that this finding may be related with the fact that the subjects included in our study had rather higher socio-economic status to have lower risks of sarcopenia because all of them were willing and able to pay more than $1,500 for their annual health checkups either by themselves or through employing companies.
Relationship Between Muscle Mass, Lordosis, Low Back Pain

Park MW, et al.

X-ray
≥ 65
Decreased LLA in LBP
X-ray

The relationship between acute low back pain (LBP) and chronic LBP.

18
48–89
-16,17,30-32
Age (yr)
Increased LLA in LBP

Also argued that the LLA was decreased in CLBP.

Christie et al. reported an association between spinal sarcopenia and which could result CLBP 203, control 683

X-ray
33

LLA was increased in patients with CLBP and thus it would be one of the causes of back pain. On the other hand, Tsuji et al. reported that LLA was decreased by approximately 4 degrees in patients with CLBP regardless of sex or age. Jackson and McManus also argued that the LLA was decreased in patients with CLBP, especially in the distal segment lordosis. There have been several studies that also reported no significant tendency, either decreasing or increasing, in LLA depending on CLBP,33 acute low back pain (LBP) and chronic LBP.31 Hansson et al.31 reported that there was no change in LLA in acute LBP, as well as, chronic LBP, and Pope et al.34 reported that there was no difference in LLA between the group that did not experience LBP, and groups with moderate back pain or severe back pain.

Table 2 provides a summary of previous published reports on the relationship between LLA and LBP, and an interesting association is noted between the age of participants and changes in LLA; in older subjects, there was a stronger tendency to observe decreases in LLA in LBP groups. This association is consistent with our study, which analyzed data from subjects older than 65 years, and found significantly decreased LLA in our CLBP group than the controls. Because the control groups were taller than the CLBP groups especially in female subjects, the possibility of confounding effects from height difference on LLA was tested by calculating correlations between the heights and LLA in our data to find little associations in the male (r = 0.087, p = 0.440) and female (r = 0.044, p = 0.691). This finding suggests that alterations of sagittal balance in the lumbar spine may operate differently in LBP of younger versus older population. In younger people who have minimal or no disc degeneration, decreases in LLA would hardly occur in LBP conditions. Instead, LBP may trigger paraspinal muscle spasm which could result in an increased LLA. However, because advanced disc degeneration is one of the predominant causes of CLBP in the elderly, severe degeneration would decrease LLA and predispose to CLBP.36,37 This speculation draws a hypothesis that preserving LLA may have preventive or therapeutic effects on CLBP in an elderly population. Nevertheless, further longitudinal studies incorporating additional radiologic parameters reflecting sagittal alignment, such as pelvic tilt and sagittal vertical axis, to substantiate this hypothesis are required.

4. Relationship Between Muscle Mass and LLA

It is noteworthy that the present study revealed significant correlations between LLA and MSMI both in male and female subjects. Proper function and integrity of trunk muscles are known to be associated with maintaining LLA19,20 and compensating for sagittal balance.21 In conjunction with previous findings showing a relation between ASM and posterior pelvic tilt,11 the substantial association observed in this study between LLA and MSMI suggests that a loss of muscle mass may lead to a decrease in LLA in the elderly population. However, in this study, the association between LLA and MSMI was observed less in subjects aged 70 years and older compared to those under 70. These findings might be related to a possible presence of coexisting spinal sarcopenia in the elderly. Previous research by Kim et al.38 reported an association between spinal sarcopenia and spinal sagittal balance in community-dwelling elderly women (mean age, 76.8 years). Also, the study of Eguchi et al.11 on community-dwelling elderly women (mean age, 74 years) demonstrated that ASM and truncal muscle mass were significantly

Table 2. Published reports on the relationship between lumbar lordotic angle and low back pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Measuring modality</th>
<th>Subgroup</th>
<th>Age (yr)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie et al.30</td>
<td>Photograph</td>
<td>LBP 39, control 20</td>
<td>18–46</td>
<td>Increased LLA in LBP</td>
</tr>
<tr>
<td>Pope et al.34</td>
<td>X-ray</td>
<td>Severe LBP 71, moderate LBP 144, control 106</td>
<td>18–55</td>
<td>No difference</td>
</tr>
<tr>
<td>Hansson et al.31</td>
<td>X-ray</td>
<td>CLBP 200, 1st injury 200, control 200</td>
<td>20–63</td>
<td>No difference</td>
</tr>
<tr>
<td>Jackson and McManus17</td>
<td>X-ray</td>
<td>LBP 100, control 100</td>
<td>20–65</td>
<td>Decreased LLA in LBP</td>
</tr>
<tr>
<td>Murrie et al.33</td>
<td>MRI</td>
<td>LBP 27, control 29</td>
<td>26–65</td>
<td>No difference</td>
</tr>
<tr>
<td>Korovessis et al.39</td>
<td>X-ray</td>
<td>LBP 120, control 120</td>
<td>20–79</td>
<td>Decreased LLA in LBP 60s</td>
</tr>
<tr>
<td>Itoi16</td>
<td>X-ray</td>
<td>LBP 75, control 25</td>
<td>48–89</td>
<td>Decreased LLA in LBP</td>
</tr>
<tr>
<td>Sakai et al.4</td>
<td>X-ray</td>
<td>CLBP 203, control 683</td>
<td>≥ 65</td>
<td>Decreased LLA in CLBP</td>
</tr>
</tbody>
</table>

LBP, low back pain; LLA, lumbar lordotic angle; CLBP, chronic low back pain; MRI, magnetic resonance imaging.

https://doi.org/10.14245/ns.2346494.247

www.e-neurospine.org 965
associated with pelvic tilt. A common thread across these studies is that the sagittal alignment of the subjects was significantly associated with the truncal skeletal muscle index. Considering the constraints of our retrospective approach, which did not include an evaluation of the paraspinal muscle, careful consideration should be given to this factor when interpreting the results.

Nevertheless, the cross-sectional design of this study inherently presents challenges in establishing causal relationships; however, the existence of potential interrelationships between LLA, muscle mass, and CLBP is suggested. There would be a series of vicious cycles, for instance, in elderly patients, reduction in skeletal muscle mass associated with decreased LLA could lead to CLBP, while CLBP could in turn compromise mobility and further exacerbate loss of muscle mass to jeopardize remaining LLA. Further delineating the interrelationships between loss of muscle mass, LLA, and CLBP could therefore have important implications for the treatment or prevention of morbidity in the elderly.

5. Limitations

This study had several limitations. First, since the present study is cross-sectional, it is not clear enough to characterize causal relationships among each parameter. Second, due to the constraints of a retrospective study, we were unable to evaluate the cross-sectional area of truncal muscles through CT/MRI images. Many previous studies have analyzed the relationship between truncal muscle mass and LBP using axial CT/MRI images. However, there is insufficient evidence to confirm that ASM, as evaluated by bioimpedance, consistently corresponds to truncal muscle mass. Therefore, the findings of this study should also be contemplated in conjunction with previous findings on the association between proximal limb muscles and the mechanical integrity of the lumbar spine. In addition, the severity, location, and chronicity of CLBP and other associated medical conditions such as osteoporosis, other radiological parameters were not assessed and quantified to better focus on our research question. Series of future studies analyzing relationships of truncal muscle mass, osteoporosis, and other radiologic parameters with CLBP and LLA will help to understand the multifactorial natures of sarcopenia and CLBP. The third limitation would be using BIA instead of DXA which is known to be more accurate in measuring fat and fat free body mass. However, through recent improvement of technology and stratification of data, BIA has become an accepted tool for measuring muscle mass as used in European and Asian consensus on definition and diagnosis stated in the Asian Working Group for Sarcopenia. Moreover, all of the participants had a standardized condition in terms of food intake and measurement time in a day because BIA measurement was done early in the morning as the first part of their medical check-up after fasting (nil-per-os) at least 8 hours by midnight null-per-oral state. Especially, the eight-polar BIA used in this study is known to offer accurate measurements of total and appendicular body composition as DXA.

CONCLUSION

The current retrospective study revealed that reduced skeletal muscle mass and decreased lumbar lordosis were associated with CLBP in the elderly. Furthermore, positive correlations were observed between skeletal muscle mass and LLA, suggesting that these factors should be considered when planning therapeutic interventions. Future research involving a larger population, including patients with very severe LBP, is warranted to determine the causal relationship.

NOTES

Supplementary Materials: Supplementary Tables 1-2 can be found via https://doi.org/10.14245/ns.2346494.247.

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Author Contribution: Conceptualization: SJP, SGC; Data curation: MWP, SJP; Formal analysis: MWP, SJP; Methodology: MWP, SJP, SGC; Visualization: MWP, SJP; Writing - original draft: MWP, SJP, SGC; Writing - review & editing: MWP, SGC.

ORCID

Myung Woo Park: 0000-0001-7531-8433
Sang Jun Park: 0009-0004-7560-7891
Sun Gun Chung: 0000-0001-5785-8110

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Supplementary Table 1. Characteristics of subjects under the age of 70

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 47)</th>
<th>CLBP (n = 19)</th>
<th>Control (n = 28)</th>
<th>p-value</th>
<th>Women (n = 52)</th>
<th>CLBP (n = 20)</th>
<th>Control (n = 32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.2 ± 1.5</td>
<td>66.3 ± 1.3</td>
<td></td>
<td>0.044*</td>
<td>67.0 ± 1.6</td>
<td>67.1 ± 1.2</td>
<td></td>
<td>0.881</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.7 ± 8.0</td>
<td>69.7 ± 7.6</td>
<td></td>
<td>0.662</td>
<td>55.4 ± 7.6</td>
<td>53.2 ± 6.5</td>
<td></td>
<td>0.268</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.2 ± 4.9</td>
<td>169.0 ± 4.9</td>
<td>0.195</td>
<td></td>
<td>154.8 ± 5.3</td>
<td>157.3 ± 5.3</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 ± 2.5</td>
<td>24.4 ± 2.4</td>
<td>0.798</td>
<td></td>
<td>23.1 ± 2.6</td>
<td>21.5 ± 2.5</td>
<td>0.033*</td>
<td></td>
</tr>
<tr>
<td>LLA (°)</td>
<td>29.4 ± 10.2</td>
<td>38.8 ± 8.7</td>
<td>0.002*</td>
<td></td>
<td>33.4 ± 11.3</td>
<td>38.6 ± 9.5</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>MSMI (%)</td>
<td>31.2 ± 2.0</td>
<td>32.3 ± 2.0</td>
<td>0.070</td>
<td></td>
<td>25.8 ± 1.9</td>
<td>27.5 ± 2.3</td>
<td>0.007*</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
CLBP, chronic low back pain; BMI, body mass index; LLA, lumbar lordotic angle; MSMI, modified skeletal muscle mass index.
*p < 0.05, statistically significant differences.
**Supplementary Table 2. Characteristics of subjects aged 70 or over**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLBP (n = 16)</th>
<th>Control (n = 18)</th>
<th>p-value</th>
<th>CLBP (n = 16)</th>
<th>Control (n = 16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>73.4 ± 3.0</td>
<td>74.6 ± 4.7</td>
<td>0.400</td>
<td>73.0 ± 2.3</td>
<td>71.7 ± 1.7</td>
<td>0.075</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.9 ± 6.4</td>
<td>66.2 ± 7.1</td>
<td>0.572</td>
<td>53.8 ± 9.5</td>
<td>56.3 ± 6.6</td>
<td>0.396</td>
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<tr>
<td>Height (cm)</td>
<td>167.4 ± 4.6</td>
<td>166.4 ± 4.5</td>
<td>0.529</td>
<td>153.9 ± 5.1</td>
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<td>0.156</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 2.1</td>
<td>23.9 ± 2.0</td>
<td>0.312</td>
<td>22.7 ± 3.2</td>
<td>23.0 ± 2.1</td>
<td>0.699</td>
</tr>
<tr>
<td>LLA (degree)</td>
<td>30.4 ± 11.3</td>
<td>34.5 ± 7.5</td>
<td>0.227</td>
<td>30.3 ± 11.2</td>
<td>37.4 ± 8.8</td>
<td>0.046*</td>
</tr>
<tr>
<td>MSMI (%)</td>
<td>31.1 ± 1.4</td>
<td>32.2 ± 1.9</td>
<td>0.056</td>
<td>26.4 ± 1.8</td>
<td>26.4 ± 1.7</td>
<td>0.924</td>
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</tbody>
</table>

Values are presented as mean ± standard deviation.
CLBP, chronic low back pain; BMI, body mass index; LLA, lumbar lordotic angle; MSMI, modified skeletal muscle mass index.
*p < 0.05, statistically significant differences.
Introduction of a New Radiographic Parameter to Predict Proximal Junctional Kyphosis in Adult Spinal Deformity: UIVPTA (Uppermost Instrumented Vertebra-Pelvic Tilt Angle)

Se-Jun Park¹, Chong-Suh Lee², Jin-Sung Park¹, Tae Soo Shin¹

¹Department of Orthopedic Surgery, Spine Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
²Department of Orthopedic Surgery, Haeundae Bumin Hospital, Busan, Korea

Objective: To introduce a new sagittal parameter, uppermost instrumented vertebra-pelvic tilt angle (UIVPTA), and to determine the effects on the proximal junctional kyphosis (PJK) development in adult spinal deformity (ASD) surgery.

Methods: Patients ≥ 60 years with ASD who underwent low thoracic spine to pelvis fusion with a minimum of 2-years of follow-up were included in this study. Two groups were created according to PJK development. Various clinical and radiographic factors were compared between PJK and non-PJK groups to identify the risk factors for PJK. Cutoff value of UIVPTA for PJK development was calculated using receiver operating characteristic curve according to different pelvic incidence groups. Linear regression analysis was performed to identify factors to affect UIVPTA.

Results: One hundred fifty-one patients were included in this study. There were 135 female patients (89.4%). Mean age was 70.5 years. PJK developed in 65 patients (43.0%). Multivariate analysis showed that overcorrection relative to age-adjusted pelvic incidence (PI) minus lumbar lordosis (LL) (PI–LL) target and lower UIVPTA were independent risk factors for PJK. The cutoff value of UIVPTA for PJK development was calculated as 4.0° in patients with PI less than 45°, 9.5° in patients with PI between 45° and 60°, and 13.0° in patients with PI greater than 60°. Linear regression analysis showed that UIVPTA was positively affected by postoperative values of LL (coefficient = 0.505), PI–LL (coefficient = 0.674), and pelvic tilt (coefficient = 0.286).

Conclusion: Optimal correction within the age-adjusted PI–LL combined with keeping UIVPTA within optimal range is suggested for the prevention of PJK.

Keywords: Uppermost instrumented vertebra-pelvic tilt angle, Proximal junctional kyphosis, Adult spinal deformity, Overcorrection, Age-adjusted PI–LL

INTRODUCTION

In surgical treatment for adult spinal deformity (ASD), optimal correction of the sagittal alignment is important for favorable clinical outcomes.¹,² Since Schwab et al.³ suggested ideal sagittal alignment goals such as pelvic incidence (PI) minus lumbar lordosis (LL) within ± 10°, pelvic tilt (PT) ≤ 20°, and sagittal vertical axis (SVA) ≤ 50 mm, these criteria has been conventionally used to determine the optimal sagittal alignment. Although the beneficial effect of these criteria on clinical outcome have
been supported in previous studies, the effect on preventing mechanical failure such as proximal junctional kyphosis (PJK) remains controversial. Meanwhile, the concept of age-adjusted sagittal alignment concept was introduced by Lafage et al. suggesting the appropriate sagittal spinopelvic parameters should be assessed in consideration of patient age. Subsequent studies supported this concept, showing that the overcorrection of PI-LL relative to the age-adjusted target increased PJK risk. Although the concept has been validated in preventing PJK development, it addresses only the amount of LL.

Recently, the clinical significance of UIV orientation such as UIV slope and inclination has been emphasized rather than LL amount itself, given that higher UIV slope and inclination may impose kyphotic force above UIV and subsequently increases PJK development. Therefore, UIV orientation as well as LL should be considered importantly together in ASD surgery. However, these conventional parameters representing UIV orientation would not be fixed and change according to different standing position. UIV orientation can be affected by pelvic rotation, amount of LL correction, and rod contour above L1. Therefore, UIV orientation needs to be comprehensively assessed with regard to all component from pelvis to UIV. Herein, we introduce a new sagittal parameter, the uppermost instrumented vertebra-pelvic tilt angle (UIVPTA), which is non-positional parameter to represent UIV orientation (Fig. 1). The present study primarily aims to demonstrate the clinical significance of UIVPTA with regard to PJK development in patients undergoing long-fusion surgery from lower thoracic vertebra to sacrum for ASD. The secondary aim was to provide the cutoff value of UIVPTA to instigate PJK development.

**MATERIALS AND METHODS**

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2022-08-128). The need to obtain informed consent was waived because of the retrospective nature of this study.

1. **Study Cohort**

This study was a retrospective case series with records retrieved from the prospective ASD database at our institution. Individuals eligible for the study included ASD patients with lumbar degenerative kyphosis (LDK) who underwent surgical correction between 2013 and 2020. The detailed inclusion criteria were as follows: (1) patients with radiographically proven sagittal malalignment (SVA ≥ 50 mm, PI–LL ≥ 10°, and PT ≥ 25°), (2) patients who showed the cardinal signs of LDK such as stooped gait, inability to lift heavy objects, difficulty in climbing slopes, and need for elbow support in front of sink with evidence of calluses on the extensor surface of the elbow, (3) patients who underwent long-segment fixation from lower thoracic spine (T9–12) to sacrum or pelvis, (4) patients with previous fusion surgery if the fusion length was ≤ 2 levels, and (5) patients who were followed up more than 2 years.

2. **Surgical Techniques**

All surgeries were performed by 1 of 3 surgeons in a single center. Corrective surgery was performed either posterior only surgery using posterior column osteotomy with or without pedicle subtraction osteotomy (PSO) or via a combined anterior-posterior approach using oblique or anterior lumbar interbody fusion (ALIF). Although the surgical methods were determined based on the patient’s deformity status, the preferred surgical technique at our institution is the combined anterior-posterior approach. All L5-S1 levels were treated by interbody fusion with either ALIF or posterior lumbar interbody fusion (PLIF). ALIF with hyperlordotic cage was preferred method to maximize the LL, but PLIF was performed in case with unfavorable iliac vessel anatomy, previous abdominal surgery, or severely obese patients. At or above L4–5 levels, lateral approaches using oblique lumbar interbody fusion or anterior column realignment technique were pre-

![Fig. 1. (A) Lateral standing radiograph showing UIVPTA. (B) Lateral standing radiograph showing UIV slope and UIV inclination. UIV, uppermost instrumented vertebra; PT, pelvic tilt; UIVPTA, uppermost instrumented vertebra.](https://doi.org/10.14245/ns.2346420.210)
ferred.

In case of rigid kyphotic deformity, PSO was performed. Pelvic fixation was routinely performed using conventional iliac screw fixation except for cases with lumbosacral fusion status due to previous fusion surgery or patients with concerns for screw prominence due to shallow soft tissue coverage. All surgeries were performed using an open method with titanium rods. Augmentation techniques at UIV to prevent PJK such as cement augmentation or posterior tether were not used.

### 3. Definition of PJK

PJK was defined radiographically as a postoperative proximal junctional angle (PJA) ≥ 10° and ≥ 10° greater than the preoperative PJA. However, the current definition of PJK used in the present study broadly included any types of PJK including soft tissue failure, fracture at UIV or UIV+1, fixation failure at implant-bone interface at UIV, and revision surgery. According to PJK development, 2 groups were created: PJK and non-PJK groups. Various clinical parameters were compared between the 2 groups with respect to patient factors, surgical factors, and radiographic parameters.

### 4. Patient and Surgical Factors

Patient factors included age, sex, T score (gm/cm²) on bone mineral density (BMD), perioperative use of an anabolic agent, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification grade, and history of diabetes mellitus (DM). Surgical variables included revision surgery, surgical approach (posterior only surgery or combined anterior-posterior approach), and PSO.

### 5. Radiographic Evaluation

Radiographic parameters were separately measured with respect to the conventional global parameters and regional parameters. Conventional global parameters included PI, LL, sacral slope (SS), PT, T1 pelvic angle (TPA), and SVA. All parameters were measured on whole-spine 36-inch standing radiographs preoperatively and 2 weeks postoperatively. In addition to comparison of conventional radiographic parameters, 3 categorical criteria were also evaluated. To assess the effect of Schwab suggestion about optimal postoperative PI–LL was classified into 3 groups: > 10°, within ± 10°, and < -10°. Global alignment and proportion (GAP) scores were calculated and 3 groups were created such as proportioned (score: 0–2), moderately disproportioned (score: 3–6), and severely disproportioned (score ≥ 7) according to the original scoring system. Finally, the effect of the age-adjusted alignment target on PJK development was also analyzed. The age-adjusted PI–LL target was calculated using a previously reported formula: PI–LL = (age–55)/2+3. According to the offset value between the actual and age-adjusted PI–LL values, the patients were divided into 3 groups: undercorrection (offset < -10°), ideal correction (offset within ± 10°), and overcorrection (offset > 10°).

Regional parameters included UIVPTA, lower LL (LLL), upper LL (ULL), lumbar distribution index (LDI), UIV-L1 angle, UIV slope, and UIV inclination. UIVPTA was determined by the angle between a line drawn from the center of femoral heads to the UIV center and a line from the center of the femoral head to the midpoint of S1 endplate (PT line) (Fig. 1A). ULL was defined as lordosis between L1 to L4, and LLL was defined as lordosis between L4-S1. LDI was calculated as LLL/LL × 100 (%). UIV-L1 angle was the angle between the cranial endplate of the UIV and the caudal end plate of L1. Positive value of UIV-L1 angle denotes kyphotic curvature. UIV slope is the angle between the UIV superior endplate and a horizontal line (Fig. 1B). UIV inclination is the angle between the best-fit line crossing the vertebral body center of UIV-2 to UIV and a vertical line (Fig. 1B).

The comparison of radiographic parameters was repeated for patients who achieved the ideal correction relative to the age-adjusted PI–LL target in order to adjust for the effect of age-adjusted PI–LL on UIVPTA.

### Table 1. Univariate analysis of patient and surgical factors for PJK development

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PJK (N = 86)</th>
<th>PJK (N = 65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69.6 ± 6.6</td>
<td>69.1 ± 7.1</td>
<td>0.677</td>
</tr>
<tr>
<td>Female sex</td>
<td>74 (86.0)</td>
<td>61 (93.8)</td>
<td>0.182</td>
</tr>
<tr>
<td>T score (g/cm²) on BMD</td>
<td>-1.3 ± 1.5</td>
<td>-1.5 ± 1.2</td>
<td>0.452</td>
</tr>
<tr>
<td>Perioperative use of anabolic agent</td>
<td>18 (20.9)</td>
<td>14 (21.5)</td>
<td>0.716</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 3.2</td>
<td>25.4 ± 3.9</td>
<td>0.173</td>
</tr>
<tr>
<td>ASA PS classification grade</td>
<td>2.2 ± 0.4</td>
<td>2.1 ± 0.4</td>
<td>0.061</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (18.6)</td>
<td>10 (15.4)</td>
<td>0.668</td>
</tr>
<tr>
<td>Revision surgery</td>
<td>34 (39.5)</td>
<td>24 (36.9)</td>
<td>0.866</td>
</tr>
<tr>
<td>Combined anterior-posterior approach</td>
<td>69 (80.2)</td>
<td>52 (80.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>PSO</td>
<td>13 (15.1)</td>
<td>16 (24.6)</td>
<td>0.151</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± standard deviation or as number (%).

PJK, proximal junctional kyphosis; BMD, bone mineral density; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; PSO, pedicle subtraction osteotomy.

https://doi.org/10.14245/ns.2346420.210
Table 2. Univariate analysis of radiographic parameters for PJK development in all patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PJK (N = 86)</th>
<th>PJK (N = 65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional global parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative PI (°)</td>
<td>53.5 ± 11.2</td>
<td>52.5 ± 10.5</td>
<td>0.579</td>
</tr>
<tr>
<td>Preoperative LL (°)</td>
<td>10.9 ± 22.7</td>
<td>11.1 ± 19.9</td>
<td>0.950</td>
</tr>
<tr>
<td>Preoperative PI–LL (°)</td>
<td>42.6 ± 21.3</td>
<td>41.4 ± 19.2</td>
<td>0.717</td>
</tr>
<tr>
<td>Preoperative SS (°)</td>
<td>18.3 ± 11.4</td>
<td>20.6 ± 12.1</td>
<td>0.240</td>
</tr>
<tr>
<td>Preoperative PT (°)</td>
<td>34.6 ± 11.4</td>
<td>32.9 ± 11.7</td>
<td>0.360</td>
</tr>
<tr>
<td>Preoperative TPA (°)</td>
<td>35.9 ± 14.5</td>
<td>33.8 ± 13.3</td>
<td>0.561</td>
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<tr>
<td>Preoperative SVA (mm)</td>
<td>14.9 ± 38.7</td>
<td>17.8 ± 32.4</td>
<td>0.617</td>
</tr>
<tr>
<td>Change in LL (°)</td>
<td>37.2 ± 23.1</td>
<td>39.8 ± 19.7</td>
<td>0.463</td>
</tr>
<tr>
<td>Change in PT (°)</td>
<td>17.5 ± 10.7</td>
<td>15.5 ± 12.1</td>
<td>0.287</td>
</tr>
<tr>
<td>Change in TPA (°)</td>
<td>22.2 ± 16.0</td>
<td>22.7 ± 12.5</td>
<td>0.585</td>
</tr>
<tr>
<td>Change in SVA (mm)</td>
<td>71.4 ± 62.5</td>
<td>54.7 ± 66.7</td>
<td>0.121</td>
</tr>
<tr>
<td>Postoperative LL (°)</td>
<td>48.1 ± 12.7</td>
<td>51.0 ± 12.1</td>
<td>0.166</td>
</tr>
<tr>
<td>Postoperative PI–LL (°)</td>
<td>5.6 ± 10.3</td>
<td>1.8 ± 9.6</td>
<td>0.022*</td>
</tr>
<tr>
<td>Postoperative SS (°)</td>
<td>35.4 ± 9.1</td>
<td>36.2 ± 9.5</td>
<td>0.621</td>
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<tr>
<td>Postoperative PT (°)</td>
<td>17.1 ± 7.3</td>
<td>17.4 ± 8.3</td>
<td>0.830</td>
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<tr>
<td>Postoperative TPA (°)</td>
<td>14.3 ± 8.5</td>
<td>13.5 ± 7.8</td>
<td>0.585</td>
</tr>
<tr>
<td>Postoperative SVA (mm)</td>
<td>14.9 ± 38.7</td>
<td>17.8 ± 32.4</td>
<td>0.617</td>
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<tr>
<td><strong>Categories by Schwab optimal PI–LL range</strong></td>
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<td>0.243</td>
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<tr>
<td>PI–LL &gt; 10°</td>
<td>26 (30.2)</td>
<td>12 (18.5)</td>
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<tr>
<td>PI–LL within ± 10°</td>
<td>55 (64.0)</td>
<td>48 (73.8)</td>
<td></td>
</tr>
<tr>
<td>PI–LL &lt; -10°</td>
<td>5 (5.8)</td>
<td>5 (7.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Categories by GAP score</strong></td>
<td></td>
<td></td>
<td>0.321</td>
</tr>
<tr>
<td>Proportioned</td>
<td>23 (35.4)</td>
<td>21 (24.4)</td>
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</tr>
<tr>
<td>Moderately disproportioned</td>
<td>31 (47.7)</td>
<td>46 (53.5)</td>
<td></td>
</tr>
<tr>
<td>Severely disproportioned</td>
<td>11 (16.9)</td>
<td>19 (22.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Categories by age-adjusted ideal PI–LL target</strong></td>
<td></td>
<td></td>
<td>0.026*</td>
</tr>
<tr>
<td>Undercorrection</td>
<td>8 (9.3)</td>
<td>2 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Ideal correction</td>
<td>56 (65.1)</td>
<td>34 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Overcorrection</td>
<td>22 (25.6)</td>
<td>29 (44.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Regional parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UIVPTA (°)</td>
<td>11.1 ± 7.2</td>
<td>6.7 ± 6.8</td>
<td>0.004*</td>
</tr>
<tr>
<td>LLL (°)</td>
<td>29.0 ± 10.6</td>
<td>31.3 ± 9.5</td>
<td>0.168</td>
</tr>
<tr>
<td>ULL (°)</td>
<td>19.1 ± 11.8</td>
<td>19.7 ± 11.0</td>
<td>0.773</td>
</tr>
<tr>
<td>LDI (%)</td>
<td>62.4 ± 17.3</td>
<td>61.5 ± 20.0</td>
<td>0.774</td>
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<tr>
<td>UIV-L1 angle (°)</td>
<td>11.1 ± 7.3</td>
<td>10.7 ± 6.8</td>
<td>0.548</td>
</tr>
<tr>
<td>UIV slope (°)</td>
<td>5.2 ± 7.3</td>
<td>5.6 ± 8.4</td>
<td>0.759</td>
</tr>
<tr>
<td>UIV inclination (°)</td>
<td>11.3 ± 6.9</td>
<td>15.0 ± 8.9</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± standard deviation or as number (%).

PJK, proximal junctional kyphosis; PI, pelvic incidence; LL, lumbar lordosis; SS, sacral slope; PT, pelvic tilt; TPA, T1 pelvic angle; SVA, sagittal vertical axis; GAP, global alignment and proportion; UIV, uppermost instrumented vertebra; UIVPTA, uppermost instrumented vertebra-pelvic tilt angle; LLL, lower lumbar lordosis; ULL, upper lumbar lordosis; LDI, lumbar distribution index.

*p < 0.05, statistically significant difference. *Age-adjusted ideal PI–LL target was calculated as follows: age-adjusted ideal PI–LL = (age–55)/2+3. Undercorrection means offset value between the actual and age-adjusted ideal PI–LL < -10°, ideal correction means offset value within ± 10°, and overcorrection means offset value > 10°.
6. Statistical Analysis

Data are presented as the frequencies with percentages for categorical variables and means with standard deviations for continuous variables. Univariate analyses were performed using the chi-square test or Fisher exact tests for categorical variables, and using independent t-test to assess differences in the continuous variables between the 2 groups. Multivariate logistic regression analysis was performed using all variables that had a significance < 0.05 in univariate analyses to identify the risk factors for PJK development. Cutoff values of UIVPTA for PJK development were calculated using receiver operating characteristic (ROC) curve as the point at which the sensitivity and specificity were equal. In addition, cutoff value of UIVPTA was calculated separately according to PI groups. Linear regression analysis was performed to identify factors to affect UIVPTA. Statistical analyses were conducted by professional statisticians using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA). A p-value of < 0.05 was considered statistically significant.

RESULTS

Among 452 adult patients who underwent the surgical correction for ASD during the study period, 151 patients met the inclusion criteria and constitute the study cohort; 135 patients (89.4%) were female and mean age was 70.5 years. Mean T score on BMD was -1.6 g/cm². The combined anteroposterior approach was performed in 121 patients (80.1%) and PSO in 29 patients (19.2%). During mean follow-up duration of 34.5 months, PJK developed in 65 patients (43.0%). With regard to the types of PJK, there were 30 patients with PJA > 20° without bony failure, 31 patients with fracture at UIV or UIV+1, and 4 patients with screw pullout.

For patient factors, there were no significant differences in terms of age, sex, T score, perioperative use of anabolic agent, BMI, ASA physical status classification grade, and history of DM (Table 1). Surgical variables also did not significantly differ between the 2 groups with respect to revision surgery, surgical approach, and PSO (Table 1).

On univariate analysis of radiographic parameters, conventional global parameters including PI, LL, PI–LL, SS, PT, TPA, and SVA showed no significant differences between the 2 groups. Also, there were no significant differences in patient distribution according to Schwab optimal PI–LL or GAP score between the 2 groups. However, there were significantly more patients with overcorrection relative to the age-adjusted PI–LL target in the PJK group than in the non-PJK group (p = 0.024). In terms of regional parameters, UIVPTA was significantly lower in the PJK group than in the non-PJK group (6.7° vs. 11.1°, p = 0.004) (Table 2). UIV inclination was significantly higher in the PJK group than in the non-PJK group (15.0° vs. 11.3°, p = 0.004) (Table 2).

Multivariate logistic regression analysis demonstrated that overcorrection relative to ideal age-adjusted PI–LL target (odds ratio [OR], 7.274; 95% confidence interval [CI], 1.477–10.752, p = 0.011), UIVPTA (OR, 0.942; 95% CI, 0.987–0.989; p = 0.017), and UIV inclination (OR, 1.066; 95% CI, 1.019–1.115; p = 0.006) were independent risk factors associated with PJK development (Table 3). To eliminate the beneficial effect of undercorrection of PI–LL value on UIVPTA, we repeated univariate analysis of radiographic parameters only for the 90 patients who achieved ideal correction relative to the age-adjusted PI–LL target. In the analysis, only lower UIVPTA was a single significant risk factor for PJK (12.8° in the non-PJK group vs. 7.8° in the PJK group, p = 0.002) (Table 4).

The cutoff value of UIVPTA for PJK development was calculated as 4.0° in patients with PI less than 45°, 9.5° in patients with PI between 45° and 60°, and 13.0° in patients with PI greater than 60° (Table 5). Linear regression analysis showed that UIVPTA was significantly affected by postoperative values of LL (coefficient = 0.505), PI–LL (coefficient = 0.674), and PT (coefficient = 0.286) (Table 6).

1. Representative Cases

Two representative cases are presented in Figs. 2 and 3. In both

Table 3. Multivariate analysis of risk factors for PJK development

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categories by age-adjusted ideal PI–LL target†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undercorrection</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Ideal correction</td>
<td>3.217 (0.458–14.478)</td>
<td>0.285</td>
</tr>
<tr>
<td>Overcorrection</td>
<td>7.274 (1.477–10.752)</td>
<td>0.011*</td>
</tr>
<tr>
<td>UIVPTA (°)</td>
<td>0.942 (0.897–0.989)</td>
<td>0.017*</td>
</tr>
<tr>
<td>UIV inclination (°)</td>
<td>1.066 (1.019–1.115)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

PJK, proximal junctional kyphosis; CI, confidence interval; PI, pelvic incidence; LL, lumbar lordosis; UIV, uppermost instrumented vertebra; UIVPTA, uppermost instrumented vertebra–pelvic tilt angle.

* p < 0.05, statistically significant difference. † Age-adjusted ideal PI–LL target was calculated as follows: age-adjusted ideal PI–LL = (age–55)/2+3. Undercorrection means offset value between the actual and age-adjusted ideal PI–LL < -10°, Ideal correction means offset value within ± 10°, and overcorrection means offset value > 10°.
cases, the PI–LL was corrected within the ideal range relative to age-adjusted PI–LL target. However, UIVPTA was smaller (4°) in patient of Fig. 3 than in patient of Fig. 2 (15°). At the last follow-up, PJK occurred in patient of Fig. 2.

Table 4. Univariate analysis of radiographic parameters for PJK development in patients who achieved ideal correction of age-adjusted PI–LL alignment (N = 90)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PJK (N = 56)</th>
<th>PJK (N = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional global parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative PI (°)</td>
<td>55.1 ± 9.9</td>
<td>53.1 ± 11.1</td>
<td>0.366</td>
</tr>
<tr>
<td>Preoperative LL (°)</td>
<td>12.2 ± 20.9</td>
<td>7.4 ± 19.1</td>
<td>0.277</td>
</tr>
<tr>
<td>Preoperative PI–LL (°)</td>
<td>42.9 ± 19.9</td>
<td>45.7 ± 19.6</td>
<td>0.523</td>
</tr>
<tr>
<td>Preoperative SS (°)</td>
<td>20.7 ± 11.1</td>
<td>17.6 ± 11.9</td>
<td>0.209</td>
</tr>
<tr>
<td>Preoperative PT (°)</td>
<td>34.4 ± 11.0</td>
<td>35.2 ± 12.2</td>
<td>0.757</td>
</tr>
<tr>
<td>Preoperative TPA (°)</td>
<td>36.5 ± 13.6</td>
<td>38.8 ± 15.7</td>
<td>0.738</td>
</tr>
<tr>
<td>Preoperative SVA (mm)</td>
<td>66.5 ± 60.3</td>
<td>89.4 ± 70.9</td>
<td>0.108</td>
</tr>
<tr>
<td>Change in LL (°)</td>
<td>34.9 ± 21.1</td>
<td>39.6 ± 21.2</td>
<td>0.306</td>
</tr>
<tr>
<td>Change in PT (°)</td>
<td>15.1 ± 11.9</td>
<td>16.3 ± 11.7</td>
<td>0.637</td>
</tr>
<tr>
<td>Change in TPA (°)</td>
<td>20.6 ± 16.1</td>
<td>23.8 ± 15.9</td>
<td>0.570</td>
</tr>
<tr>
<td>Change in SVA (mm)</td>
<td>46.7 ± 62.4</td>
<td>70.5 ± 75.4</td>
<td>0.109</td>
</tr>
<tr>
<td>Postoperative LL (°)</td>
<td>47.0 ± 9.3</td>
<td>46.9 ± 11.3</td>
<td>0.972</td>
</tr>
<tr>
<td>Postoperative PI–LL (°)</td>
<td>8.3 ± 5.7</td>
<td>6.4 ± 5.8</td>
<td>0.125</td>
</tr>
<tr>
<td>Postoperative SS (°)</td>
<td>35.8 ± 8.3</td>
<td>34.3 ± 10.0</td>
<td>0.456</td>
</tr>
<tr>
<td>Postoperative PT (°)</td>
<td>19.4 ± 6.4</td>
<td>18.9 ± 7.4</td>
<td>0.764</td>
</tr>
<tr>
<td>Postoperative TPA (°)</td>
<td>15.9 ± 6.9</td>
<td>15.0 ± 7.4</td>
<td>0.586</td>
</tr>
<tr>
<td>Postoperative SVA (mm)</td>
<td>19.9 ± 30.9</td>
<td>18.9 ± 40.4</td>
<td>0.895</td>
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<tr>
<td>Categories by conventional optimal PI–LL range</td>
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<td>0.819</td>
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<tr>
<td>PI–LL &gt; 10°</td>
<td>18 (32.1)</td>
<td>10 (29.4)</td>
<td></td>
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<tr>
<td>-10° ≤ PI–LL ≤ 10°</td>
<td>38 (67.9)</td>
<td>24 (70.6)</td>
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<tr>
<td>PI–LL &lt; -10°</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Categories by GAP score</td>
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<td>0.896</td>
</tr>
<tr>
<td>Proportioned</td>
<td>13 (23.2)</td>
<td>8 (23.5)</td>
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</tr>
<tr>
<td>Moderately disproportioned</td>
<td>32 (57.1)</td>
<td>18 (52.9)</td>
<td></td>
</tr>
<tr>
<td>Severely disproportioned</td>
<td>11 (19.6)</td>
<td>8 (23.5)</td>
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</tr>
<tr>
<td>Regional parameter</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>UIVPTA (°)</td>
<td>12.8 ± 5.7</td>
<td>7.8 ± 5.7</td>
<td>0.002*</td>
</tr>
<tr>
<td>LLL (°)</td>
<td>28.7 ± 9.3</td>
<td>29.6 ± 9.4</td>
<td>0.645</td>
</tr>
<tr>
<td>ULL (°)</td>
<td>18.3 ± 11.0</td>
<td>17.3 ± 9.6</td>
<td>0.657</td>
</tr>
<tr>
<td>LDI (%)</td>
<td>62.2 ± 20.5</td>
<td>63.6 ± 18.1</td>
<td>0.752</td>
</tr>
<tr>
<td>UIV-L1 angle (°)</td>
<td>11.5 ± 7.1</td>
<td>12.3 ± 6.9</td>
<td>0.091</td>
</tr>
<tr>
<td>UIV slope (°)</td>
<td>4.6 ± 7.7</td>
<td>2.8 ± 7.2</td>
<td>0.296</td>
</tr>
<tr>
<td>UIV inclination (°)</td>
<td>10.8 ± 6.7</td>
<td>11.9 ± 8.1</td>
<td>0.501</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± standard deviation or as number (%).
PJK, proximal junctional kyphosis; PI, pelvic incidence; LL, lumbar lordosis; SS, sacral slope; PT, pelvic tilt; TPA, T1 pelvic angle; SVA, sagittal vertical axis; GAP, global alignment and proportion; UIV, uppermost instrumented vertebra; UIVPTA, uppermost instrumented vertebra-pelvic tilt angle; LLL, lower lumbar lordosis; ULL, upper lumbar lordosis; LDI, lumbar distribution index.

*p < 0.05, statistically significant difference.
Table 5. Cutoff value of UIVPTA to develop PJK according to pelvic incidence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff value</th>
<th>AUC (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI &lt; 45° (N = 35)</td>
<td>4.0°</td>
<td>0.618 (0.462–0.773)</td>
<td>0.622</td>
<td>0.633</td>
<td>0.004*</td>
</tr>
<tr>
<td>45° ≤ PI &lt; 60° (N = 74)</td>
<td>9.5°</td>
<td>0.712 (0.603–0.820)</td>
<td>0.658</td>
<td>0.627</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PI ≥ 60° (N = 42)</td>
<td>13.0°</td>
<td>0.669 (0.520–0.818)</td>
<td>0.694</td>
<td>0.746</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

UIV, uppermost instrumented vertebra; UIVPTA, uppermost instrumented vertebra-pelvic tilt angle; PJK, proximal junctional kyphosis; AUC, area under the curve; CI, confidence interval; PI, pelvic incidence.

*p < 0.05, statistically significant difference.

Table 6. Linear regression analysis showing factors to affect UIVPTA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized B</th>
<th>Coefficients SE</th>
<th>Standardized coefficients beta</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>7.661</td>
<td>2.653</td>
<td>2.887</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>-0.286</td>
<td>0.162</td>
<td>-0.436</td>
<td>-1.772</td>
<td>0.079</td>
</tr>
<tr>
<td>LL</td>
<td>0.505</td>
<td>0.197</td>
<td>0.857</td>
<td>2.563</td>
<td>0.012*</td>
</tr>
<tr>
<td>PI–LL</td>
<td>0.674</td>
<td>0.175</td>
<td>0.928</td>
<td>3.845</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PT</td>
<td>0.286</td>
<td>0.074</td>
<td>0.328</td>
<td>3.880</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDI</td>
<td>0.060</td>
<td>0.090</td>
<td>0.165</td>
<td>0.662</td>
<td>0.777</td>
</tr>
<tr>
<td>UIV-L1 angle</td>
<td>-0.027</td>
<td>0.058</td>
<td>-0.029</td>
<td>-0.475</td>
<td>0.636</td>
</tr>
</tbody>
</table>

UIV, uppermost instrumented vertebra; PT, pelvic tilt; UIVPTA, uppermost instrumented vertebra-pelvic tilt angle; SE, standard error; PI, pelvic incidence; LL, lumbar lordosis; LDI, lumbar distribution index.

*p < 0.05, statistically significant difference.

DISCUSSION

LL correction is a key step for obtaining optimal sagittal alignment in ASD surgery. There have been several guidelines such as Schwab PI–LL criteria or Lafage age-considered sagittal alignment concept, regarding the degree of LL that should be corrected.10,24 Although these criteria have been validated for preventing mechanical failure such as PJK,13,25 several aspects were still overlooked such as the shape of LL (represented by LDI) and contour of the construct above L1, particularly in cases of proximal fixation extending beyond L1. UIV would be differently positioned even under the same amount of LL. Recent studies demonstrated that the dorsal orientation of the UIV, by imposing the reciprocal kyphotic forces above the UIV, is more important than LL itself as a risk factor for PJK development.26-29 Therefore, UIV orientation and degree of LL should be both im-

Fig. 2. A 63-year-old-woman presented with severe kyphotic deformity in lumbar spine with PI–LL of 70°. After surgery including 3-column osteotomy and multilevel oblique lumbar interbody fusion, LL was corrected to 56° with PI–LL of 8°, which belongs within age-adjusted ideal correction target. UIVPTA was measured 15° postoperatively. During 3-year follow-up, proximal junctional kyphosis (PJK) did not develop. PI, pelvic incidence; LL, lumbar lordosis; PT, pelvic tilt; SS, sacral slope; SVA, sagittal vertical axis; UIVPTA, uppermost instrumented vertebra-pelvic tilt angle; Immed PO, immediate postoperatively.
Fig. 3. A 61-year-old-woman with lumbar degenerative kyphosis underwent surgical correction using multilevel anterior column realignments. After surgery, LL was corrected from 10° to 57° and postoperative PI–LL was 2°. Although postoperative PI–LL belongs within age-adjusted ideal correction target, the value of UIVPTA was relatively small (4°). At 2 years postoperatively, proximal junctional kyphosis (PJK) developed along with fractures at UIV and UIV+1. PI, pelvic incidence; LL, lumbar lordosis; PT, pelvic tilt; SS, sacral slope; SVA, sagittal vertical axis; UIVPTA, uppermost instrumented vertebra-pelvic tilt angle; Immed PO, immediate postoperatively.

Fig. 4. Lateral standing radiographs showing the changes of UIV slope, UIV inclination, and UIVPTA according to different standing position. Note that UIV slope and inclination are changed according to different standing position, but UIVPTA is fixed regardless of patient’s position. UIV, uppermost instrumented vertebra; UIVPTA, uppermost instrumented vertebra-pelvic tilt angle.
portant considerations. This fact inspired us to develop a new radiographic parameter, UIVPTA, which reflects both the degree of LL and UIV orientation.

The clinical utility of UIVPTA in predicting PJK development was demonstrated in this study. We showed that lower UIVPTA was a significant risk factor for PJK in univariate and multivariate analyses. Lower value of UIVPTA equates the UI movement away from the vertical axis and toward the PT line thereby potentially increasing UIV slope or inclination. However, lower UIVPTA does not necessarily mean higher UIV slope or UIV inclination because UIVPTA include the pelvis position and UIV slope or inclination does not. Assuming the pelvis is fixed, the change of UIVPTA may be directly reflected on the changes of UIV slope or inclination. However, because the pelvis is not fixed structure, UIVPTA can be also affected by pelvic position. UIVPTA would decrease by anterior rotation of pelvis and conversely increase by posterior pelvic rotation. We could calculate the cutoff value of UIVPTA using ROC analysis. The cutoff values were differently presented according to PI. We can expect that patients with low PI would have smaller UIVPTA and patients with high PI have higher UIVPTA. As to our expectation, the ROC analysis showed that the cutoff values were smallest in low PI patients and greatest in high PI patients.

UIVPTA is an angle which is formed by the influence of several parameters. To identify the parameters to affect UIVPTA, linear regression analysis was performed. It reveals that UIVPTA was positively affected by LL, PI–LL, and PT. This result indicates that UIVPTA is not simply explained by conventional over- or undercorrection of LL. With regard to correction amount, greater LL means overcorrection of LL, while greater PI–LL and PT means undercorrection. In case of overcorrection, greater LL tends to shift UIV posteriorly (toward increasing UIVPTA) and rotate pelvis anteriorly (toward decreasing UIVPTA) at the same time. Therefore, simply correction amount of LL is not enough to predicting UIV orientation. We thought that the issue of correction amount needs to be assessed including pelvic rotation. In that sense, UIVPTA could be used to appropriately define the over- and undercorrection.

In the linear regression analysis, UIVPTA was also positively affected by PI–LL. This indicates that high PI–LL, which means undercorrection, leads to greater UIVPTA and decreases the PJK risk. However, based on the previous reports, undercorrection should be avoided due to an association with worse clinical outcomes. Therefore, undercorrection beyond the designated degree cannot be permitted just to increase UIVPTA. Considering the clinical importance of the age-adjusted PI–LL target on PJK development in the previous studies and the current study, we assumed that the maximum degree of postoperative PI–LL gap should be within the range of the age-adjusted PI–LL target. Therefore, we surmised the necessity of repeating an analysis with eliminating the potential beneficial effect of undercorrection on UIVPTA by including only patients who achieved ideal correction. Re-analysis also demonstrated that only UIVPTA was a significant risk factor for PJK development. This result suggests that UIVPTA combined with age-adjusted PI–LL target can better predict PJK development compared with use of only age-adjusted PI–LL target.

Lastly, the UIVPTA has additional advantages regarding the measurement issue. Because UIVPTA is non-positional parameter, the postoperative UIVPTA will not change according to patient’s position (Fig. 4). Our concept of UIVPTA is similar to the background of introduction of TPA, which is irrelevant to the posture unlike PT in 2014. However, unlike TPA, UIVPTA can be measured during surgery and it would not change postoperatively, although all UIVPTAs were measured postoperatively in this study. This study has a few limitations. First, this study was performed with patients having UIV at lower thoracic spine (T9–12). Therefore, it may be applied universally to patients with UIV of mid- and upper thoracic spine. A single UIVPTA value may not be applied when UIV is located at mid-to upper thoracic vertebra because the kyphotic curvature of thoracic spine. However, it is reported that the mode of PJK is different between upper and lower thoracic vertebra as site of UIV. The incidence of PJK is reported to be higher in UIV at lower thoracic spine compared to upper thoracic spine. With regard to the failure mode, the fracture type PJK develops more frequently in patients with UIV at lower thoracic vertebra and PJK with soft tissue failure or spondylolisthesis occurs more in patients with UIV at upper thoracic vertebra. In addition, there are few patients who require long fusion to upper thoracic vertebra due to LDK in our institution although LDK is the leading diagnoses which requires a long fusion surgery. Because the main deformed pathologic lesion in LDK is located within lumbar spine, it is common to stop at the lower thoracic spine. These are the reason why we included only patients with UIV at lower thoracic vertebra. Second, we defined PJK as any form of kyphosis with PJA > 20°. Therefore, the PJK in this study indicates the radiographic term without clinical consideration. Thus, PJK group might include the patients without significant clinical deterioration. However, a recent study demonstrated that even if soft tissue type PJK was asymptomatic at initial development, it progressed radiographically with time and even-

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ually gave a negative impact on the clinical outcomes in long-term follow-up.35 In addition, PJK group in this study included patients with proximal junctional failure (PJF) such as soft tissue failure, fracture or screw pullout. It is well known that the clinical outcome was significantly inferior in patients with PJF compared to those without PJF.36,37 Therefore, we believe that all radiographic PJKs should be considered importantly regardless of the initial symptom. Despite the limitations, we believe that UIVPTA could provide a new guide for PJK prevention. More importantly, UIVPTA can be measured intraoperatively and does not change with position.

CONCLUSION

Overcorrection relative to the age-adjusted PI–LL target and lower UIVPTA were independent risk factors for PJK. Therefore, optimal correction within the age-adjusted PI–LL combined with keeping UIVPTA within optimal range is suggested for the prevention of PJK.

NOTES

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Author Contribution: Conceptualization: SJP, CSL; Data curation: SJP, JSP, TSS; Formal analysis: SJP, JSP; Methodology: TSS; Project administration: SJP; Writing - original draft: SJP; Writing - review & editing: SJP.

ORCID
Se-Jun Park: 0000-0002-2412-9437
Chong-Suh Lee: 0000-0003-2790-9225
Jin-Sung Park: 0000-0001-6517-8609
Tae Soo Shin: 0000-0003-4020-7690

REFERENCES


Surgical and Clinical Outcomes Associated With the Use of Barbed Sutures and Self-Adhering Mesh System and Polymeric Glue for Wound Closure in Multilevel or Revision Spinal Surgery: A Matched Cohort Comparative Study With Conventional Wound Closure Procedure

Junho Mun¹, Seung-Jae Hyun¹, Jae-Koo Lee¹, Sungjae An², Ki-Jeong Kim¹

¹Department of Neurosurgery, Spine Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Korea
²Department of Neurosurgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

Objective: Multilevel or revisional posterior spinal surgery is prone to infection and delayed wound healing, related with the wound closure time and suture strength. Knotless barbed suture is an innovative self-locking, multianchor suture. This study aims to evaluate the safety and efficacy of the knotless barbed suture and self-adhering mesh with polymeric glue in multilevel or revisional posterior spinal surgery.

Methods: This is a single-center retrospective matched cohort study. Patients were divided into 2 groups based on the wound closure method: barbed suture group with novel wound closure, and conventional suture group with conventional wound closure, 1:1 matched by the level of surgery and sex, resulting in 120 subjects each. Total operation time and wound closure time were measured intraoperatively, and perioperative clinical outcome parameters including postoperative wound complication were investigated for the first 3 months postoperatively. The distribution of continuous variables was assessed for normality by Shapiro-Wilk test, then parametric or nonparametric tests were applied accordingly (paired t-test or Wilcoxon signed-rank test).

Results: Wound closure time was significantly shorter with the novel barbed suture than with conventional suture in all subgroups divided by the level of spinal surgery: 3–5, 6–9, ≥ 10 levels (p < 0.001). The 2 groups showed no significant differences in surgical complications (p = 1.000). Specially, total operation time and wound-closing time were significantly shorter in revisional subgroup.

Conclusion: Absorbable knotless barbed suture and self-adhering mesh with polymeric glue can shorten spinal wound closure time with noninferiority in complications for multilevel or revisional spinal surgery.

Keywords: Knotless barbed suture, Suture techniques, Spine, Revision surgery
INTRODUCTION

The traditional surgical wound-closing method using knotted suture materials has several inherent limitations that are challenging to overcome. Commonly used absorbable suture materials along with nylon sutures or staplers may cause infection, scarring, and limitations in everyday activities.1

In a multilevel spinal surgery, a long-wound closure time is also associated with surgical site infection. Additionally, postoperative wound complications such as wound dehiscence, surgical site infection, granuloma formation are a concern for revisional operations, the preformed scar tissue formation and adhesions cause difficulty in wound closure.2-4

Studies on the parameters for determining the level of operation segment are being investigated due to the increase in long level of segments spinal surgery, including adult spinal deformity.5-7 Additionally, there is a growing interest on the complications of long level of segment spinal surgery, and the research of which materials used for wound closure might significantly reduce the length of an operation.8-10

Barbed suture, also known as self-retaining or knotless suture, is a unidirectional/bidirectional antibacterial monofilament and synthetic absorbable device prepared from polydioxanone. The surgical sutures are designed with small barbs or hooks along their length and barbs have innovative self-locking and multianchor properties that engage with the surrounding tissue, providing secure and stable closure without the need for traditional knots (Figs. 1, 2). Barbed sutures excel in tissue approximation, save time owing to knotless application, and are suitable for a wide range of surgical procedures. Furthermore, they have the major advantages of reducing the wound closure time and retaining better suture strength without requiring continuous tensile force (Figs. 3, 4). They differ from the traditional interrupted Vicryl sutures (Ethicon, Johnson & Johnson Medical Ltd, Livingston, UK) in that they retain strength for a longer period of time during suture.11 Therefore bare suture have been utilized in a various surgical procedures, including gastric bypass surgery, laparoscopic surgery, and arthroplasty.12 However, only few studies have investigated the effectiveness of barbed sutures in spine surgeries.13-15

A self-adhering mesh system is a user-friendly wound closure method involving mesh materials with adhesive backing. It offers easy application, secure closure, breathability, flexibility, and reduced scarring. The mesh directly adheres to the skin or wound edges, providing mechanical support and tension to promote proper healing.16-18 Polymeric glue, also known as a tissue adhesive or surgical glue, is a noninvasive alternative to traditional sutures or staples for wound closure. It is applied topically and forms a strong bond, eliminating the need for invasive closure methods. Polymeric glue has a rapid application and biocom-

Fig. 1. Schematic diagram of the muscle-fascia suture of intermittent conventional nylon suture (A) and continuous barbed suture (B). Unlike conventional sutures, the continuous barbed suture has the advantage of maintaining tension owing to the self-locking and multianchor properties.

Fig. 2. Knotless unidirectional barbed suture with a thickness of 1.0. The figure illustrates the densely arrayed unidirectional barbs with the distal end for anchoring.
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Compatibility, provides flexibility, and is associated with minimal scarring. Therefore, we evaluated the safety and effectiveness of a self-adhering mesh system, polymeric glue, and knotless barbed sutures for wound closure in multilevel and revisional posterior spinal surgery to broaden the evidence and knowledge regarding their clinical use.

MATERIALS AND METHODS

The single-center, retrospective, matched cohort study was approved by the appropriate Institutional Review Board of Seoul National University Bundang Hospital (WC-2019-15), and the informed consent was waived. From the electronic medical system, we identified patients (1) who underwent multilevel, defined as at least 3 levels, or revisional posterior spinal surgery between August 2013 and March 2021; (2) who were followed up for at least 3 months; and (3) whose data regarding wound closure time and total operation time were available. We excluded patients who underwent cervical spinal surgery and included those who underwent thoracolumbar surgery. Patients who underwent for fascia and subcutaneous tissue approximation using knotless barbed sutures and skin closure using a self-adhering mesh and polymeric glue were selected as the experimental group (Fig. 5). Furthermore, within the same patient pool, the control group was selected using a 1 to 1 matching for sex and number of segments operated (with 1 level of difference tolerated) who underwent conventional wound closure using Vicryl interrupted sutures and skin staplers.

Wound closure in all patients was performed by 2 fellowship-trained spine surgeons with at least 1–2 years of experience at a single academic institution. For patients who underwent surgery in different years, other fellow surgeons performed wound closure. Each surgeon received sufficient training before using the barbed suture, and the risk of microperforation was prevented by double gloving during the suturing.

Baseline demographic data including age, sex, body mass index, height, smoking status, and diabetes were collected. The wound closure time and total operation time were measured intraoperatively and recorded. Main operation time was defined as the value obtained by subtracting the wound closure time from the total operation time. Pre- and postoperative 3-month back pain assessments using the visual analogue scale, hospital-...
ization days, and postoperative wound complications were also retrieved retrospectively from electronic records. Postoperative wound complications were defined as wound dehiscence or surgical site infection within 3 months of the surgery. We also checked the outpatient medical records for skin complications such as contact dermatitis.

Patients were subdivided into 3 groups (3–5, 6–9, and ≥ 10 levels) to evaluate the difference in wound closure time and total operation time between the groups stratified by surgical level. Furthermore, patients who underwent revisional thoracolumbar surgery in the experimental and control groups were included in the subgroup analysis.

The distribution of continuous variables was assessed for normality using the Shapiro-Wilk test, and then parametric or non-parametric tests were performed using the paired t-test or Wilcoxon signed-rank test, respectively. Parameters did not satisfy the normality requirement were presented as median (interquartile range) and were analyzed using the Wilcoxon signed-rank test for between-group differences. Significance level was set at 0.05, and statistical analyses were performed using IBM SPSS Statistics ver. 29.0 (IBM Co., Armonk, NY, USA).

### Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Barbed suture (n = 120)</th>
<th>Conventional suture (n = 120)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56.7 ± 20.7</td>
<td>57.9 ± 20.4</td>
<td>0.697</td>
</tr>
<tr>
<td>Female sex</td>
<td>71 (59.2)</td>
<td>71 (59.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>No. of segments operated</td>
<td>7.2 ± 3.7</td>
<td>7.2 ± 3.6</td>
<td>1.000</td>
</tr>
<tr>
<td>3–5 group</td>
<td>3.9 ± 0.8</td>
<td>4.0 ± 0.7</td>
<td>0.330</td>
</tr>
<tr>
<td>6–9 group</td>
<td>7.2 ± 1.0</td>
<td>7.1 ± 1.3</td>
<td>0.916</td>
</tr>
<tr>
<td>≥ 10 group</td>
<td>12.0 ± 2.1</td>
<td>11.9 ± 2.1</td>
<td>0.775</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.9 ± 11.0</td>
<td>157.0 ± 16.7</td>
<td>0.644</td>
</tr>
<tr>
<td>3–5 group</td>
<td>157.4 ± 8.6</td>
<td>157.4 ± 10.2</td>
<td>0.998</td>
</tr>
<tr>
<td>6–9 group</td>
<td>158.7 ± 12.9</td>
<td>160.2 ± 9.5</td>
<td>0.616</td>
</tr>
<tr>
<td>≥ 10 group</td>
<td>158.1 ± 12.7</td>
<td>157.9 ± 10.5</td>
<td>0.944</td>
</tr>
<tr>
<td>Scoliosis†</td>
<td>27 (22.5)</td>
<td>27 (22.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>AIS</td>
<td>16 (13.3)</td>
<td>15 (12.5)</td>
<td>0.848</td>
</tr>
<tr>
<td>Adult scoliosis</td>
<td>4 (3.3)</td>
<td>7 (5.8)</td>
<td>0.452</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 ± 5.2</td>
<td>23.8 ± 4.5</td>
<td>0.178</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (18.3)</td>
<td>19 (15.8)</td>
<td>0.609</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (12.5)</td>
<td>24 (20.0)</td>
<td>0.116</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). AIS, adolescent idiopathic scoliosis; BMI, body mass index.

†Scoliosis include ‘adolescent idiopathic scoliosis,’ ‘adult scoliosis,’ ‘juvenile idiopathic scoliosis,’ ‘neuromuscular scoliosis,’ and ‘failed back scoliosis.’

### Table 2. Total operation time, main operation time and wound closure time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Barbed suture group (n = 120)</th>
<th>Conventional suture group (n = 120)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>120</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>256.0 (201.3–305.0)</td>
<td>264.0 (215.0–353.3)</td>
<td>0.054</td>
</tr>
<tr>
<td>No. of operation segments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>56</td>
<td>53</td>
<td>0.360</td>
</tr>
<tr>
<td>6–9</td>
<td>26</td>
<td>32</td>
<td>0.306</td>
</tr>
<tr>
<td>≥ 10</td>
<td>38</td>
<td>35</td>
<td>0.065</td>
</tr>
<tr>
<td>Main operation time (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>120</td>
<td>0.897</td>
</tr>
<tr>
<td>No. of operation segments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>56</td>
<td>53</td>
<td>0.671</td>
</tr>
<tr>
<td>6–9</td>
<td>26</td>
<td>32</td>
<td>0.716</td>
</tr>
<tr>
<td>≥ 10</td>
<td>38</td>
<td>35</td>
<td>0.491</td>
</tr>
<tr>
<td>Wound closure time (min)</td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>No. of operation segments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>56</td>
<td>53</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>6–9</td>
<td>26</td>
<td>32</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>≥ 10</td>
<td>38</td>
<td>35</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range). p-values are calculated from Wilcoxon signed-rank test between corresponding subgroups divided by the operation levels.

*p < 0.05, statistically significant differences.

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Table 3. Subgroup analysis for revisional operations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Barbed suture group (n = 46)</th>
<th>Conventional suture group (n = 23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>29 (63.0)</td>
<td>13 (56.5)</td>
<td>0.607</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.4 ± 9.1</td>
<td>157.4 ± 10.4</td>
<td>0.420</td>
</tr>
<tr>
<td>No. of operation segments</td>
<td>6.8 ± 3.8</td>
<td>7.6 ± 3.5</td>
<td>0.424</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>257.2 ± 96.2</td>
<td>329.3 ± 122.5</td>
<td>0.009*</td>
</tr>
<tr>
<td>Main operation time (min)</td>
<td>233.3 ± 92.1</td>
<td>277.7 ± 111.2</td>
<td>0.083</td>
</tr>
<tr>
<td>Wound closure time (min)</td>
<td>23.9 ± 9.2</td>
<td>51.6 ± 16.8</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. p-values are calculated from paired t-test between corresponding subgroups divided by the operation levels. *p < 0.05, statistically significant differences.

RESULTS

We included 120 patients each in the experimental (barbed suture) and control (conventional suture) groups (Table 1). There were no significant differences between groups regarding sex, age, height, body mass index, number of scoliosis, and diabetes mellitus.

Each group was divided into 3 subgroups according to the number of operated spinal levels: 3–5, 6–9, and ≥ 10 (Table 2). The difference in total operation time, main operation time, and wound closure time for each corresponding subgroup was analyzed. All corresponding subgroups showed significantly less wound-closing time in the barbed suture group than in the conventional suture group (3–5 levels of segments; 20.0 (16.3–30.0) minutes vs. 40.0 (30.3–50.0) minutes, p < 0.001; 6–9 level of segments; 26.5 (18.5–33.5) minutes vs. 45.5 (38.0–50.0) minutes, p < 0.001; ≥ 10 levels of segments; 30.5 (25.0–36.0) minutes vs. 59.7 (50.0–65.0) minutes, p < 0.001).

Furthermore, the total operation time, main operation time, and wound closure time for the revisional operation was analyzed (Table 3). Among the patients, 46 patients in the barbed suture group and 23 in the conventional suture group underwent revisional surgery. Including operation time, the wound-closing time showed statistically significant differences with more time consumption for the conventional suture subgroups. Moreover, the barbed suture group had a significantly shorter time reduction in operation time and wound closure time. The ratio of wound closure time to operation time in the revision surgery group was approximately 16% in the conventional suture group and 9% in the barbed suture group.

The perioperative clinical outcome parameters were also measured and compared (Table 4). Both groups showed no significant differences in postoperative back pain scores, hospitalization days, and postoperative wound complications. In the barbed suture group, 3 of 4 patients had wound dehiscence (48, 58, and 64 days after surgery), and one had surgical site infection. In the conventional suture group, 2 of 3 patients had wound dehiscence (30 and 37 days after surgery), and 1 patient developed a surgical site infection. We also found that 1 of 120 patients (1.7%) treated with the 2-octyl cyanoacrylate and polymeric glue acquired contact dermatitis during the follow-up period.

DISCUSSION

Our study demonstrated the efficacy and safety of knotless barbed sutures for revision or long-level posterior spine surgery. We found that compared to using conventional sutures, using barbed sutures significantly decreased wound closure time, which is associated with decreased total operation time, and showed comparable perioperative clinical outcomes. In posterior spinal surgery, wound closure is conventionally performed separately using interrupted suture techniques separately for each layer. Although this is a familiar method, it has inherent disadvantages regarding wound closure strength and time. Skin wound from revision surgeries have scar tissue that requiring stronger tension than the normal skin which is why wound suture in revisional surgeries require more time for close. Moreover, wound closure time might increase proportionately with the increasing number of operated segments using the interrupted suture technique. Wound dehiscence and surgical site infection are major concerns as they usually involve reoperation, implant failure, or prolonged hospital stays with devastating results sometimes. Multilevel or revisional posterior spinal surgeries are especially concerning as it requires more wound closure time than short-level or virgin spinal surgeries; furthermore, they are associated with increased hospital stays and surgical complications.
with higher postoperative wound complication rates.\textsuperscript{23-21}

In contrast to interrupted sutures, barbed sutures can firmly hold the tissue in place without continuous tension being applied.\textsuperscript{22} These advantages relieve stress and reduce the time required to close the wound at every step of suturing. Furthermore, owing their favorable biomechanical properties, they have been used for tendon repair and veterinary medicine.\textsuperscript{23-28} Several studies have demonstrated the safety and efficacy of this novel wound closure material, but evidence in thoracolumbar spinal surgery is scarce.\textsuperscript{27-32}

Wound closure time for all surgical level subgroups was measured and compared (Table 2). It was shown that all segmental subgroups of barbed suture had significantly shorter wound closure time than the conventional suture group. Furthermore, there were no significant differences in the main operation time between the subgroups. The similar main operation time in relation to shorter total operation time which demonstrates the advantages of barbed sutures in terms of the closing time, especially when more spinal levels are involved, in which the operation time was significantly shorter in the barbed suture group than in the conventional suture group although no significant difference in the main operation time was observed between the groups. Clearly, the group employing barbed suture materials for wound closure significantly shortened the wound closure time compared to the group using conventional sutures, and they also reduced the overall operation time.

Despite the shorter wound closure time, there were no differences in the measured perioperative outcomes between the 2 groups (Table 4). Both groups had no significant difference in postoperative back pain scores after 3 months and hospitalization days. Notably, the barbed suture group was comparable in terms of postoperative wound complications within 3 months, reflecting the suture material’s clinical safety and strength. Interestingly, we found that wound problems occurred later in the barbed suture than in the conventional group. The reason is that the tensile strength of the barbed suture is maintained at a high level; therefore, wound issues will emerge in the latter. There are not enough wound problem cases between groups; more data is needed for generalization. The number of patients with contact dermatitis in the barbed suture with self-adhering mesh and polymeric glue was minimal, according to review of medical records. From this, it can be assumed that the self-adhering mesh and polymeric glue is biocompatible with the study participants’ postoperative wound. Additionally, wound complexity may potentially impact wound closure time. However, the number of scoliosis patients was the same in both groups, and there was no significant difference (27 patients in each group). Although precise measurements did not take, it can be inferred that there was no significant difference in wound complexity between the 2 groups in our research.

Our study had several limitations. First, the total operation time was multifactorial and also affected by the time required for wound dissection and main procedures, such as screw insertion, osteotomies, or interbody fusion. However, we found no significant difference between the 2 groups when comparing the main operation time for each group. Consequently, it was confirmed how the difference in wound closure time between the 2 groups had a significant effect on efficiently reducing the surgical time by using a barbed suture. Second, this is a single-center retrospective study. However, it also had the advantage of providing valuable information because of matched analysis of the experimental and control groups, both of which included more than 100 patients.

We expect that our study will extend our knowledge regarding the safety and efficacy of this novel suture material for posterior spinal multilevel surgery.

**CONCLUSION**

Compared to using the conventional interrupted Vicryl suture, using the knotless barbed suture decreased the time and effort to close surgical wounds in posterior spinal surgeries with comparable safety and clinical outcomes. Our study results support the use of barbed sutures, especially in multilevel and revisional spinal surgeries.

**NOTES**

**Conflict of Interest:** The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: SJH; Data Curation: JM, SJH, JKL, SA; Formal Analysis: JM, SJH, JKL; Investigation: JM, SJH, JKL, SA; Project Administration: JM, SJH, JKL, SA, KJK; Writing – Original Draft: JM, JKL, SA; Writing – Review & Editing: JM, SJH, JKL, SA, KJK.

**ORCID**

Junho Mun: 0000-0002-7904-8407
Seung-Jae Hyun: 0000-0003-2937-5300
Jae-Koo Lee: 0000-0001-7968-6743

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Long-term Outcomes of Posterior Multilevel Crack Osteotomy: Revisional Surgery for Scoliosis With a Fusion Mass

Mi Hyun Song1,*, Jae Hyuk Yang2,*, Dong-Gune Chang3, Yunjin Nam4, Seung Woo Suh4

1Division of Pediatric Orthopaedics, Department of Orthopaedic Surgery, Seoul National University Children’s Hospital, Seoul National University College of Medicine, Seoul, Korea
2Department of Orthopaedic Surgery, Korea University Medical Center, Anam Hospital, Seoul, Korea
3Department of Orthopaedic Surgery, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea
4Department of Orthopaedic Surgery, Korea University Medical Center, Guro Hospital, Seoul, Korea

Objective: Osteotomies are required for the mobilization of spinal segments in patients with revisional scoliosis surgery with a fusion mass; however, only a few techniques have shown efficacy and safety, and their mid- and long-term outcomes remain unelucidated. This study aimed to analyze long-term outcomes of the posterior multilevel crack osteotomy (PMCO) technique for revisional surgery for scoliosis with a fusion mass.

Methods: Data from 18 patients who underwent revisional scoliosis surgery using PMCO between 2009 and 2015 and had more than 5-year follow-up were retrospectively reviewed. The Cobb angle and coronal and sagittal balance parameters were examined preoperatively, postoperatively, and during the final follow-up. Perioperative parameters and complications were also assessed.

Results: Preoperative and postoperative Cobb angles were 60.5° and 29.9°, respectively (p < 0.001); this improvement was maintained until the final follow-up (33.4°, p = 0.058). The difference in preoperative and postoperative coronal balance was statistically significant (15.9 mm and 9.2 mm, respectively; p < 0.001); this was maintained until the final follow-up (p = 0.071). There was no change in sagittal balance parameters over the 3 measurement periods. Only 1 patient showed PMCO-related motor weakness, but he spontaneously recovered 3 months after postsurgery. Pseudarthrosis was not observed during the follow-up period.

Conclusion: Incomplete osteotomy using PMCO provided satisfactory deformity correction without severe complications during revisional surgery for scoliosis with a fusion mass. It may be a less invasive procedure that maintains cortical continuity, preserves soft tissues, and provides sufficient mobility for the correction of spinal segments.

Keywords: Scoliosis, Revisional surgery, Multilevel osteotomy, Incomplete osteotomy, Deformity correction

INTRODUCTION

Revisional scoliosis surgery is performed when the spinal curve progresses or when loss of truncal balance develops after primary scoliosis surgery.1-4 However, revisional scoliosis surgery is challenged with the presence of spinal fusion masses and difficulty in screw insertion due to the distorted anatomy from the previous surgery.5 The screw insertion point is frequently indistinguishable in revisional scoliosis surgery, even though C-arm images are used to identify the pedicle for screw insertion points.6,7
For mobilization of fused spinal segments, various spinal osteotomy techniques, such as Smith-Petersen osteotomy (SPO), pedicle subtraction osteotomy (PSO), vertebral column resection (VCR), and posterior VCR (PVCR) have been introduced. However, only some of these techniques have been verified for their efficacy and safety, particularly in revisional surgery for scoliosis with a fusion mass. In addition, only a few studies have investigated the mid- and long-term outcomes of this type of surgery.

We previously introduced the novel technique of posterior multilevel crack osteotomy (PMCO) for revisional scoliosis surgery in the presence of a fusion mass, which we have consistently updated since 2008. This study aimed to analyze the long-term outcomes of PMCO, focusing on coronal and sagittal balance correction and the safety of this surgical technique.

MATERIALS AND METHODS

1. Study Population

Patients who underwent revisional scoliosis surgery using PMCO between January 2009 and December 2015 were included in this study. The inclusion criteria were as follows: (1) patients with more than 50° of scoliosis or who showed progression of spinal deformity after primary scoliosis surgery, (2) those who underwent PMCO for correction, and (3) those who were followed up for more than 5 years. The exclusion criteria were as follows: (1) patients who underwent surgery for spinal deformity due to trauma or infection and (2) those who were followed up for less than 5 years or were lost to follow-up. Among the 42 patients who underwent PMCO, 18 met the inclusion criteria.

2. Ethical Considerations

This study was designed as a retrospective case series, approved by the hospital’s Institutional Review Board of Korea University Guro Hospital (K2020-2373-001), and conducted in accordance with the Declaration of Helsinki. The need for obtaining informed consent was waived by the review board because of the retrospective design of the study.

3. Surgical Procedure

PMCO surgeries were performed by a single senior surgeon (SWS). The procedure involved an incomplete 3-column osteotomy of the vertebral body by cracking the anterior cortical shell while maintaining anterior bony continuity to preserve the surrounding soft tissues including the anterior longitudinal ligament. The previously published surgical procedure of PMCO was followed in this study.

Pedicle screw insertion was performed using the free-hand technique from a facet-based entry point which was the intersection of the lines passing through the base and midportion of the facet, while the trajectory was perpendicular to the surface of the facet. When the entry point was indistinguishable due to anatomical changes from the primary surgery, tracing of the facet joint was performed over the fusion mass and/or surrounding structures, such as the rib head or transverse process, and the alignment of previously inserted screws was used as a reference.

Briefly, the PMCO procedure used in this study is as follows. A linear laminotomy involving the pars interarticularis from the convex to the concave side was performed using a Kerrison punch or a 4-mm round diamond burr (Midas Rex, Medtronic Inc., Dublin, Ireland). The osteotomy was completed up to the anterior one-third of the vertebral body using an osteotome or a 4-mm round diamond burr (Midas Rex). The final depth of osteotomy was meticulously determined depending on the depth of the vertebral body, measured on preoperative computed tomography (CT) scans, to avoid vascular and pulmonary injury due to penetration of the chest cavity. A dural protector covered the dural sac to avoid dural tears or injuries. A cracking maneuver via twisting or shaking the osteotome in the cephalad and caudal directions, with it remaining in situ, was performed until the incomplete osteotomy extended to the anterior cortex of the vertebral body, and mobility of the vertebral segment was obtained (see Supplementary video clips 1–2). Precontoured rods were then mounted over the pedicle screws on both sides, and a derotation maneuver was performed to correct the curve. After curve correction, the wedge-shaped openings on the concave side of the osteotomy sites were filled with bone grafts and a hemostatic gelatin sponge for fusion and bleeding control, respectively. After the decortication of the posterior laminae, posterior fusion was performed using a mixture of cancellous allograft chips and demineralized bone matrix (GS Medical Co., Ltd., Cheongju, Korea). In cases with residual rib hump deformity, a thoracoplasty (partial rib resection) was performed selectively. The wound was closed in layers over the 2 drainage tubes.

4. Radiological Evaluation

Standard whole-spine radiographs, CT scans, and magnetic resonance imaging were performed. The Cobb angle was measured preoperatively, postoperatively, and during the last follow-up, using the standard method on posterior–anterior radiographs.
Coronal balance was defined as the horizontal distance between a vertical line from the center of C7 to the midline of the sacrum. Sagittal balance was measured using thoracic kyphosis (TK), lumbar lordosis (LL), and sagittal vertical axis (SVA). TK was measured as the angle between the upper endplate of T2 and the lower endplate of T12, whereas LL was assessed between the upper endplates of T12 and S1. SVA was defined as the horizontal distance between a vertical line from the center of C7 to the posterosuperior corner of S1. All radiological parameters were measured preoperatively, postoperatively, and during the last follow-up visit.

5. Perioperative Parameters and Complications

Perioperative parameters, such as estimated blood loss (EBL), surgery duration, and hospitalization duration, were assessed. In addition, complications including neurological deficits, pulmonary and gastrointestinal problems, and pseudarthrosis were investigated. Intraoperative neurological events were defined as motor evoked potential (MEP) signal changes, failed wake-up tests, or peripheral temperature changes. Postoperative neurological deficits and recovery were assessed. As suggested by Kim et al., pseudarthrosis was confirmed when the following findings were observed on plain radiographs within 4 postoperative years: instrumentation failure (implant breakage, dislodgement of rod, or screw loosening) and progression of deformity with or without pain.

6. Statistical Analyses

Data are presented as mean ± standard deviation. Since the total sample size was relatively small, the Friedman test or Wilcoxon rank-sum test was used as the nonparametric statistical method. A p-value less than 0.05 was regarded as statistically significant. All statistical analyses were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Patient Demographics

Eighteen patients with an average age of 19.4 ± 8.4 years (range, 9–40 years) underwent PMCO revisional surgery (Table 1). The initial causes of scoliosis were neuromuscular (n = 5), syndromic (n = 1), congenital (n = 11), and idiopathic (n = 1). PMCO was performed over an average of 3.2 ± 1.5 levels (range, 1–6 levels). Postoperatively, the number of fusion levels increased to 11.3 ± 3.1

Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Fusion mass extent</th>
<th>Osteotomy level</th>
<th>Osteotomy site</th>
<th>Follow-up period (yr)</th>
<th>Fixation extent</th>
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</thead>
<tbody>
<tr>
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<td>M</td>
<td>22</td>
<td>Congenital scoliosis</td>
<td>T4–L5</td>
<td>2</td>
<td>T10/11/12</td>
<td>10</td>
<td>T4-L5</td>
</tr>
<tr>
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<td>T4–T9</td>
<td>2</td>
<td>T5/6/7</td>
<td>5</td>
<td>T4-T9</td>
</tr>
<tr>
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<td>M</td>
<td>13</td>
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<td>T4–L5</td>
<td>3</td>
<td>T6/7, L1/2/3</td>
<td>5</td>
<td>T4-L5</td>
</tr>
<tr>
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<td>40</td>
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<td>T9–S1</td>
<td>2</td>
<td>T12/L1/2</td>
<td>5</td>
<td>T9-S1</td>
</tr>
<tr>
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</tr>
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<td>M</td>
<td>15</td>
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<td>L2/3</td>
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<td>35</td>
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<td>T4/5, T6/7, T8/9, T10/11, T12/L1, L2/3</td>
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</tr>
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<tr>
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<td>M</td>
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<td>F</td>
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<td>T4–L4</td>
<td>6</td>
<td>T6/7/8/9/10/11, T12/L1</td>
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<td>T4-L4</td>
</tr>
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<td>F</td>
<td>23</td>
<td>Neuromuscular scoliosis</td>
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<td>4</td>
<td>T6/7/8/9/10</td>
<td>7</td>
<td>T3-L3</td>
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<tr>
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<td>M</td>
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<td>Neuromuscular scoliosis</td>
<td>T5–L3</td>
<td>5</td>
<td>T7/8/9/10/11/12</td>
<td>7</td>
<td>T5-L3</td>
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<td>17</td>
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<td>7</td>
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<td>T3–L3</td>
<td>2</td>
<td>T12/L1/2</td>
<td>5</td>
<td>T3-L3</td>
</tr>
</tbody>
</table>

AIS, adolescent idiopathic scoliosis.
levels (range, 5–15 levels). Nine patients concomitantly underwent thoracoplasty for the remaining rib hump deformities associated with PMCO. The patients were followed up for a mean duration of 7.2 ± 2.7 years (range, 5–14 years).

### 2. Preoperative, Postoperative, and Last Follow-up Radiologic Parameters

Preoperative and postoperative Cobb angles were $60.5° ± 21.8°$ and $29.9° ± 16.0°$, respectively ($p < 0.001$) (Fig. 1) and this improvement was maintained until the final follow-up (Cobb an-

![Fig. 1. Comparison of the Cobb angle during the 3 measurement periods (preoperatively, postoperatively, and during the final follow-up). *$p < 0.05$.](image1)

![Fig. 2. Comparison of coronal balance during the 6 measurement periods (preoperatively, postoperatively, and during the final follow-up). *$p < 0.05$.](image2)

**Table 2. The intraoperative estimated blood loss, operation time, hospitalization duration, and complications**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Operation time (min)</th>
<th>Blood loss (mL)</th>
<th>Hospitalization duration (day)</th>
<th>Intraoperative MEP change</th>
<th>Complications</th>
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<tbody>
<tr>
<td>1*</td>
<td>340</td>
<td>2,500</td>
<td>131</td>
<td>+</td>
<td>Neurologic deficit, hemothorax</td>
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<tr>
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<td>288</td>
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<td>3*</td>
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<td>-</td>
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<td>+</td>
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<td>28</td>
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<td>285</td>
<td>500</td>
<td>10</td>
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</table>

MEP, motor evoked potential.

*These patients concomitantly underwent thoracoplasty for the remaining rib hump deformity.
3. Intraoperative EBL, Surgery Duration, Hospitalization Duration, and Complications

Intraoperative EBL, surgery duration, hospitalization duration, and complications in each case are shown in Table 2. The average surgery duration, intraoperative EBL, and hospitalization duration were 372 ± 119.6 minutes, 3,352.8 ± 1,850.0 mL, and 27.4 ± 27.5 days, respectively.

During surgery, MEP signal change was observed in 5 patients (28%), but 4 of them showed negative results on the Stagnara wake-up test, suggesting a false-positive MEP with no neurological abnormalities. Only one patient showed mild motor weakness during the postoperative period; however, he recovered 3 months after postsurgery. Ten cases of pulmonary complications (hemothorax, pneumothorax, and pleural effusion) were observed, but all of these were associated with partial rib resection for mobilization of the segments. Two patients with superior mesenteric artery syndrome were observed. All patients with pulmonary and gastrointestinal complications were discharged without any complications. During the final follow-up, radiographic signs of nonunion, such as screw and rod breakage, screw loosening, and decompensation, were not observed in any patient. None of the patients required follow-up revisional surgery after PMCO.

4. Illustrative Case (Patient 17)
A male patient was diagnosed with congenital scoliosis at the age of 2 years and subsequently underwent deformity correction and posterior spinal fusion from T8 to L1. The patient underwent concomitant surgery for anal obstruction, anorchia, and polydactyly, after which crank shaft phenomena developed. The Cobb angle progressed to 93° with Risser stage 3 at the age of 12 years (Fig. 3A-C). A fusion mass over the T2 to L2 vertebral bodies extending anteriorly and posteriorly, and sacral spina bifida were found on preoperative computed tomography scans.

Fig. 4. The patient underwent T2 to L5 fusion and multiple crack osteotomy at T3, T7, and T9 levels. (A–C) The postoperative Cobb angle improved to 38°. There were no mechanical complications during the follow-up duration of 7 years.

Fig. 3. A 14-year-old boy with a history of spinal surgery. At the age of 2 years, he was diagnosed with congenital scoliosis and underwent anterior release and posterior fusion with bone grafting from T8 to L1. (A–C) The scoliosis worsened, and the coronal Cobb angle was 93° at 14 years of age. (D, E) A fusion mass over T2 to L2 extending anteriorly to posteriorly, fused ribs from T2 to T12, and sacral spina bifida were found on preoperative computed tomography scans.
na bifida were found on preoperative CT scans (Fig. 3D, E). The patient underwent PMCO at the T5, T8, and T9 levels and correction and fusion from T2 to L5 (see Supplementary video clip 3). The postoperative Cobb angle improved to 38° (Fig. 4). No mechanical complications were observed during 7 years of follow-up.

DISCUSSION

This is a retrospective analysis of the long-term outcomes of the PMCO technique, used to correct spinal deformity in the context of revisional surgery for scoliosis with a fusion mass, focusing on coronal and sagittal balance correction, and the safety of this surgical technique. Our findings indicated that PMCO was effective in correcting spinal deformities with minimal complications. Moreover, none of the patients required follow-up revisional surgery or showed any signs of pseudarthrosis.

Revisional scoliosis surgeries are not rare and are performed even after satisfactory corrections of the primary spinal deformity. These surgeries are reportedly performed at rates ranging between 12.9% and 47.5%. Deformity progression or pseudarthrosis are the main indications for revisional surgery. This is consistent with our findings. Revisional surgeries were required mostly owing to deformity progression by the crankshaft phenomenon, topping off, or decompensation of the proximal and distal junctions of previous instrumentation.

Fused spinal segments are a major obstacle in revisional scoliosis surgeries. Various osteotomy techniques have been performed depending on the degree of deformity correction. SPO can be used for less than 15° of deformity correction. PSO or PVCR is conventionally used for severe spinal deformities, which involve resection of the apex of the deformity. The PMCO technique was devised to achieve a larger amount of spinal deformity correction through an incomplete 3-column osteotomy by cracking the anterior cortical shell while maintaining the integrity of the vertebral segments and preventing excessive movement, stepping off, or transitioning at the osteotomy sites; this technique may, therefore, be safer than conventional techniques. Only 1 of the 18 patients had motor weakness over an average of 3.2 levels of PMCO in this study, but he spontaneously recovered 3 months after postsurgery. In contrast, the complication rates of conventional techniques are reportedly high. Lenke et al. in their multicenter cohort study reported that 27% of patients undergoing VCR showed intraoperative neurological events. Yang et al. concluded that neurological deficit (8%) was the most common complication of PMCO after performing a systematic review (390 patients in 7 studies), with cord injury persisting in 2% of the patients. The high incidence rate of neurological complications in conventional techniques is presumed to result from damage to the microvascular blood supply of the spinal cord, physical injury to the cord during vertebral body resection, or spinal cord kinking or compression caused by stepping off or translation during docking of resected vertebral ends.

In addition, PMCO has sufficient mechanical stability comparable to that of conventional techniques. In our study, even though it was performed for revisional scoliosis surgery, there were no cases of mechanical complications (i.e., fixation failure and pseudarthrosis), and none of the patients required additional surgery during the study period. However, when PVCR is performed for either primary or revisional scoliosis surgery, the rate of fixation failure has been reported to range between 7%–10.7%. Moreover, pseudarthrosis was reported to develop in 6.7% of cases. This may occur because the main PVCR procedure involves resecting the vertebral segment, and the resulting deficient segment or large gap is vulnerable to pseudarthrosis or fixative failure. In contrast, an incomplete osteotomy is performed in PMCO, which enables continuity of the cortical shell and preservation of the surrounding soft tissues while permitting mobility between osteotomized segments. Preserving soft tissue and cortical shell continuity aids bone healing and stable fixation.

Furthermore, the correction capacity of PMCO was comparable to that of PVCR. The average correction rate of PMCO for revisional scoliosis surgery alone has been reported to be 50.5%, whereas that of PVCR for either primary or revisional surgery is 62.1% and 61.6%, respectively.

One of our concerns was the considerable amount of EBL. The vertebra is a blood-rich cancellous structure with abundant vascular channels around the spinal cord that can cause major bleeding during spinal osteotomy. We expected the amount of EBL in PMCO to be much larger than in PVCR, as PMCO involves performing osteotomies at multiple levels. However, the mean EBL of 3,352.8 mL in PMCO was comparable to that of PVCR (1,103–7,034 mL). It may be associated with the formation of a narrower gap in the vertebral body by the cracking maneuver in an incomplete osteotomy, as compared with PVCR, which involves resection of the blood-rich vertebra as a block. We attempted to further reduce the EBL using the following techniques: (1) bone bleeding from a crack or narrow gap created by an incomplete osteotomy was packed with hemostatic materials, such as a gelatin sponge (Spongostan; Ethicon, Somerville, NJ); and (2) the vertebral body was packed with bone cement to achieve hemostasis. These techniques were effective in reducing EBL.
NJ, USA) or an Avitene Sheet (Davol Inc., Warwick, RI, USA), and (2) the osteotomy was performed using a 4-mm round diamond burr (Midas Rex), rather than an osteotome.

The average hospitalization duration in our study was 27.4 days, which was longer than that in a previous study. In our group, a longer hospitalization duration was observed for a case of partial neurological deficit (131 days) and 2 cases of hemothorax (52 and 30 days). The average duration of hospital stays, excluding these 3 cases, was 18.7 days. This was 3–5 days longer than the 10- to 14-day duration of primary scoliosis surgery at our institute. This trend of longer hospital stays could be due to the country's unique medical insurance system, which allows patients to stay in the hospital until sufficient recovery has been achieved. All patients were discharged after they recovered their ability to perform daily activities.

This study had a few limitations. The small number of patients in a heterogeneous population could be the main limitation in producing statistically conclusive results. In addition, this study was not randomized but was a retrospective observational case series, which reduced its statistical power. Despite these limitations, all the surgeries in our study were performed by a single surgeon at a single institution. Moreover, the follow-up period was sufficient to offer reliable results, which increased the credibility of our results while reducing bias. The long-term follow-up results of this study suggest that PMCO can overcome the disadvantages of other surgical osteotomy techniques. Future prospective studies should be conducted using properly managed evidence-based protocols.

**CONCLUSION**

Incomplete osteotomy using PMCO provided satisfactory deformity correction without severe complications during revisional scoliosis surgery. It is an effective and safe technique for revisional scoliosis surgery in the presence of a fusion mass, as the less invasive procedure has the advantage of maintaining cortical continuity and preserving soft tissues while providing sufficient mobility for spinal deformity correction.

**NOTES**

**Supplementary Materials:** Supplementary video clips 1-3 can be found via https://doi.org/10.14245/ns.2346568.284.

Supplementary video clip 1. Animation of posterior multilevel crack osteotomy.

Supplementary video clip 2. Posterior multilevel crack osteotomy being performed using a cadaver.

Supplementary video clip 3. Posterior multilevel crack osteotomy being performed in the surgical setting.

**Conflict of Interest:** The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: JHY, DGC, SWS; Data curation: JHY, DGC, YN; Formal analysis: MHS, JHY, YN; Methodology: MHS; Writing - original draft: MHS; Writing - review & editing: DGC, SWS.

**ORCID**

Mi Hyun Song: 0000-0003-4082-1455
Jae Hyuk Yang: 0000-0001-6949-6954
Dong-Gune Chang: 0000-0001-6731-1063
Yunjin Nam: 0000-0003-2294-3280
Seung Woo Suh: 0000-0002-1536-4611

**REFERENCES**

Comparative Efficacy of Clinical Interventions for Sacroiliac Joint Pain: Systematic Review and Network Meta-analysis With Preliminary Design of Treatment Algorithm

Yanting Liu1,*, Siravich Suvithayasiri2,*, Jin-Sung Kim1

1Department of Neurosurgery, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
2Department of Orthopedics, Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, Thailand

Objective: We aimed to identify the most effective clinical treatment method for sacroiliac joint (SIJ)-related pain based on the systematic review and network meta-analysis (NMA) to evaluate the comparative efficacy of clinical interventions for sacroiliac joint pain by pooling the randomized controlled trials (RCTs).

Methods: Our team conducted a systematic review and NMA of RCTs to determine the most effective clinical treatment for SIJ-related pain. We searched the PubMed (MEDLINE), Web of Science, Cochrane Library, and Scopus databases for RCTs until February 2023. The PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines were followed. Pairwise and network meta-analyses were conducted using a random effects model.

Results: Based on the search strategy and inclusion criteria, our systematic review and NMA included 9 randomized studies with 652 participants. Research has mainly focused on various radiofrequency sources, but their number is still low. In the network analysis, according to the NMA and mean ranking probabilities for the improvement of pain intensity (PI) and quality of life (QoL), sacroiliac joint fusion and cooled radiofrequency were associated with high treatment rank for improving PI and QoL in patients with sacroiliac joint pain.

Conclusion: This NMA suggest that SIJ fusion and cooled radiofrequency could be potential options for improving the QoL and relieving pain in patients with SIJ-related pain. Comparison studies of outcomes between these 2 procedures with solid methodology and a low risk of bias would be very beneficial to identify the optimal treatment option for this challenging disease.

Keywords: Sacroiliac joint syndrome, Systematic review, Network meta-analysis, Treatment algorithm, Radiofrequency ablation, Fusion

INTRODUCTION

Sacroiliac joint (SIJ) pain is a common etiology of chronic low back pain worldwide, with an approximate prevalence of 10%–33%.1-3 The joint acts as a solid bridge connecting the lumbosacral spine and the ilium while transferring the load from the axial spine to both lower extremities. Due to its complex morphology, various innervation patterns, and overlapping clinical findings from various sources of possible pain generators around the lumbosacral spine and hip girdles, decisions regarding diagnosis and treatments are very challenging.

In general, the clinical manifestations of SIJ pain vary. Possible regions of aching pain are the lower back (up to 38%),4,5 followed by the pelvis or buttock, hip or groin, thighs, or rarely the...
lower legs. A history of sitting intolerance, the number of child deliveries, trauma, previous treatments, and back surgery are also important factors associated with SIJ pain. SIJ pain may be strongly correlated with SIJ pathologies, such as SIJ instability or adjacent segment disease. Many free-ending nerve fibers and mechanoreceptors from the SIJ joint have been observed, and high levels of dermatome in the SIJ can also make the clinical presentation of pain uncertain. This could also cause SIJ pain to be underdiagnosed, thus leading to premature bias in treatment decision-making.

In recent years, there has been a growing interest in research related to SIJ interventions, driven by the increasing prevalence of SIJ pain and the continuous search for effective treatments. Advancements in diagnostic techniques and novel therapeutic approaches have contributed to a better understanding of the SIJ’s complex nature and its related pain. Consequently, a surge in scientific publications has been observed, reflecting the expanding body of knowledge on SIJ interventions and their potential benefits (Fig. 1). Against this background, this study aims to present a systematic review and network meta-analysis (NMA) to assess the comparative efficacy of various types of current clinical interventions for treating SIJ pain.

**MATERIALS AND METHODS**

1. Search Strategy and Data Extraction

This study was reported in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines. The study protocol for this systematic review and meta-analysis was registered on the PROSPERO (International Prospective Register of Systematic Reviews; No. CRD42 023401777). For nonhuman interventional research, ethical approval and informed consent are not needed. We searched the PubMed (MEDLINE), Cochrane Library, Scopus, and Web of Science electronic databases from inception to 2 February 2023. The search strategy for each database is shown in the Supplementary Material. We also manually searched for published, preprint RCTs. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, 2 independent investigators extracted the demographic (author, publication year, follow-up time) and intervention data (surgical technique, measurement metrics).

We included RCTs comparing various clinical interventions for treatment without restrictions regarding age, sex, or race. The primary diagnosis of SIJ pain should be performed by the standard clinical operationalized method. According to the predefined categories, the treatment methods were grouped into different homogeneous groups. Among them, various details of treatment methods were examined because the purpose of our research was to focus on technique differences. There were also no restrictions regarding the threshold ranges of the demographic baseline, the minimum number of participants, and the technology device used. YT and SS independently extracted data to Excel (Microsoft Corp., Redmond, WA, USA, 2018. Microsoft Excel) using a structured and standardized form. In addition to outcomes, information on a vast array of clinical and methodological aspects was included.
ological trial characteristics were extracted, as described in the protocol. In cases of discrepancies among the evaluators concerning the extracted data, a third reviewer (JSK) was consulted to achieve a consensus. The following data were extracted from eligible studies: the author's name, publication date, study design, age, sample size, follow-up duration, intervention measures, and outcome indicators.

2. Risk of Bias Assessment and Outcome Indicators

Two reviewers (YT and SS) independently assessed the risk of bias (RoB) of included studies using the revised tool to assess RoB 2 tool) in randomized trials. A visualization tool (Robvis) was used for visualizing risk of bias assessments in our systematic review and NMA. The RoB 2 tool comprises 5 domains for assessing the RoB. We included 2 parameters in our NMA model: pain intensity (PI; visual analogue scale or Numerical Rating Scale) and quality of life (QoL; Oswestry Disability Index [ODI], EuroQoL-5 dimension, or 36-item Short Form health survey). For these indicators, a treatment hierarchy was estimated by the surface under the cumulative ranking curve (SUCRA) analysis, which ranks the order of superiority of each clinical intervention based on the probability values compared against others.

3. Data Synthesis and Statistical Analysis

First, we planned to perform pairwise meta-analyses using a fixed or random effects model for direct comparisons with at least 2 studies based on the heterogeneity test results. The test for heterogeneity was performed using a standard chi-square and I² statistic. All results associated with the 95% confidence interval (CI) of the pairwise meta-analysis and heterogeneity estimates are presented in the Supplementary Material. According to the Cochrane Handbook, the range of I² values indicating substantial heterogeneity higher than 75%.

Second, we performed the NMA in Stata with the “network” and “mvmeta” packages, the analytic process based on the random effects model frequentist framework, to synthesize the results reported by the RCTs. This program assumes that all included treatment contrasts have the same heterogeneity variance. Then, we defined our research characteristics as indirect treatment comparison or mixed treatment comparison based on the loop results of network geometry. If a study involves different arms with a minor difference in the clinical intervention, the similar arms will be merged with the single arm. For all missing data, we will contact the original author to support the data. Otherwise, the appropriate statistical methods will be applied to estimate the blank. In the NMA, a random effects model was considered to estimate and pool the heterogeneous outcomes. We strictly limited the methodology based on our inclusion criteria and exclusion criteria (Supplementary Material).

To ensure the validation of the overall effect size, a series of prior statistical assumptions were conducted to verify the consistency of the NMA model. The network geometry was illustrated by drawing a network plot to intuitively visualize the connection characteristics between the included studies. Then, inconsistency was further statistically tested in each treatment with the node-splitting method. Then, we estimated the effect size and uncertainties in pairwise comparisons included in our NWA by using the confidence interval and predictive intervals considering the heterogeneity level to better assess the proportions of contribution to each study’s indirect and direct comparison. The consistency is statistically examined to ensure no significant statistical discrepancy of outcomes between the direct and indirect evidence from different treatment effects in NWA by using hypothesis logical inference that allows for inconsistency. In addition, we formally assessed the publication bias in NMA by the asymmetry of the comparison-adjusted funnel plot to detect the potential small study size effect. We constructed a contribution plot using weighted squares based on the effect sizes with variances to represent the different pieces of evidence within the NMA. Moreover, we evaluated the inconsistency and uncertainties separately in each closed loop of networks of interventions using the method of moments estimator. Finally, the treatment hierarchy was drawn under the cumulative ranking (SUCRA) to illustrate the probability ranking of interventions. Statistical analysis and graph construction were performed using the network packages in Stata using Stata/MP (StataCorp, 2021. Stata Statistical Software: Release 17. College Station, TX, USA: StataCorp LLC).

RESULTS

1. Study Characteristics

The process of evaluating studies according to the inclusion and exclusion criteria is illustrated in Fig. 2. After screening the abstracts and reviewing the complete texts, 9 RCTs with 652 patients were ultimately included in the NMA. As shown in Table 1, a total of 6 different clinical interventions were reported: conservative therapy, cooled radiofrequency (CRF), thermal radiofrequency (TRF), pulsed radiofrequency (PRF), intra-articular injection (II), and SIJ fusion. The most common groups
were the SIJ fusion (23.47%) and IJ group (23.62%), followed by TRF (23.31%), CRF (9.05%), and PRF (2.30%). The mean age of all participants was 49.88 years. Overall, 66.7% of the included studies were reported in the United States or Europe from 2006 to 2018. Six studies were considered to have a moderate level of bias. Three studies were considered to have a high risk of missing data due to the large proportion of patients who were lost to follow-up as well as bias in the selection of the reported results due to an oversized effect size, which was induced by support from the device manufacturer. The most common domain in the RoB tool was deviations from the intended interventions, which was due to concealed treatment allocation (Fig. 3). Of the 9 studies, only one provided data for one clinical outcome parameter. For the standard pairwise meta-analyses in NMA, the assessment results of heterogeneity and inconsistency are reported in the Supplementary Material.

2. Pairwise Meta-analysis

In the pairwise meta-analysis of PI, a significant treatment difference, as measured by the VAS, was reported for CRF versus conservative (-2.95; 95% CI, 1.53–4.37; p = 0.085; I² = 59.4%)
## Table 1. Overview of clinical trials on sacroiliac joint pain interventions: comparative study design, outcomes, and results

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Region</th>
<th>Clinical trial registration No.</th>
<th>Intervention</th>
<th>Control</th>
<th>Sponsor</th>
<th>Implant or device used</th>
<th>Follow-up time (mo)</th>
<th>Measured outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al., 25 (2008)</td>
<td>RCT</td>
<td>USA</td>
<td>NCT00373724</td>
<td>Cooled RF</td>
<td>Placebo</td>
<td>Baylis Medical</td>
<td>Baylis RF System</td>
<td>1, 2, 6</td>
<td>Pain NRS, ODI, analgesic used, GPE</td>
</tr>
<tr>
<td>Patel et al., 29 (2012)</td>
<td>RCT</td>
<td>USA</td>
<td>NR</td>
<td>Cooled RF</td>
<td>Placebo</td>
<td>Baylis Medical</td>
<td>Baylis RF System</td>
<td>1, 3, 6, 9</td>
<td>Pain NRS, ODI, SF-36, AQoL, GPE</td>
</tr>
<tr>
<td>Zheng et al., 26 (2014)</td>
<td>RCT</td>
<td>China</td>
<td>ChiCTR-TRC-12002483</td>
<td>Thermal RF</td>
<td>Medication</td>
<td>No</td>
<td>Baylis RF System</td>
<td>3, 6</td>
<td>Pain VAS, ASAS20, ASDAS, BASMI, BASFI, serum CRP</td>
</tr>
<tr>
<td>Whang et al., 24 (2015)</td>
<td>RCT</td>
<td>USA</td>
<td>NCT01681004</td>
<td>SIJF</td>
<td>All types of NSM*</td>
<td>SI-BONE</td>
<td>Triangular Titanium Implant (iFuse)</td>
<td>1, 3, 6</td>
<td>Pain VAS, ODI, EQ-5D, SF-36, ambulatory or work status, analgesic used, physical examination</td>
</tr>
<tr>
<td>Canovas Martinez et al., 27 (2016)</td>
<td>RCT</td>
<td>Spain</td>
<td>NR</td>
<td>Thermal RF</td>
<td>SIJI</td>
<td>No</td>
<td>Cosman</td>
<td>3</td>
<td>Pain VAS</td>
</tr>
<tr>
<td>Van Tilburg et al., 28 (2016)</td>
<td>RCT</td>
<td>Netherlands</td>
<td>ISRCTN45914408</td>
<td>Thermal RF</td>
<td>SIJI</td>
<td>No</td>
<td>Neurotherm</td>
<td>1, 3</td>
<td>Pain NRS, GPE</td>
</tr>
<tr>
<td>Dengler et al., 30 (2017)</td>
<td>RCT</td>
<td>USA</td>
<td>NCT01741025</td>
<td>SIJF</td>
<td>CM†</td>
<td>SI-BONE</td>
<td>Triangular Titanium Implant (iFuse)</td>
<td>1, 3, 6, 12</td>
<td>Pain VAS, ODI, ASLR, EQ5D, Zung Depression Scale, Satisfaction Questionnaires, Walking Distance</td>
</tr>
<tr>
<td>Dutta et al., 31 (2018)</td>
<td>RCT</td>
<td>India</td>
<td>NR</td>
<td>Pulsed RF</td>
<td>SIJI</td>
<td>No</td>
<td>Baylis RF System</td>
<td>0.5, 1, 3, 6</td>
<td>Pain NRS, ODI, GPE</td>
</tr>
<tr>
<td>Mehta et al., 32 (2018)</td>
<td>RCT</td>
<td>UK</td>
<td>NCT01726608</td>
<td>Cooled RF</td>
<td>Placebo</td>
<td>No</td>
<td>Neurotherm</td>
<td>3, 6</td>
<td>Pain NRS, SF-12, HADS, EQ-5D</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; SIJF, sacroiliac joint fusion; NSM, nonsurgical management; VAS, visual analogue scale; ODI, Oswestry Disability Index; EQ-5D, EuroQoL-5 dimension; SF-36, 36-item Short Form health survey; NRS, Numerical Rating Scale; GPE, Global Perceived Effect; ASAS20, Assessment of SpondyloArthritis International Society Response Criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; RF, radiofrequency; CRP, C-reactive protein; NR, not related or not available; SIJI, sacroiliac joint injection; AQoL, Assessment of Quality of Life assessment tool; CM, conservative management; ASLR, Active Straight Leg Raise Test; HADS, Hospital and Depression Scale.

*Non-surgical management including all conservative management and radiofrequency ablation. †Conservative management including medical therapy, physiotherapy, and stabilization exercises.
and for TRF versus IJ (-1.85; 95% CI, -2.88 to 0.83; \( p = 0.116; I^2 = 59.6\%\)). The results indicated that CRF is superior to conservative treatment and that TRF is superior to IJ for SIJ pain relief. On the other hand, in the pairwise meta-analysis of QoL, a significant treatment difference, as measured by the QoL scores, was observed for conservative versus CRF (0.95; 95% CI, 1.20–0.70; \( p = 0.133; I^2 = 50.4\%\)). The results showed that CRF is superior to conservative treatment for improving QoL. More data are needed for additional pairwise comparisons. The contribution distribution from each direct pairwise study in the mixed and indirect models was estimated by calculating the effect size and variances in the contribution plot (Fig. 4).

3. NMA and Ranking Probabilities
The head-to-head comparison results of the PI and QoL for each intervention for SIJ pathology are shown in the net league (Fig. 5). In terms of PI (9 RCTs, 628 participants), the top clinical intervention for SIJ pain was SIJ fusion (-3.29; 95% CI, -4.83 to 1.74; \( p \leq 0.001\)), followed by CRF (-2.94; 95% CI, -4.26 to 1.63; \( p \leq 0.001\)), PRF (-0.82; 95% CI, -3.36 to 1.73; \( p = 0.529\)), TRF

### “Contribution plot”

Direct comparisons in the network

![Network contribution plot](image-url)

**Fig. 4.** Network contribution plot. The contribution proportion of treatments from the estimation in the mixed model and indirect model: A, conservative therapy; B, cooled radiofrequency; C, thermal radiofrequency; D, pulsed radiofrequency; E, injection; F, fusion.

<table>
<thead>
<tr>
<th>Fusion (PI)</th>
<th>-3.19 (-6.00, -0.38)</th>
<th>-4.21 (-7.73, -0.68)</th>
<th>-1.29 (-4.71, 2.13)</th>
<th>-5.54 (-7.96, -3.13)</th>
<th>-7.47 (-9.91, -5.02)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF</td>
<td>-1.02 (-5.52, 3.48)</td>
<td>1.90 (-2.52, 6.32)</td>
<td>-2.36 (-3.79, -0.93)</td>
<td>-4.28 (-7.99, -0.56)</td>
<td></td>
</tr>
<tr>
<td>PRF</td>
<td>-2.13 (-4.99, 0.74)</td>
<td>2.92 (-0.57, 6.40)</td>
<td>-1.34 (-5.60, 2.93)</td>
<td>-3.26 (-5.80, -0.72)</td>
<td></td>
</tr>
<tr>
<td>TRF</td>
<td>-2.70 (-4.75, -0.66)</td>
<td>-0.58 (-2.83, 1.67)</td>
<td>-4.26 (-8.43, -0.08)</td>
<td>-6.18 (-8.57, -3.79)</td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>-3.29 (-4.33, -2.13)</td>
<td>-0.82 (-3.36, 1.73)</td>
<td>-0.24 (-1.80, 1.32)</td>
<td>-1.32 (-3.03, 0.40)</td>
<td>-1.92 (-5.53, 1.51)</td>
</tr>
<tr>
<td>IJ (QoL)</td>
<td>-3.81 (-6.60, -1.03)</td>
<td>-4.26 (-6.42, -2.10)</td>
<td>-2.13 (-4.02, -0.25)</td>
<td>-1.56 (-3.79, -0.32)</td>
<td>-1.32 (-3.03, 0.40)</td>
</tr>
</tbody>
</table>

**Fig. 5.** Network meta-analysis net league for pain intensity (PI) and quality of life (QoL). Numbers underlined represent statistically significant results. CRF, cooled radiofrequency; PRF, pulsed radiofrequency; TRF, thermal radiofrequency; IJ, injection.
(-0.24; 95% CI, -1.80 to 1.32; p = 0.763), IJ (1.32; 95% CI, -0.40 to 3.03; p = 0.132). The results of SIJ fusion and CRF showed a significant decrease in PI scores compared to conservative therapy. There was no other statistical evidence among any other 3 clinical interventions. In terms of QoL (8 RCTs, 568 participants), the top clinical intervention was SIJ fusion (5.54; 95% CI, 3.13–7.96; p ≤ 0.001), followed by CRF (2.36; 95% CI, 0.93–3.79; p = 0.001), TRF (4.26; 95% CI, 0.08–8.43; p = 0.046), PRF (1.34; 95% CI, -2.93 to 5.60; p = 0.539), IJ (-1.92; 95% CI, 3.13–7.96; p = 0.272). Additionally, we depicted the comparative efficacy of

![Fig. 6. Forest plot of comparisons in pain intensity (PI) and quality of life (QoL) to estimate the effect size and uncertainty. The red horizontal lines represent the predictive confidence interval (CI). CRF, cooled radiofrequency; TRF, thermal radiofrequency; PRF, pulsed radiofrequency; IJ, injection; FUS, fusion; 95% Prl, 95% predictive interval.](https://doi.org/10.14245/ns.2346586.293)

![Fig. 7. Hierarchical ranking of probability on the impact of pain intensity (PI) and quality of life (QoL) illustrated by the cumulative ranking curve. RF, radiofrequency; TRF, thermal RF; CRF, cooled RF; PRF, pulsed RF; IJ, injection; PI, pain intensity.](https://www.e-neurospine.org)
different clinical interventions from each individual study for treating SIJ pain (Fig. 6). The results suggested that SIJ fusion, CRF, and TRF led to significant statistical improvement in QoL compared to conservative therapy. There was no statistical evidence among any other 2 clinical interventions compared to conservative treatment.

According to the ranking probabilities and SUCRA for improving PI and QoL, the probabilities efficacious of treatment rank are illustrated in Fig. 7. Based on our analysis, SIJ fusion had the highest probability (SUCRA, PI: 92.2%, QoL: 95%) of being the most efficacious procedure for relieving SIJ pain and improving QoL, followed by CRF (SUCRA, PI: 85.7%, QoL: 57.2%), TRF (SUCRA, PI: 38.4%, QoL: 79.1%), and PRF (SUCRA, PI: 50.5%, QoL: 42.7%). In contrast, IJ (SUCRA, PI: 1.8%, QoL: 3.2%) was the least efficacious compared to conservative therapy; this difference was not significant.

4. Consistency Test and Heterogeneity Analysis

According to our statistical analysis, the design-by-treatment interaction inconsistency model is fit with no evidence for inconsistency in PI and QoL using the restricted maximum likelihood. In the pairwise meta-analysis of PI and QoL, the pooled effect size showed no heterogeneity and no evidence of intra-loop inconsistency in PI ($I^2 = 1.30$, $p = 0.254$; loop, $I^2 = 1.954$, $p = 0.014$, $r^2 = 0$) (Supplementary Material). However, the ODIs do not have a reticulated loop structure that cannot perform loop-specific tests. Therefore, heterogeneity arises in the test of inconsistency. To determine whether heterogeneity was due to external or internal models, node-splitting was performed to determine whether heterogeneity still existed between the included studies. The results of node-splitting showed no statistical inconsistency in estimating the effect size between the direct and indirect intervention analyses. Furthermore, there was no evidence of any potential small study effect bias by inspecting the comparison-adjusted symmetrical funnel plots of PI and QoL (Supplementary Material).

DISCUSSION

Our research advances a structured, stepped treatment algorithm for SIJ pain management, recommending CRF as the primary intervention owing to its minimally invasive character. This comprehensive approach provides an effective roadmap for handling SIJ pain, thereby improving patient outcomes. It underscores CRF’s advantage in minimizing surgical trauma linked to more invasive procedures like open SIJ fusion, hence permitting clinicians to alleviate pain while mitigating patient risk and discomfort. Our study also highlights the effectiveness of SIJ fusion, CRF, and even the older technique of TRF in pain relief and enhancing QoL, implying their suitability as alternatives to conservative treatments. These findings could assist the development of health policy and guidelines. Furthermore, our results support the ongoing healthcare trend towards less invasive procedures and emphasize the need for personalized patient care, considering factors such as comorbidities, specific pain patterns, and patient preferences.

In our study, we implemented both pairwise meta-analyses and NMA. The pairwise meta-analyses were used to compare the effectiveness of 2 interventions at once, whereas NMAs provided an avenue for us to compare multiple interventions concurrently. This is especially advantageous when direct evidence from RCTs is not sufficiently robust. We adopted the surface under the cumulative ranking curve as a measure to rank the efficacy of each intervention. Further, we assessed the consistency and heterogeneity among the studies integrated into the meta-analysis. The term consistency in our context relates to the agreement level between direct and indirect sources of evidence within the network. Heterogeneity, on the other hand, pertains to the variability observed in the outcomes of the studies. The results we found show that SIJ fusion, CRF, and TRF are the preferred operations to improve the patient’s postintervention parameters in the PI or QoL evaluation scales. Among them, SIJ fusion seemed to be the best choice compared to other interventions. Generally, the treatment of SIJ pain can be divided into nonsurgical and surgical management. Nonsurgical management (NSM), such as medication and physical therapy, is usually considered the first line of treatment. However, if those conservative measures fail, nonsurgical interventions will come into play. SIJ injection is the standard procedure to enhance the accuracy of the diagnosis of SIJ pain. Several physician societies have recommended the positive threshold to be 50% to 75%. Local anesthetic is used as a diagnostic agent, but the appropriate amount of volume is still under debate. Corticosteroids can also be added to facilitate the combined therapeutic effect. Although several studies have demonstrated promising results in pain control after corticosteroid injection of the SIJ, others revealed its short-term benefit with poor longevity compared to other interventions.

Radiofrequency ablation (RFA) is usually the next step of NSM if the patients have already confirmed the diagnosis of SIJ pain and the effects of the initial SIJ injection have waned out with relapsing pain. It is a minimally invasive procedure that aims to
provide more longevity of pain control by destroying the nerve endings using an insulated needle. PRF originates from the concept that voltage fluctuation will cause a strong magnetic field and could relieve pain more than direct tissue destruction by heat. Therefore, the surrounding temperature could be controlled to avoid permanent nerve tissue damage (<45°C). TRF uses the ‘palisade’ technique to place bipolar electrodes and facilitate long continuing thermal lesions along the course of several lateral branch nerves. The recently developed CRF enhances larger lesions to ablate the nerve to be created. This is because the specialized probe has an internal cooling system that prevents the surrounding tissue from charring, allowing the lesion radius to increase by up to 3 times compared to TRF. Many studies have reported comparable or better CRF outcomes than other NSM techniques. Mild complications, such as soreness or numbness at the intervention site, were reported, which could be resolved entirely within 2 weeks. Comparing the 3 RFA interventions, one systematic review and meta-analysis showed that CRF was more efficacious than TRF and PRF; however, the differences were not significant.

Recently, RFA has also been proven to preserve the surrounding muscles well. Oswald et al. retrospectively reviewed symptomatic facet joint pain patients treated with RFA. They used magnetic resonance imaging analysis to compare the lumbar paraspinal musculature before and at least 6 months after the surgery. No fatty degeneration occurred on the operated side. Therefore, less iatrogenic damage to surrounding tissue after RFA could be expected. The findings from this study could be aligned well with the aim of minimally invasive procedures, as they could preserve the patient’s function while achieving better outcomes.

Fusion is the main objective of surgical management in patients with chronic back pain from the SIJ. It should be the last resort of options in cases of failed NSM or pain relapse. Those patients also needed to prove the cause of chronic low back pain to be from the SIJ in origin (e.g., relieving pain more than 50%–75% from previous SIJ injection). To summarize, we have proposed a comprehensive algorithm for diagnostic and treatment pathways for chronic low back pain, specifically for SIJ pathology (Fig. 8). Building on previous discussions pertaining to the established positive threshold for pain reduction following SIJ interventions as advocated by various medical associations, we have subsequently defined the efficacy of our algorithm to be 50%. Minimally invasive SIJ fusion was introduced using the iFuse Implant System (SI-BONE Inc., Santa Clara, CA, USA), followed by many afterward. Many studies have reported good results regarding using iFuse compared with other NSMs. Polly et al. reported 2-year outcomes from a multicenter RCT study comparing SIJ fusion using iFuse and NSM. The SIJ fusion group yielded more significant improvements in clinical parameters than the NSM group. Another RCT compared conservative management and SIJ fusion outcomes and reported similar results. They concluded that the iFuse implant system was safe and more effective. However, complications, such as increas-

Fig. 8. Algorithm of diagnosis and treatment for low back pain (A) and sacroiliac joint pain (B). MBB, medial branch block; SIJ, sacroiliac joint; RFA, radiofrequency ablation.
ed pain around the injection site, hematoma, deep wound infection, or nerve root impingement, are all possible up to 16.4%. Shamrock et al. also reported an overall complication rate of 11.1%, of which the most common are wound infection and nerve root impingement, with occurrence rates of 2% and 1.6%, respectively.

Previous systematic reviews and meta-analyses also revealed similar outcome results. Dengler et al. conducted a pooled analysis of 2 multicenter RCTs and 1 single-arm prospective trial. They concluded that SIJ fusion leads to better treatment outcomes than NSM. Another systematic review and meta-analysis by Abbas et al. showed that the standardized mean difference regarding SIJ fusion was better than that of conservative treatment at the 6-month follow-up. They concluded that SIJ fusion is a potential option in surgical management regarding SIJ pathology. However, the confidence level in the evidence presented in their review was mentioned as ‘very low’. Moreover, 5 out of 6 studies included in their research were industry-funded. Therefore, there was a high risk of publication bias. This finding is also consistent with the quality assessment of the included papers performed in our study.

More concerns regarding SIJ fusion studies exist. Although most of them are RCTs, all of those studies conducted a comparison study between iFuse and NSM. NSM consists of various kinds of treatment, ranging from medication or physical therapy to interventions such as SIJ injection or many types of RFA. They also have different levels of therapeutic effects. Therefore, this may lead to information bias. Surprisingly, there is no direct comparison of the efficacy between these 2 procedures and their cost-effectiveness in previous literature. Future studies directed at comparisons between SIJ fusion and a specific kind of NSM, such as RFA (with or without endoscope assistance), as well as its cost-effectiveness, will fill this enormous knowledge gap.

Recently, endoscopic spine surgery (ESS) has evolved rapidly in the last decade and has successfully proven its use in many spinal procedures, such as discectomy, spinal canal decompression, or interbody fusion. The use in more complicated spine diseases, for example, spinal infection or malignancy, was also reported. ESS has also proven good results in assisting neuroablation surgery in patients diagnosed with facet joint pain. However, its use in patients with SIJ pain was initially reported by Choi et al. It yielded good results with improved PI and QoL scales immediately and could be maintained at least 6 months after the surgery. The proposed advantages of the endoscope are better visualization of bony landmarks, as it could better identify the lateral branches of S1 to S3. Furthermore, it could locate the area that has already been ablated. This could prevent excessive damage to the surrounding soft tissue and lessen postoperative pain and dysesthesia risk. Subsequent studies regarding endoscopic-assisted RFA, with or without the use of navigation guidance, also yielded good results with decent longevity after the procedure when treating SIJ pain in chronic low back pain patients.

For future research, it is recommended that more high-quality RCTs be conducted to further compare the effects of different clinical interventions on SIJ pain, especially the less common ones like PRF. Future studies could also focus on the long-term effects of these interventions. Additionally, studies could also explore the reasons behind the effectiveness of SIJ fusion and CRF to better understand their mechanisms and potentially improve their efficacy even further. It’s worth mentioning that the findings should be interpreted with caution due to the moderate level of bias identified in 6 of the studies included in this NMA. As a result, future research should strive to minimize bias, such as concealed treatment allocation, and should carefully account for potential confounding factors. Researchers should ensure to report all relevant results to avoid selection bias.

There are several limitations to our study. First, half of the included studies reported concern about the RoB due to unclear or intact allocation concealment that impacts the reliability of the pooled effect size of clinical intervention on SIJ pathology. Second, the consolidation of treatment arms with minor differences could potentially oversimplify interventional disparities, possibly masking subtle but clinically relevant nuances. Although we aimed to objectively classify ‘minor differences’, the inherent subjectivity of this process could introduce bias. To counteract this, we ensured transparency by providing a detailed table outlining each study’s specific characteristics. Third, a notable limitation of our NMA is the absence of closed loops within the network map in the assessment of QoL. This gap potentially constrains the depth of our comparative findings, limiting our ability to robustly cross-validate the relative effectiveness of these interventions. Fourth, we only considered the efficacy of interventions for SIJ pathology based on clinical statistical scales. We could not extract the data from the current data with satisfaction as the binary outcome to estimate the acceptability of participants facing interventions. Fifth, our strategy for managing missing data had to resort to statistical imputation methods. We acknowledge that statistical imputation can facilitate more comprehensive analyses, it cannot completely substitute for actual data. The specific extent of this bias is often challenging to quan-
tify due to the underlying assumptions made during the imputation process, which may or may not hold true. When data are missing completely at random, the potential for bias is reduced, but our study becomes less precise, leading to a larger uncertainty interval. Conversely, if missing data are not random but are linked to factors within our study, this can introduce bias. Moreover, the potential impact of missing data is more complicated due to the complex network structure and how it affects both direct and indirect comparisons. Therefore, we hope readers consider the potential impact of these data limitations when interpreting our findings. Additionally, the application of SIJ interventions may vary, leading to differences in surgical techniques and potentially increasing the heterogeneity of the results.

**CONCLUSION**

The systematic review and NMA suggested that for the consideration of clinical intervention methods, SIJ fusion and CRF could be the first 2 clinical options to relieve PI and improve QoL in patients who complained of SIJ pain. However, due to RoB, the current evidence cannot lead to a definite conclusion. Additionally, more RCTs, especially those comparing SIJ fusion and CRF, are recommended to identify the best treatment option for this long-standing challenging disease.

**NOTES**

**Supplementary Material:** Supplementary Material can be found via https://doi.org/10.14245/ns.2346586.293.

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**ORCID**

Yanting Liu: 0000-0002-9591-3042
Siravich Suvithayasiri: 0000-0001-5597-701X
Jin-Sung Kim: 0000-0001-5086-0875

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Electroacupuncture-Modulated MiR-106b-5p Expression Enhances Autophagy by Targeting Beclin-1 to Promote Motor Function Recovery After Spinal Cord Injury in Rats

Shuhui Guo, Jianmin Chen, Ye Yang, Xiaolu Li, Yun Tang, Yuchang Gui, Jianquan Chen, Jianwen Xu

1Department of Rehabilitation Medicine, The First Affiliated Hospital of Guangxi Medical University, Guangxi, China
2Department of Rehabilitation Medicine, The First Affiliated Hospital of Fujian Medical University, Fujian, China
3Department of Orthopedics, The First Affiliated Hospital of Guangxi University of Chinese Medicine, Guangxi, China

Objective: Electroacupuncture (EA) has a definite effect on the treatment of spinal cord injuries (SCIs), but its underlying molecular mechanism remains unclear. Meanwhile, MiR-106b-5p is an autophagy- and apoptosis-related microribonucleic acid, but whether it regulates the progression of autophagy and apoptosis in SCIs is yet undetermined. As such, this study aimed to elucidate the involvement of miR-106b-5p in the EA treatment of an SCI.

Methods: The miR-106b-5p level was detected by quantitative real-time polymerase chain reaction. In vitro, SH-SY5Y cells were transfected with miR-106b-5p mimics or inhibitors to regulate the miR-106b-5p expression, while in vivo, SCI rats were treated with EA for 7 days at the bilateral Zusanli (ST36) and Jiaji (EX-B2) acupoints. The motor function was evaluated using the Basso-Beattie-Bresnahan (BBB) criteria. Further, autophagic vacuoles, pathological damage, and neuronal cell morphology were observed by transmission electron microscopy, as well as by hematoxylin and eosin and Nissl staining, respectively.

Results: The miR-106b-5p level, which can interact directly with Beclin-1 by influencing its expression, as well as the expressions of P62, Caspase-3, and Bax, was upregulated after an SCI, but it decreased after EA. Moreover, the ratio of LC3-II to LC3-I was upregulated after EA. EA can enhance autophagy, reduce neuronal apoptosis, and minimize motor dysfunction and histopathological deficits after an SCI. More importantly, however, all the above effects induced by EA can be reversed after an injection of miR-106-5p agomir to produce an overexpression of miR-106b-5p.

Conclusion: EA treatment could downregulate miR-106b-5p to alleviate SCI-mediated injuries by promoting autophagy and inhibiting apoptosis.

Keywords: Spinal cord injury, Electroacupuncture, Autophagy, Apoptosis

INTRODUCTION

A spinal cord injury (SCI) is an extremely serious neurological event characterized by permanent disability in the body below the injured region. The affected individual’s resulting inability to work (labor) and the costs of long-term treatment impose a heavy financial burden on their family and the wider community. Despite concerted efforts focused on SCIs in global terms, no effective breakthrough has yet been made toward a cure for the neurological dysfunction caused by an SCI. Thus, it is imperative to further explore the pathophysiological mechanism of and to develop effective rehabilitation strategies for SCIs.
The pathophysiological progression of an SCI is generally included 2 phases: primary injury and secondary injury. The primary injury leads to irreversible neuronal damage to the spinal cord. The secondary injury, including apoptosis, autophagy, inflammation and so on, that jointly result in tissue destruction and microenvironment changes in the SCI region and lead to nerve repair difficulties. Autophagy is a catabolic process designed to maintain cell homeostasis by degrading cytoplasmic components and organelles in lysosomes, and the inhibition of autophagic flux after an SCI can lead to a poorer functional recovery. Meanwhile, apoptosis is a leading cause of neurological dysfunction and death after an SCI, but appropriate autophagy activation can act as a protective mechanism against the apoptosis of neuronal cells and can provide a favorable microenvironment for nerve regeneration after an SCI. Some researchers believe autophagy is a potential therapeutic target of SCIs. Thus, the adoption of rehabilitation strategies capable of halting apoptosis and activating autophagy during the secondary injury is crucial to limiting the spread of secondary damage, affecting nerve regeneration positively, and promoting functional recovery.

Electroacupuncture (EA) is a therapy derived from traditional Chinese medicine that involves the insertion of sterile, single-use needles into acupoints according to a system of meridians and the application of an electrical current through the needles. The utilization of EA to alleviate pathological damage and improve functional recovery in the treatment of SCIs has gained much popularity in recent years. With fundamental studies having indicated that EA can promote nerve repair and increase motor outcomes by regulating cell autophagy and apoptosis post-SCI. For example, Liu and Wu performed a microarray analysis of SCI samples and EA-induced SCI samples harvested at 7, 14, and 28 days, revealing that a large set of microribonucleic acids (miRNAs) had altered expressions upon EA treatment. Thus, EA may exert therapeutic effects against motor dysfunction in SCIs by modulating miRNA expression profiles.

MiRNAs are a class of endogenous, noncoding, small RNAs with 22–24 nucleotides working as master administrative molecules to regulate gene expressions. This is achieved by binding to the 3’ or 5’ untranslated regions of the target messenger RNA (mRNA) to inhibit translation and induce degradation. Though relatively small in number, miRNAs are believed to be involved in multiple specific biological activities in the body and to play a crucial role in the modulation of secondary injury after an SCI. For example, He et al. observed that the overexpression of miR-92a-3p can promote neurological recovery by inhibiting cell apoptosis in mice with SCIs. Further, Zhou et al. concluded that blocking the expression of miR-378-3p can increase cell viability by regulating apoptosis and autophagy in in vitro SCI models. Thus, certain miRNAs represent potential promising therapeutic targets for SCI repair. To date, the aberrant miR-106b-5p expression has been implicated in many neurological disorders, and it leads to abnormal cell apoptosis and autophagy. However, the role of miR-106b-5p in SCI remains unclear, warranting further investigation. Therefore, we aimed to explore the relationship between the miR-106b-5p expression and EA treatment of SCIs and, furthermore, to validate the speculation that the regulation of apoptosis and autophagy might be responsible for the EA-mediated repair of motor function via downregulation of the miR-106b-5p expression.

**MATERIALS AND METHODS**

1. SCI Patients

Patients with an SCI (n = 10) were enrolled between December 2022 and January 2023 from the Department of Rehabilitation Medicine of the First Affiliated Hospital of Guangxi Medical University. Inclusion criteria were as follows: an age of ≥ 18 years, a first-time SCI, a disease duration of less than one year, and a motor-incomplete injury. Another 10 healthy volunteers without evidence of an SCI were selected as controls during the same period and were age- and sex-matched with the patients. The exclusion criteria were as follows: a previous history of neurological disease, renal dysfunction, severe liver disease, a known or suspected malignancy, surgery, or a skeletal muscle injury within the previous 6 month. Samples of about 5 mL of venous blood were taken from each participant via ethylenediaminetetraacetic acid anticoagulant tubes (Sanli, Liuyang, China) in the morning after 12 hours of fasting. All participants gave their written informed consent to participate in this study, and all procedures performed involving human participants were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (approval number: 2022-K143-01). The chictr.org identifier is ChiCTR2200066985 (https://www.chictr.org.cn/edit.aspx?pid = 186333&htm = 4). The animal experimental protocol was approved by the Guangxi Medical University Animal Research Ethics.

2. Luciferase Reporter Assay

A bioinformatics analysis was performed using BiBiServ (https://bibiserv.ccbj.uni-bielefeld.de/rnahybrid) to identify a favorable binding site between miR-106b-5p and Beclin-1. The
sequences of Beclin-1 3’UTR fragments containing a wild-type (WT) or mutant (Mut) binding site of miR-106b-5p were ordered and synthesized by GeneChem (Shanghai, China), and the GV272 vector (GeneChem) was used to construct the Beclin-1-WT and Beclin-1-MUT recombinant vectors. HEK-293T cells (2 × 10⁴ cells/well) were seeded in 24-well plates followed by cotransfection with p-miR-Beclin-1 3’UTR, p-miR-Beclin-1-mutant-3’UTR, and miR-106b-5p mimics or a negative control (NC) using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Luciferase activity was assessed 48 hours after transfection using a Dual-Luciferase Assay System (Promega, Madison, WI, USA) and normalized according to Renilla luciferase activity (GeneChem).

3. Cell Culture and Transfection

The human neuroblastoma cell line, SH-SY5Y, is a commonly used tool in human in vitro SCI research; herein, SH-SY5Y cells were purchased from the Shanghai Cell Bank of the Chinese Academy of Sciences (Shanghai, China) and maintained per their guidelines. The cells were stored at 37°C and 5% CO₂ in Dulbecco Modified Eagle’s Medium (DMEM; Gibco, Carlsbad, CA, USA) supplemented with 8% fetal bovine serum (FBS; Gibco) and a 1% penicillin-streptomycin-mixed solution (Gibco). The SH-SY5Y cells were randomly distributed into the following 4 groups: (1) an miR-106b-5p mimic group, (2) a NC mimic group, (3) a miR-106b-5p inhibitor group, and (4) an NC inhibitor group. For miRNA transfection, cells were seeded in a six-well plate at 3 × 10⁴ cells per well and transiently transfected 1 d later using Lipofectamine 3000 (Invitrogen) in the OptiMEM medium (Invitrogen) according to the manufacturer’s instructions (Fig. 1A). Moreover, miR-106b-5p mimics and inhibitors, along with their corresponding NC mimics and NC inhibitors, were purchased from Bioneer Corporation (Shanghai, China).

4. Experimental Animals and SCI Model

Adult female Sprague Dawley rats (8 weeks old, 200–220 g) were purchased from the Animal Experimental Center (Guangxi Medical University, Nanning, China), all of which were housed in a specific pathogen-free environment at 22°C–24°C with available food and water. The Guangxi Medical University Animal Research Ethics Committee (approval No. 202209002) approved the ethics application concerning animal protocols. The rats were randomized into a sham group, SCI group, SCI+EA group, SCI+EA+miR-106b-5p agomir group, and SCI+EA+miR-106b-5P NC group, and random numbers were generated using the RAND function in Microsoft Excel (Microsoft Corp., Albuquerque, NM, USA). In total, 130 rats were used in this study.

The SCI model was established based on a modified Allen’s method, and the rats were intraperitoneally (i.p.) injected with...
pentoobarbital (1%, 50 mg/kg) to create sufficient anesthesia, followed by a laminectomy at T10 to expose the spinal cord completely. Thereafter, the rats were fixed to the stereotaxic apparatus (Ruitiwo Life Science Co., Ltd, Shenzhen, China) with the back facing upward. A 10-g impact rod with a 3-mm diameter was dropped from a vertical height of 5 cm through a glass tube, directly impacting the dura mater and spinal cord, with the striking force on the latter measuring 50 gf.cm. The SCI model was successfully constructed, as indicated by the observable hyperemia on the spinal cord surface surrounding the lesion site, spasmotic tail flicks, transient twitches of the body and lower limbs, and sluggish movement or hindlimb paralysis.21

The rats in the sham group received a partial laminectomy of the T10 vertebrae and the dura was opened, but no contusion was performed. Subsequently, the rats in the SCI+EA+miR-106b-5p agomir and SCI+EA+miR-106b-5P NC groups received 5 μL of lentivirus vectors (about 4 × 10^10 TU LV-miR-106b-5p agomir or LV-miR-106b-5p-NC) at 2.5 mm caudal and rostral to the spinal cord lesion (2.5 μL at each point). After injection, the 10-μL microliter syringe (Gaoge, Shanghai, China) was left in for 5 minutes and then removed at a speed of 1 mm/min to avoid regurgitation of the injected material.34,25 All rats were injected with penicillin (80,000 U/d) i.p. after the operation and then once daily for 3 days. Manual bladder expression was performed twice daily in all SCI rats until the bladder was emptied. Finally, lentivirus was constructed by GeneChem Biomedical Co., Ltd. (Shanghai, China), and its titer was determined, where the original lentiviral vector titers for agomir contained 7 × 10^10 transduction units (TU)/mL and the NC ones 1 × 10^8 TU/mL. (Fig. 1B).

5. Evaluation of Locomotor Capacity

Functional recovery of the hindlimbs in rats was evaluated using the Basso-Beattie-Bresnahan (BBB) scale,26 the scores of which ranged from 0 (complete paralysis) to 21 points (normal locomotion). Briefly, the rats were dynamically evaluated using the scale at 1, 3, 5, and 7 days after surgery in an open field for locomotion. Briefly, the rats were dynamically evaluated using the scale at 1, 3, 5, and 7 days after surgery in an open field for locomotion. The rats were dynamically evaluated using the scale at 1, 3, 5, and 7 days after surgery in an open field for locomotion. The day after modeling, all rats in the SCI+EA, SCI+EA+miR-106b-5p agomir, and SCI+EA+miR-106b-5P NC groups underwent an EA stimulus procedure at the Jiaji and Zusani acupuncture points along the T9/T11 levels (EX-B2, bilaterally on the spinous process of the back, and ST36, bilaterally on the hindlimbs below the fibular head by 5 mm, respectively). Disposables, sterilized stainless-steel acupuncture needles sized 0.25 × 25 mm (Huatuo, Suzhou Medical Co., Ltd., Jiangsu, China) were inserted to a depth of 4–5 mm, until the tip made contact with the vertebral lamina. Then, the needles were connected to the Hua Tuo acupoint neurostimulator (Model SDZ-II EA, Suzhou Medical Co., Ltd.) using 3 pairs of electrodes. The stimulation parameters were set as sparse-dense waves of 2 Hz for 20 min/day at a 0.5-mA intensity once daily for 7 days.25 Meanwhile, the rats in the SCI and sham groups underwent prone positioning without EA treatment for 20 minutes (Fig. 1C).

7. Hematoxylin and Eosin and Nissl Staining

A 10-mm section of the injured spinal cord tissue, at the epicenter of the injury site, was carefully harvested on the seventh day after surgery. The sample was fixed in 4% paraformaldehyde for 24 hours and embedded in paraffin, and cross-sections (4-μm thick) were made on slides with a poly-L-lysine coating for the analysis of diseased tissue based on hematoxylin and eosin (H&E) and Nissl staining, after being deparaffinized and rehydrated. An optical microscope (BX53, Olympus, Tokyo, Japan) was used to capture images.

8. Transmission Electron Microscopy

The fresh spinal cord samples from T10 were harvested and prefixed in 2.5% glutaraldehyde at 4°C for overnight fixation. Then, the samples were sequentially washed, fixed, dehydrated, and soaked in a 1:1 epoxy resin mixture and pure acetone at 40°C for 6 hours. Hereafter, they were embedded in pure epoxy resin at 40°C for 4 hours and then embedded. Ultrathin sections (60 nm) were prepared and double-stained with uranyl acetate (2%) and lead citrate (1%). After rinsing 3 times with double-distilled water, the ultrastructural evaluation of the mitochondria was observed using TEM (HT7800; Hitachi, Tokyo, Japan).

9. RNA Extraction and Quantitative Real-Time Polymerase Chain Reaction

Total RNA in tissues or cells was extracted using a NucleoZol RNA reagent (Macherey-Nagel, Duren, Germany), and complementary DNA was synthesized according to the instructions of the RNA polymerase chain reaction (PCR) kit (code no. 638315 or code no. RR036A, Takara, Japan). A PCR reaction was achi-
We performed a dual-luciferase reporter assay, and based on the results, the 3’-UTR of Beclin-1 was confirmed to bind to miR-106b-5p (Fig. 3a). Next, to confirm this, we first utilized bioinformatics to analyze the nucleotide sequence of the 3’-UTR of Beclin-1 and the predicted target sites for miR-106b-5p. The results showed that miR-106b-5p could potentially bind to the 3’-UTR of Beclin-1 (Fig. 3a). Furthermore, using luciferase reporter assays, we found that transfection of luciferase reporter plasmids containing the 3’-UTR of Beclin-1 with miR-106b-5p could significantly inhibit luciferase activity compared to the control group (Fig. 3b).

**RESULTS**

### 1. MiR-106b-5p is Upregulated in SCI Patients’ Blood and Rat SCI Model Spinal Tissue

MiR-106b-5p levels were measured in the blood of SCI patients (n = 10) and healthy controls (n = 10), though the demographic and clinical data did not differ between the 2 groups (Table 1, Supplementary Table 2). A quantitative real-time PCR (qRT-PCR) analysis suggested that miR-106b-5p levels were upregulated in the blood of SCI patients compared to healthy controls (p < 0.01) (Fig. 2A), and the expression of miR-106b-5p in the spinal cords of rats at 1-, 3-, 7-, and 14-day post-surgery was significantly increased in the SCI group compared to the sham group (p < 0.05) (Fig. 2B).

### 2. Beclin-1 is a Direct Target of MiR-106b-5p

To study the relationship between miR-106b-5p and Beclin-1, we first utilized bioinformatics to analyze the nucleotide sequences, and the results showed that miR-106b-5p could potentially bind to the 3’-UTR of Beclin-1 (Fig. 3a). Next, to confirm this, we performed a dual-luciferase reporter assay, and based on the results, we found that transfection of luciferase reporter plasmids containing the 3’-UTR of Beclin-1 with miR-106b-5p could significantly inhibit luciferase activity compared to the control group (Fig. 3b).

### Table 1. Demographic and clinical data

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<th>Parameter</th>
<th>SCI patient</th>
<th>Healthy control</th>
<th>p-value</th>
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Values are presented as number or mean ± standard deviation. SCI, spinal cord injury.
Fig. 2. MiR-106b-5p was highly expressed in spinal cord injuries (SCIs). (A) The expression level of miR-106b-5p in the blood of SCI patients (n = 10) was significantly higher than that in healthy controls (n = 10). (B) The miR-106b-5p level in the spinal cord tissue of the SCI group at 1-, 3-, 7-, and 14-day postsurgery was higher than that in the sham group (n = 6/group). Data are expressed as the mean ± standard deviation, and differences between each group were compared by Student t-test. All experiments were repeated at least thrice. **p < 0.01.

Fig. 3. Beclin-1 was the target gene of miR-106b-5p. (a) Potential binding sites between Beclin-1 and miR-106b-5p. (b) Luciferase activity markedly increased in cells both cotransfected with miR-106b-5p mimics and Beclin-1-WT-NC and cotransfected with miR-106b-5p mimics and Beclin-1-MUT. (c) The relative expression of Beclin-1 mRNA was determined by qRT-PCR in SH-SY5Y cells following transfection with miR-106b-5p mimics/NC mimics and inhibitors. One-way analysis of variance and the LSD multiple comparisons test were used in panel B, and the Student t-test was used in panel C. All results are shown as the mean ± standard deviation (n = 3/group), and all experiments were repeated at least thrice. qRT-PCR, quantitative real-time polymerase chain reaction; NC, negatively control; WT, wild type; MUT, mutant. **p < 0.01.

binding sequences, Beclin-1-WT and Beclin-1-MUT were constructed. Compared with miR-106b-5p mimics and Beclin-1-WT, the luciferase activity markedly increased in cells cotransfected with miR-106b-5p mimics and Beclin-1-WT-NC (p < 0.01) or in cells cotransfected with miR-106b-5p mimics and Beclin-1-MUT (p < 0.01) (Fig. 3b). Meanwhile, the qRT-PCR results showed that the Beclin-1 expression was negatively regulated by miR-106b-5p (Fig. 3c), supporting the notion that miR-106b-5p directly targets Beclin-1.

3. MiR-106b-5p Affects SH-SY5Y Cell Autophagy and Apoptosis In Vitro

In vitro, miR-106b-5p mimics/NC mimics and miR-106b-5p inhibitors/NC inhibitors were transfected into SH-SY5Y cells, respectively, the efficiency of which was assessed by qRT-PCR, which detected the miR-106b-5p expression. As a result, the transfection of miR-106b-5p mimics dramatically increased the expression level of miR-106b-5p (p < 0.01), though it was significantly decreased after transfection with the miR-106b-5p inhibitors (p < 0.01) (Fig. 4a). Subsequently, Western blot (WB) assay findings revealed that the ratio of LC3-II to LC3-I and the expression of Beclin-1 were upregulated, while the expressions of P62, Bax, and Caspase-3 were downregulated in the miR-106b-5p inhibitor group compared with the NC inhibitor group; the opposite results were found in the miR-106b-5p mimic group compared to the NC mimic group (p < 0.05) (Fig. 4b–g).
Fig. 4. MiR-106b-5p regulated the expressions of autophagy and apoptosis proteins in vitro. (a) A qRT-PCR analysis determined the expression of miR-106b-5p in SH-SY5Y cells transfected with miR-106b-5p mimics/NC mimics and miR-106b-5p inhibitors/NC inhibitors. (b–g) Representative Western blot (WB) bands and the corresponding quantification data of P62, Beclin-1, Caspase-3, Bax and, LC3 in SH-SY5Y cells; GAPDH was used as an endogenous control. Continuous characteristics were compared using Student t-tests, and all the results are shown as the mean ± standard deviation (n = 3/group). Further, all experiments were repeated at least thrice. qRT-PCR, quantitative real-time polymerase chain reaction; NC, negative control. *p < 0.05. **p < 0.01, as compared with the NC inhibitor group. †p < 0.05. ††p < 0.01, as compared with the NC mimics group.

4. EA Attenuates Tissue Damage and Improves the Functional Status of Neuronal Cells and Motor Function in SCI Rats by Downregulating MiR-106b-5p

To explore further the function of miR-106b-5p in the neuroprotection of EA for SCIs, miR-106b-5p agomir or miR-106b-5p NC was administered immediately postsurgery. The expression level of miR-106b-5p in the injured spinal segment was significantly decreased after EA treatment in the SCI+EA group.
Fig. 5. Electroacupuncture (EA) alleviates spinal cord tissue damage and promotes motor function recovery after an spinal cord injury (SCI). (a) The expression of miR-106b-5p was confirmed by qRT-PCR in spinal tissue from different groups. (b) The BBB scores of rats in each group at various times, where a lower score indicates a more severe injury. (c) Representative HE-stained transverse sections (scale bars = 200 or 50 μm). (d) Observation of Nissl bodies in neurons of the spinal cord tissue of each group by Nissl staining (scale bars = 200 or 50 μm). Blue staining represents a Nissl body, where the darker the color of the Nissl bodies or the tabby shape, the better the neuronal state. qRT-PCR, quantitative real-time polymerase chain reaction; BBB, Basso-Beat-tie-Bresnahan locomotor scale; HE, hematoxylin and eosin. *p < 0.05, as compared with the SCI group. †p < 0.05. ns, p > 0.05, as compared with the SCI+EA group. §§ p < 0.01, as compared with the SCI+EA+miR-106b-5p NC group.
Fig. 5. Electroacupuncture (EA) alleviates spinal cord tissue damage and promotes motor function recovery after an spinal cord injury (SCI). (a) The expression of miR-106b-5p was confirmed by qRT-PCR in spinal tissue from different groups. (b) The BBB scores of rats in each group at various times, where a lower score indicates a more severe injury. (c) Representative HE-stained transverse sections (scale bars = 200 or 50 μm). (d) Observation of Nissl bodies in neurons of the spinal cord tissue of each group by Nissl staining (scale bars = 200 or 50 μm). Blue staining represents a Nissl body, where the darker the color of the Nissl bodies or the tabby shape, the better the neuronal state. qRT-PCR, quantitative real-time polymerase chain reaction; BBB, Basso-Batz-Bresnahan locomotor scale; HE, hematoxylin and eosin. *p < 0.05, as compared with the SCI group. †p < 0.05, as compared with the SCI+EA group. ‡‡p < 0.01, as compared with the SCI+EA+miR-106b-5p NC group. (Continued)

compared to the SCI group (p < 0.05). However, miR-106b-5p agomir could significantly reverse the above-mentioned change in the SCI+EA+miR-106b-5p agomir group (p < 0.05) (Fig. 5a).

The BBB scale was utilized to investigate motor recovery, scores of which were similar among all groups before the SCI (p > 0.05), while scores in other groups were significantly lower than those in the sham group 1-day post-surgery (all p < 0.01). No significant differences were observed between the SCI and SCI+EA groups on the third day postsurgery (p > 0.05), while the scores of the rats in the SCI+EA group were higher than those in the SCI group on the fifth (p < 0.01) and seventh (p < 0.01) days postsurgery. However, the effect of EA treatment was reversed by the overexpression of miR-106b-5p, and the BBB score in the SCI+EA+miR-106b-5p agomir group was remarkably lower than those in the SCI+EA and SCI+EA+miR-106b-5p NC groups from 5 to 7 day postsurgery (all p < 0.01) (Fig. 5b, Table 2).
EA Treatment for SCI

5. EA Facilitates Microstructure and Autophagosome Changes to Injured Spinal Cord Tissue

Ultrastructural changes to the spinal cord tissue were examined using TEM (×3,000 magnification). In the sham group, the structure of the nuclei and organelles was normal, and no autophagosomes and autolysosomes were observed (Fig. 6A). In the SCI group, the cells exhibited intracellular edema, and the number of lysosomes (yellow arrow) and autolysosome (green arrow) increased (Fig. 6B). Further, in the SCI+EA group, more autophagosomes (red arrow) and autolysosomes (green arrow) could be observed when compared with the SCI group (Fig. 6C), and in the SCI+EA+miR-106b-5p NC group, the number of autophagosomes (red arrow) was greater than that in the SCI group (Fig. 6D). Further, in the SCI+EA+miR-106b-5p agomir group, cells were swollen, and several lysosomes (yellow arrow) could be seen (Fig. 6E). These results illustrate how EA can enhance the autophagy flux, while the overexpression of miR-106b-5p can reverse the effects induced by EA.

6. EA Promotes Autophagy and Suppresses SCI-Induced Apoptosis by Downregulating Mir-106b-5p

The expressions of the autophagy-related proteins LC3, Beclin-1, and P62, as well as of the apoptotic-related proteins Bax and Caspase-3, in spinal cord tissues were detected by WB analysis. After normalization with the internal reference protein GAPDH or Tubulin, no significant difference was observed in the expression of Beclin-1 between the SCI and sham groups; meanwhile, the expressions of P62 (p < 0.01), Caspase-3 (p < 0.01), and Bax (p < 0.05) in the SCI group were significantly increased compared to those in the sham group. In addition, in comparison to the SCI group, EA decreased the expressions of P62 (p < 0.05), Caspase-3 (p < 0.01), and Bax (p < 0.05) and increased the ratio of LC3-II to LC3-I (p < 0.01) and the expression of Beclin-1 (p < 0.05). These results support the view that EA plays an important role in promoting autophagy and inhibiting apoptosis.

Table 2. BBB scores at various times pre- and postsurgery

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<td>SCI+EA+miR-106b-5p agomir</td>
<td>21.00 ± 0.00</td>
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Values are presented as mean ± standard deviation of 6 rats per group per time point, where lower BBB scores indicate poorer locomotor function. BBB, Basso-Beattie-Bresnahan locomotor scale; SCI, spinal cord injury; EA, electroacupuncture; NC, negative control. One-way analysis of variance followed by least significant difference or Dunnett T3 post hoc test (where equal variances were not assumed) was applied for multiple comparisons. *p < 0.01, as compared with sham group. **p < 0.01, as compared with SCI group. ***p < 0.01, as compared with SCI+EA+miR-106b-5p agomir group.
Fig. 6. Observation of microstructure and autophagosome changes in each group by transmission electron microscopy. (A) In the sham group, the nucleus was regular and intact, without autophagosomes and autolysosomes. (B) In the spinal cord injury (SCI) group, neurons showed swelling with vacuolization and karyopyknosis, and the number of lysosome and autolysosomes increased. (C) In the SCI+EA group, the morphology of the nuclei was nearly normal; the mitochondria exhibited swelling to a lesser extent; and the number of the autophagosomes and autolysosomes were increased. (D) In the SCI+EA+miR-106b-5p NC group, some autolysosomes and autophagosomes can be found. (E) In the SCI+EA+miR-106b-5p agomir group, cell swelling, a pyknotic nuclei, and several lysosomes were observed. Scale bars = 5 μm and 500 nm. The red asterisk identifies the nuclei; the yellow arrow indicates lysosomes; the green arrow points to autolysosomes; the red arrow identifies autophagosomes. EA, electroacupuncture.

after an SCI. However, the overexpression of miR-106b-5p can reverse the changes induced by EA treatment (p < 0.05). No significant difference was found between the SCI+EA and the SCI+EA+miR-106b-5p NC groups (p > 0.05) (Fig. 7), and the above expression patterns of Beclin-1, P62, Bax, and Caspase-3 were confirmed by qRT-PCR (Fig. 8) and immunohistochemical
Fig. 7. Upregulating the miR-106b-5p expression reversed the effect of electroacupuncture (EA) in rats after a spinal cord injury (SCI) evaluated by Western blot assay. (a–f) Western blot assay and quantitative analysis of integrated optical densities for autophagy-related (P62 [b], Beclin-1 [c], LC3B [f]) and apoptosis-related (Bax [e] and Caspase-3 [d]) proteins; GAPDH or Tubulin was used as an endogenous control. One-way analysis of variance followed by least significant difference or Dunnett T3 post hoc test was used. All the results are shown as the mean ± standard deviation (n = 3/group). All experiments were repeated at least thrice. *p < 0.05. **p < 0.01. ***p > 0.05, as compared with the SCI group. †p < 0.05. ††p < 0.01. ‡‡p > 0.05, as compared with the SCI+EA group. §§‡p < 0.01, as compared with the SCI+EA+miR-106b-5p NC group.

Fig. 8. Upregulating the miR-106b-5p expression reversed the effect of electroacupuncture (EA) in rats after a spinal cord injury (SCI) was evaluated by qRT-PCR. The mRNA levels of P62 (a), Beclin-1 (b), Caspase-3 (c), and Bax (d) were determined by qRT-PCR; GAPDH was selected as the internal reference. One-way analysis of variance followed by least significant difference or Dunnett T3 post hoc test was used. All the results are shown as the mean ± standard deviation (n = 3/group). All experiments were repeated at least thrice. qRT-PCR, quantitative real-time polymerase chain reaction. *p < 0.05. **p < 0.01, as compared with the SCI group. †p < 0.05. ††p < 0.01. ‡‡p > 0.05, as compared with the SCI+EA group. §§‡p < 0.01, as compared with the SCI+EA+miR-106b-5p NC group.

staining (Fig. 9).

DISCUSSION

This is a novel study investigating the role of autophagy and apoptosis in the protection offered by EA treatment of SCIs. In this experiment, we first found that the expression of miR-106b-5p was markedly increased after an SCI, and we subsequently determined that EA can regulate autophagy and apoptosis by suppressing the expression of miR-106b-5p. These data might contribute to a better understanding of the mechanism involved in EA treatment at the molecular level following an SCI and pro-
**Fig. 9.** Effects of EA in injured rat spinal cords evaluated by immunohistochemical staining. (a) Immunohistochemical staining assay for Beclin-1, P62, Caspase-3, and Bax proteins (scale bars = 20 μM). (b) Quantitative analysis of the mean optical density for these proteins. One-way analysis of variance followed by least significant difference or Dunnett T3 post hoc test was used. All the results are shown as the mean ± standard deviation (n = 3/group). All experiments were repeated at least 3 thrice. SCI, spinal cord injury; EA, electroacupuncture. **p < 0.01, as compared with the SCI group. ††p < 0.01, as compared with the SCI+EA group. §§p < 0.01, as compared with the SCI+EA+miR-106b-5p NC group.
provide a new therapeutic strategy for SCI treatment.

EA is a modified method based on traditional acupuncture combined with modern electrotherapy, and it has been examined as an important alternative and adjunctive treatment option for SCIs in recent years. EA has been reported to have a variety of beneficial effects by stimulating special acupoints and conducting them from the meridians and channels to the target site. The mechanisms of EA to create a better microenvironment for neuroprotection after an SCI may lead to reduced inflammatory responses and lipid peroxidation; apoptosis inhibition; regulated oxidative stress; enhanced autophagy; the promotion of neural stem cell proliferation, neuronal survival, and axonal regeneration; the activation of the propriospinal neuronal network; and more. The selection of acupoints is a critical factor that can determine the efficacy of acupuncture. Previous studies have documented that the Jiaji (EX-B2) acupoint has a synergistic effect on reducing neuronal damage post-SCI by regulating autophagy and apoptosis. In addition, there is mounting evidence that EA at the Zusanli (ST36) acupoint promotes recovery from SCIs via the protection of nerve cells and the prevention of apoptosis in SCI rats. Consistent with these results, our data also demonstrate that EA treatment at the Jiaji (EX-B2) and Zusanli (ST36) acupoints can increase BBB scores, improve the survival of motor neurons, and alleviate pathological tissue damage. Together, these results further verify that EA is an effective therapeutic means to restore motor function after an SCI.

As important regulators of normal nervous functions, miRNAs are closely related to morphological and functional changes in the nervous system. Following a SCI, the homeostasis of many miRNAs is disturbed, and the aberrantly dysregulated miRNAs can either alleviate or aggravate conditions after an SCI, as dictated by their downstream target genes. For example, miR-21 has been found to play an important role in limiting secondary neuronal apoptosis following an SCI, while Zhou et al. demonstrated that miR-27a can facilitate SCI recovery by regulating the autophagy flux for neuroprotection. Moreover, EA treatment of SCIs in rats induces changes to miRNA expression profiles, and it has been demonstrated in previous studies. MiR-106b-5p, a member of the 106b-25 cluster and a parologue of the 17–92 cluster, has been well-studied in many diseases, including breast cancer and acute renal injury. Recently, miR-106b-5p was found to be abnormally expressed in the spinal cords of mice models of neuropathic pain. The level of which in these diseases is markedly increased, while the knockdown miR-106b-5p expression can regulate apoptosis and autophagy, as well as inhibit cell proliferation and induce cell cycle arrest. However, relatively little is known regarding the regulatory role of miR-106b-5p in neurological functional recovery after SCI. In the current study, we validated a significantly increased miR-106b-5p expression in the blood of SCI patients and the spinal cord tissue of SCI rats, where apoptosis was inhibited, and autophagy was enhanced after downregulating miR-106b-5p through EA treatment, indicating that EA treatment has a regulative effect by inhibiting miR-106b-5p expression.

Appropriate autophagy activation has been proposed as an approach to nerve regeneration by reducing secondary injury. Autophagy is a dynamic, multi-step process with several regulatory steps, including autophagy induction, vesicle nucleation, expansion, and autophagosome maturation and degradation. Beclin-1 is recognized as a regulator of autophagy and a key player in isolation membrane (also called a phagophore) formation, which signals the initiation of the autophagic process. In this study, we demonstrated that miR-106b-5p can directly target the Beclin-1 gene using the dual-luciferase reporter assay. Further, LC3 plays a crucial role in promoting the expansion and maturation of autophagosomes, where, during autophagy activation, LC3-I in the cytoplasm is converted into LC3-II and recruited to the autophagosome membrane. Thus, a higher LC3-II to LC3-I ratio indicates an increased autophagy flow. Further, LC3-II can interact with P62, an autophagy cargo protein, the accumulation of which signals autophagy suppression. Previously, the inhibition of the autophagy flux was reported to contribute to neuronal cell damage in SCIs and to be associated with worse functional outcomes, but in the present study, we found that EA treatment significantly increased the Beclin-1 expression and LC3-II to LC3-I ratio and decreased the P62 level in SCI rats, demonstrating increased functional autophagic flux under EA conditions. Moreover, autophagosome and autolysosome accumulation were observed by TEM following EA treatment, indicating that autophagic flux in the SCI+EA group was significantly enhanced.

Previous studies have found that the death of spinal cord neurons after an SCI occurs primarily via apoptosis, which is fundamental to the pathological mechanism of secondary injury, leading to permanent or long-term functional deficits following an SCI. However, activating a suitable degree of autophagy to allow lysosomes to degrade damaged mitochondria can protect spinal cord neurons against SCI-induced apoptosis and promote neuronal survival. Furthermore, autophagy can limit neuronal death by selectively reducing the abundance of proapoptotic proteins in the cytosol. Moreover, it has been revealed that...
EA can contribute to functional recovery by attenuating SCI-induced Bax and Caspase-3 upregulation in injured spinal cords. In this study, our data show that an EA-enhanced autophagy flux was accompanied by inhibition in apoptosis, manifested as a gradual decrease in Bax and Caspase-3 levels. In addition, many studies have proven that EA can also create a better microenvironment to inhibit apoptosis by increasing microcirculation and blood flow, triggering the synthesis and secretion of neurotrophic factors, reducing the levels of pro-inflammatory cytokines, and so on.

To illustrate the underlying role of miR-106b-5p in EA treatment better, we next sought to treat rats using EA combined with injections of miR-106b-5p agomir. As expected, the over-expression of miR-106b-5p could reverse the effects of EA on autophagy and apoptosis. Thus, the regulation of autophagy and apoptosis induced by EA plays a vital role in promoting neuronal survival, accelerating nerve regeneration, and improving motor function after an SCI. Many studies have utilized cortical motor-evoked potentials, somatosensory evoked potentials, or neural tracing techniques to demonstrate EA’s ability to promote neural circuitry reconstruction and functional recovery. In this study, we also observed via TEM and H&E staining that the inner environment in the injury segment and the ultrastructure of neurons were significantly improved after EA treatment. The results of Nissl staining further demonstrate that neuronal function and survival were significantly increased post-EA treatment. However, these protective effects of EA could be reversed by the overexpression of miR-106b-5p.

This study has some limitations. First, we did not perform a microarray analysis of spinal cord samples from SCI rats before and after EA treatment. Second, we did not use autophagy inhibitors to explore the effects of EA. Third, whether miR-106-5p inhibitors affect motor function after an SCI remains unclear, and fourth, SH-SY5Y cells were chosen to mimic the SCI model in vitro, as they were identified as commonly used in human in vitro SCI research. Meanwhile, it is true that there exist differences between the SH-SY5Y cell line and the spinal cord, but it will be much more convincing if primary spinal cord neuronal cells or other neuronal cell lines were chosen to confirm our conclusion further. As such, future studies should identify the precise molecular and cellular mechanisms underlying the negative correlation between EA and motor dysfunction in SCIs.

CONCLUSION

In summary, EA can decrease the miR-106b-5p expression to reverse remarkably the unfavorable microenvironment of the SCI segment by regulating autophagy and apoptosis, which is crucial for nerve regeneration and functional recovery. Thus, EA may have great potential applications in SCIs, and miR-106b-5p could be a potential therapeutic intervention following an SCI.

NOTES

Supplementary Materials: Supplementary Tables 1-2 can be found via https://doi.org/10.14245/ns.2346446.223.

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: SG, JC; Formal Analysis: SG; Investigation: YY; Methodology: XL, JC; Project Administration: YT, YG; Writing – Original Draft: JC; Writing – Review & Editing: JX.

ORCID

Shuhui Guo: 0000-0002-7643-437X
Jianmin Chen: 0000-0002-0528-5354
Ye Yang: 0000-0002-3831-2320
Xiaolu Li: 0009-0009-4673-2016
Yun Tang: 0000-0002-8217-5132
Yuchang Gui: 0000-0002-5966-2573
Jianquan Chen: 0009-0000-7581-5552
Jianwen Xu: 0000-0002-8095-591X

REFERENCES


### Supplementary Table 1. Primer sequence for quantitative real-time polymerase chain reaction

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### Supplementary Table 2. Demographic details of the participants

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SCI, spinal cord injury; ASIA, American Spinal Injury Association; Injury level: C, cervical; T, thoracic; L, lumbar.
Three-Dimensional Quantitative Assessment of Pedicle Screw Accuracy in Clinical Utilization of a New Robotic System in Spine Surgery: A Multicenter Study

Byeong-Jin Ha, Jong-Min Lee, Seon-Jin Yoon, Byung-Kwan Kim, Junseok Lee, Suhun Lee, Seungjae Ryu, Yongyeob Cha, Sungteac Hwang, Donggi Woo, Chang Kyu Lee, Dong Ah Shin, Yoon Ha, Sung Uk Kuh, Keung Nyun Kim, Dongwuk Son, Seong Yi

Objective: The objective of this study was to evaluate the accuracy of pedicle screw placement in patients undergoing percutaneous pedicle screw fixation with robotic guidance, using a newly developed 3-dimensional quantitative measurement system. The study also aimed to assess the clinical feasibility of the robotic system in the field of spinal surgery.

Methods: A total of 113 patients underwent pedicle screw insertion using the CUVIS-spine pedicle screw guide system (CUREXO Inc.). Intraoperative O-arm images were obtained, and screw insertion pathways were planned accordingly. Image registration was performed using paired-point registration and iterative closest point methods. The accuracy of the robotic-guided pedicle screw insertion was assessed using 3-dimensional offset calculation and the Gertzbein-Robbins system (GRS).

Results: A total of 448 screws were inserted in the 113 patients. The image registration success rate was 95.16%. The average error of entry offset was 2.86 mm, target offset was 2.48 mm, depth offset was 1.99 mm, and angular offset was 3.07°. According to the GRS grading system, 88.39% of the screws were classified as grade A, 9.60% as grade B, 1.56% as grade C, 0.22% as grade D, and 0.22% as grade E. Clinically acceptable screws (GRS grade A or B) accounted for 97.54% of the total, with no reported neurologic complications.

Conclusion: Our study demonstrated that pedicle screw insertion using the novel robot-assisted navigation method is both accurate and safe. Further prospective studies are necessary to explore the potential benefits of this robot-assisted technique in comparison to conventional approaches.

Keywords: Robot-assisted spine surgery, Pedicle screws, Dimensional measurement accuracy

INTRODUCTION

In the field of spine surgery, the precise placement of pedicle screws is crucial. While percutaneous pedicle screw systems have gained popularity in minimally invasive surgery, they can pose risks of radiation exposure to both patients and operating room staff. It has been reported that fluoroscopically guided pedicle screw insertion in minimally invasive surgery leads to a 2-fold...
higher dose of radiation compared to pedicle screw insertion in open surgery.\(^1\) Robotic-assisted surgical systems have been developed to simplify pedicle screw insertion, streamline surgical workflows, reduce operative times, minimize surgical complications, improve clinical outcomes, lower radiation exposure, and potentially decrease costs by reducing hospital stays.\(^2-6\)

Inserting thoracolumbar pedicle screws is technically demanding, and inaccurate screw placement can lead to serious complications such as neurological, vascular, or visceral injuries.\(^7\) The rate of screw misplacement ranges from 4.9\% to 13.3\%, and can increase up to 15.7\% when evaluated with computed tomography (CT) scans.\(^8\) As a result, navigation and robotic-assisted surgery have been developed to enhance accuracy and reduce complications.\(^5,8,12\) Various robotic systems for spine surgery have been developed and tested including SpineAssist, Renaissance, Mazor X (Mazor Robotics Inc., Caesarea, Israel), Mazor X Stealth Edition (Medtronic, Minneapolis, MN, USA), ExcelsiusGPS (Globus Medical, Inc., Audubon, PA, USA), ROSA Spine (Medtech, Montpellier, France), Tianji (Beijing Tinavi Medical Technology Co., Beijing, China), and Cirq (Brainlab, Munich, Germany).\(^9-16\) Previous studies comparing navigated robot-assisted technology with the freehand technique have demonstrated improved accuracy in screw placement and reduced radiation exposure.\(^9,10,17,18\) However, when measuring the accuracy of robotic-guided pedicle screw placement using 3-dimensional (3D) quantitative methodology, there is still a risk of error.\(^4\)

In our previous studies, we assessed the accuracy of pedicle screw placement using a novel navigation-based spine surgery robotic system in porcine and cadaver models. We confirmed the system’s safety and accuracy in executing planned trajectories and screw path.\(^19-20\) Building on the successful results from animal experiments and cadaver studies, we implemented the robot-assisted spine surgery system in clinical practice. Recognizing the higher accuracy and safety requirements in human surgeries compared to animal experiments, we conducted comprehensive verification of the spine surgery robotic system before using it on patients who required precise pedicle screw insertion.

To the best of our knowledge, there have been limited multicenter studies investigating the 3D quantitative accuracy assessment of spine robots. The objective of our multicenter retrospective study was to evaluate the accuracy and safety of robot-assisted spinal surgery in patients, utilizing a unique methodology for calculating 3D offsets.

MATERIALS AND METHODS

1. Patient Population

The study enrolled a total of 116 consecutive patients who underwent robot-guided pedicle screw fixation between September 2020 and June 2022. The study was conducted at multiple centers and received approval from the Institutional Review Boards (IRBs) of Yonsei University Severance Hospital (IRB No. 1-2020-0025) and Pusan National University Yangsan Hospital (IRB No. 05-2023-118). The study adhered to the principles outlined in the Declaration of Helsinki. Informed consent was waived as the study was retrospective, and patient records were anonymized for analysis.

The inclusion criteria for the study were patients aged 19 and older with a diagnosis of thoracolumbar degenerative stenosis, degenerative or spondyloytic spondylolisthesis, or degenerative scoliosis. Patients with prior thoracolumbar surgery or radiotherapy, metastatic spinal tumors, infectious spondylitis, traumatic vertebral fractures, or inability to undergo robot-guided screw insertion were excluded. Two different surgical techniques, posterior lumbar interbody fusion (PLIF) and oblique lateral interbody fusion (OLIF), were used for interbody fusion. The procedures were performed by 3 experienced spinal neurosurgeons. Intraoperative imaging was performed using either O-arm system (Medtronic, Dublin, Ireland) for 3D CT scans or the C-arm system (OEC 9900 Elite, GE Healthcare, Chicago, IL, USA) for 2-dimensional (2D) digital spot fluoroscopy.

Demographic information such as age, sex, body mass index (BMI), bone mineral density (BMD) and preoperative diagnosis were collected from the patients. Perioperative data including operative time, duration of robot procedure, time per robot screw, intraoperative estimated blood loss, dose of intraoperative radiation exposure, and length of hospital stay were also collected. The duration of the robot procedure was defined as the time from skin incision to the placement of pedicle screws. The dose of intraoperative radiation exposure was measured using the dose length product, which is the product of the volume CT dose index (CTDIvol) and the scan length. Overall, the data collected included patient demographics, surgical details, and perioperative parameters to assess the effectiveness and safety of the procedure.

2. Surgical Robotic System

CUVIS-spine (CUREXO Inc., Seoul, Korea) is a surgical robotic system that utilizes image-guided navigation to provide precise spatial positioning and orientation of anatomical struc-
tures for surgeons during pedicle screw insertion surgeries. The main components of CUVIS-spine include a robotic arm, an optical tracking system (Polaris Vega, NDI, Waterloo, ON, Canada) and a real-time surgical planning system (Fig. 1). During the surgery, a patient marker is attached to the surgical site and scanned along with the surgical tools, enabling image-robot registration. The system registers the intraoperative images, either 2D or 3D, with the robotic system using information from the optical markers in the operative field. Surgeons can then plan the pedicle screw insertion path for each target on the intraoperatively scanned images directly through a touch screen monitor. The navigated surgical instruments are guided by the

![CUVIS-spine diagram](image)

**Fig. 1.** CUVIS-spine (CUREXO Inc., Seoul, Korea); robotic arm (A) and main console (B). OTS, optical tracking system; NDI, Northern Digital Incorporated; SUI, surgical use interface.

![Robot surgical procedure](image)

**Fig. 2.** Robot surgical procedure: skin incision (A), muscle dilation (B), drilling the entry point (C), tapping (D), screw insertion guided robot arm (E) (photos of cadaver lab).
robotic manipulator to the planned target position and visualized on the intraoperative images with the planning information (Fig. 2, Supplementary Fig. 1). The system also provides real-time feedback on the lateral repulsive force generated when the surgical tool encounters the bone surface, displaying its direction and level on the screen to aid in more accurate targeting. Additionally, the movement of the patient marker is continuously monitored in real-time to correct the target position and posture as needed.

3. Accuracy Assessment

After the placement of pedicle screws using CUVIS-spine, postoperative CT images were obtained to evaluate the accuracy of screw placement. The images were segmented to isolate the instrumented vertebrae in both pre- and postoperative images. Paired-point registration was then performed using anatomical markers on the vertebral surfaces to align the 2 sets of images. This alignment was achieved using an iterative closest point registration algorithm to minimize the differences between the 2 sets of points and reconstruct 2D or 3D surfaces (Supplementary Fig. 2). The resulting image registration errors were calculated as the difference between the original planned path of the screws based on intraoperative O-arm scans and the transformed path of the screws on the postoperative CT images (Fig. 3). Successful registration was defined as an error of less than 2 mm.

To compare the planned screw trajectories with the actual inserted screw positions, image overlay analysis was performed. Additionally, quantitative 3D measurements of screw offsets, including the anterior-most portion of the screw (target), the posterior-most portion of the screw (entry), depth, and angulation of the screw were obtained from CT scans. Depth offset was calculated as the distance between the planned target position and the transposed target on the planned screw path. Angular offset was calculated as the difference in angle between the vector of the planned screw and the placed screw. The 3D distances and angles between the placed screw position and the intended trajectory were measured (Fig. 4).

To evaluate the accuracy of each screw, the Gertzbein-Robbins system (GRS) was used based on postoperative CT scans.
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According to the GRS classification, screw position was categorized as follows: within the pedicle (group A), cortical breach of less than 2 mm (group B), cortical breach of 2 mm or more but less than 4 mm (group C), cortical breach of 4 mm or more but less than 6 mm (group D), and cortical breach of 6 mm or more (group E). Slight deviations with breaches of less than 2 mm were considered clinically acceptable. All measurements were independently performed by 2 blinded neurosurgeons, and any disagreements were resolved through further image review to reach a consensus.

4. Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA). Descriptive statistics were used to provide a summary of the demographic and clinical characteristics of the patients in this study. Continuous variables were expressed as means accompanied by their corresponding standard deviations, while categorical variables were presented as frequencies and percentages. The patients were categorized into 2 groups based on the screw insertion technique and interbody fusion method. To compare the GRS grade distribution between the groups, a Fisher exact test was performed. To assess the statistical significance of the mean offset differences between the groups, an independent t-test was performed. A p-value threshold of less than 0.05 was considered statistically significant. The learning curve of robot-guided pedicle screw placement was evaluated using logarithmic curve fitting regression analysis from 2 perspectives: operation time and offset. The fitting equation $y = a\ln(x) + b$ [where $x$ is the number of cases, and $y$ represents the time per screw or offset] reflected the trend of robot procedure time and offset changing with the number of operation cases.

RESULTS

The results showed that a total of 116 patients underwent robot-assisted spine surgery from 2020 to 2022. Among these cases, 3 were aborted due to technical difficulties, and 113 patients were ultimately enrolled in the study. The average age of the patients was 68.0 ± 7.9 years, with 79 (69.9%) being female. The mean BMI was 24.7 ± 3.4 kg/m² and the mean BMD was -0.9 ± 1.5. The mean intraoperative estimated blood loss was 392.6 mL and the average length of hospital stay was 9.3 days. Out of the enrolled patients, 5 underwent PLIF with open screw placement under robot assistance, 56 underwent PLIF with percutaneous screw placement, and 52 underwent OLIF with percutaneous screw placement. Among the PLIF cases, 6 patients underwent intraoperative C-arm scan for image registration with the robot system.

A total of 448 screws were placed in the 113 enrolled patients, with an average of 4.2 screws were inserted in 2.2 vertebrae per case. The mean duration of the robot-assisted procedure was 68.9 minutes, and the mean time per screw was 5.9 minutes. Demographic data including surgical parameters are provided in Table 1. The postoperative CT images were used to assess all inserted pedicle screws. As shown in Table 2, 448 screws in 113 patients were distributed from T11 to S1, with L4 and L5 accounting for 79.9% of the total. The image registration success rate was 95.16%. Table 3 presents the descriptive statistics of mean offset values and GRS classification based on the screw insertion technique in the cohort of patients who underwent robot-assisted spinal surgery. A total of 29 screws were inserted using an open approach in the setting of robot assistance and categorized into the open group. The remaining 419 screws were classified as the percutaneous group. The overall mean offsets were as follows: entry offset 2.86 ± 1.64 mm, target offset 2.48 ± 1.74 mm, depth offset 1.99 ± 2.13 mm, and angular offset 3.07 ± 2.31 mm. While the open group exhibited slightly higher mean offsets (entry, target, depth) compared to the percutaneous group, the percutaneous group showed a slightly higher mean angular offset. However, the difference between the groups did not reach
According to the GRS grading system, 396 screws (88.39%) were classified as grade A, 43 screws (9.60%) as grade B, 7 screws (1.56%) as grade C, 1 screw (0.22%) as grade D, and 1 screw (0.22%) was grade E. Clinically acceptable screws (GRS grade A or B) accounted for 97.99%. There was a statistically significant difference between the open and the percutaneous groups in terms of GRS grades.

In Table 4, the descriptive statistics and p-values for the type of interbody fusion are presented. The mean entry offset was 2.66 ± 1.36 mm for PLIF and 3.08 ± 1.89 mm for OLIF, with a statistically significant difference (p = 0.009). There were no statistically significant differences observed in the mean target offset (p = 0.362) and depth offset (p = 0.191) between the 2 groups. However, the mean angular offset differed significantly, with PLIF having a mean of 2.33 ± 1.57 mm and OLIF having a mean of 3.87 ± 2.69 mm (p < 0.001). Additionally, the GRS grade distribution showed a statistically significant difference between the

Table 2. Segmental distribution and 3-dimensional assessment of screw accuracies using offset measurements

<table>
<thead>
<tr>
<th>Level</th>
<th>Overall (n = 448)</th>
<th>Entry offset (mm)</th>
<th>Target offset (mm)</th>
<th>Depth offset (mm)</th>
<th>Angular offset (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T11</td>
<td>5 (1.1)</td>
<td>1.11 ± 0.72</td>
<td>1.58 ± 0.97</td>
<td>1.43 ± 1.84</td>
<td>2.35 ± 1.53</td>
</tr>
<tr>
<td>T12</td>
<td>5 (1.1)</td>
<td>2.70 ± 1.29</td>
<td>3.54 ± 1.82</td>
<td>2.35 ± 3.10</td>
<td>2.68 ± 2.81</td>
</tr>
<tr>
<td>L1</td>
<td>4 (0.9)</td>
<td>5.16 ± 3.34</td>
<td>8.24 ± 6.56</td>
<td>3.47 ± 1.47</td>
<td>6.72 ± 6.74</td>
</tr>
<tr>
<td>L2</td>
<td>13 (2.9)</td>
<td>1.65 ± 0.72</td>
<td>1.57 ± 0.82</td>
<td>0.84 ± 1.09</td>
<td>2.15 ± 1.53</td>
</tr>
<tr>
<td>L3</td>
<td>58 (12.9)</td>
<td>3.07 ± 2.18</td>
<td>2.19 ± 1.30</td>
<td>1.77 ± 2.05</td>
<td>3.64 ± 3.43</td>
</tr>
<tr>
<td>L4</td>
<td>191 (42.6)</td>
<td>2.97 ± 1.63</td>
<td>2.53 ± 1.67</td>
<td>1.89 ± 1.93</td>
<td>3.13 ± 2.06</td>
</tr>
<tr>
<td>L5</td>
<td>167 (37.3)</td>
<td>2.76 ± 1.37</td>
<td>2.44 ± 1.57</td>
<td>2.17 ± 2.26</td>
<td>2.87 ± 1.89</td>
</tr>
<tr>
<td>S1</td>
<td>5 (1.1)</td>
<td>2.76 ± 1.50</td>
<td>3.12 ± 0.89</td>
<td>4.64 ± 4.63</td>
<td>1.26 ± 1.16</td>
</tr>
<tr>
<td>Total</td>
<td>448 (100)</td>
<td>2.86 ± 1.64</td>
<td>2.48 ± 1.74</td>
<td>1.99 ± 2.13</td>
<td>3.07 ± 2.31</td>
</tr>
</tbody>
</table>

Table 3. Descriptive statistics of mean offset values and GRS classification according to the screw insertion technique in patients who underwent robot-assisted spinal surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 448)</th>
<th>Open (n = 29)</th>
<th>Percutaneous (n = 419)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry offset (mm)</td>
<td>2.86 ± 1.64</td>
<td>2.99 ± 1.92</td>
<td>2.85 ± 1.62</td>
<td>0.714</td>
</tr>
<tr>
<td>Target offset (mm)</td>
<td>2.48 ± 1.74</td>
<td>2.94 ± 1.92</td>
<td>2.45 ± 1.72</td>
<td>0.144</td>
</tr>
<tr>
<td>Depth offset (mm)</td>
<td>1.99 ± 2.13</td>
<td>2.83 ± 2.52</td>
<td>1.93 ± 2.10</td>
<td>0.072</td>
</tr>
<tr>
<td>Angular offset (mm)</td>
<td>3.07 ± 2.31</td>
<td>2.34 ± 1.91</td>
<td>3.12 ± 2.33</td>
<td>0.081</td>
</tr>
</tbody>
</table>

GRS, Gertzbein-Robbins system.
Table 4. Descriptive statistics of mean offset values and GRS classification according to the type of interbody fusion in patients who underwent robot-assisted spinal surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>PLIF (n = 234)</th>
<th>OLIF (n = 214)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry offset (mm)</td>
<td>2.66 ± 1.36</td>
<td>3.08 ± 1.89</td>
<td>0.009</td>
</tr>
<tr>
<td>Target offset (mm)</td>
<td>2.41 ± 1.39</td>
<td>2.56 ± 2.05</td>
<td>0.362</td>
</tr>
<tr>
<td>Depth offset (mm)</td>
<td>1.86 ± 2.15</td>
<td>2.13 ± 2.11</td>
<td>0.191</td>
</tr>
<tr>
<td>Angular offset (mm)</td>
<td>2.33 ± 1.57</td>
<td>3.87 ± 2.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GRS grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade A</td>
<td>217 (92.7)</td>
<td>179 (83.6)</td>
<td></td>
</tr>
<tr>
<td>Grade B</td>
<td>14 (6.0)</td>
<td>29 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Grade C</td>
<td>2 (0.9)</td>
<td>5 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Grade D</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Grade E</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). PLIF, posterior lumbar interbody fusion; OLIF, oblique lateral interbody fusion; GRS, Gertzbein-Robbins system.

Fig. 5. A scatter plot for entry, target, depth, and angular offset. The learning curves of robot-guided screw placement for each offset.

Fig. 6. A learning curve for robot-guided screw placement. Patients were charted chronologically and compared by the mean time per screw.

PLIF and OLIF groups (p = 0.023).

Most of the clinically unacceptable screws (GRS grade C, D or E) showed lateral cortical breach (8/9 screws, 88.89%). One screw classified as GRS grade E which was misplaced laterally at right L4 pedicle is shown in (Supplementary Fig. 3). No patients experienced iatrogenic neurovascular damage or postoperative infection, and there were no cases of symptomatically misplaced screws requiring revision. The 3D offsets gradually decreased with an increasing number of operation cases (Fig. 5). The time per screw also showed a tendency to decrease with an increasing number of cases (y = -1.594 ln(x) + 11.001, R² = 0.308) (Fig. 6).
DISCUSSION

According to the previous studies, the conventional techniques used in pedicle screw placement cause screw misplacement, with rates ranging from 3% to 55%. As precise pedicle screw insertion is one of the most important factors in spine surgery, navigation systems and robotic assistance techniques have gained popularity to improve accuracy. Since the bone-mounted miniature SpineAssist (Mazor Robotics Ltd.) became the first U.S. Food and Drug Administration-approved robotic system for spine surgery in 2004, various robots have been developed and clinical trials using CT-based navigation systems have been conducted. However, according to a prospective randomized comparison to conventional freehand screw insertion, the accuracy assessment by Gertzbin-Robbins classification indicates that the conventional freehand technique (A+B, 93%) is superior to the robotic-guided technique (A+B, 85%). A prospective randomized controlled trials (RCTs) performed by Kim et al. reported that there was no significant difference between robot-assisted techniques and conventional freehand techniques in terms of accuracy of the screw placement. Meanwhile, Fan et al. performed a meta-analysis based on 5 RCTs and several cohort studies and found that the robot-assisted technique showed significantly higher accuracy of pedicle screw placement than the freehand technique. Therefore, controversies regarding the accuracy and safety of robot-assisted pedicle screw placement remain. In our study, using the CUVIS-spine robot with a navigation system, we observed breached pedicles in 11.61% of screws in 113 consecutive patients, with the majority of breaches being less than 2 mm. Clinically acceptable screws, categorized as GRS grade A or B, accounted for 97.99% of our results, which is comparable or superior to previous studies using other robotic systems.

It is important to investigate quantitative accuracy data to improve surgical precision and minimize screw malposition in spine surgery. However, most of the previous studies demonstrated only GRS grade as the assessment of screw accuracy based on postoperative CT scans, and few studies have assessed quantitative measurements comparing preoperatively planned screw paths with the actual inserted screw paths. Godzik et al. reported mean 3D accuracy of 5.0 ± 2.4 mm, mean 2D accuracy of 2.6 ± 1.1 mm, and mean angular offset of 5.6° ± 4.3° among 17 patients (70 screws). In comparison, our study found lower errors in intraoperative 3D image-based planning, with mean entry offset of 2.86 ± 1.64 mm, target offset of 1.99 ± 2.13 mm, depth offset of 1.86 ± 2.15 mm, and angular offset of 3.07 ± 2.31 mm.

Furthermore, we performed a comparative analysis to evaluate the difference in accuracy between the open and percutaneous approaches for screw insertion. In the initial stages of clinical application of this new robotic system, there was a lack of confidence in its accuracy. Therefore, we performed the initial 5 cases using an open approach with a layer-by-layer verification to ensure precision. However, we discovered that this approach actually introduced additional sources of error rather than improving accuracy. The pushing effect exerted by the surrounding musculature caused greater errors than anticipated errors which could arise from bone surface skiving. Consequently, we shifted to using the percutaneous approach exclusively, which yielded more accurate results with reduced errors. The reason behind this improvement can be attributed to the percutaneous approach’s ability to evenly distribute resistance from the surrounding structures along the screw path, thereby minimizing errors. Based on our findings, we advocate for the principle of using percutaneous approach for the robot-assisted screw insertion in thoracolumbar area. In cases where an open approach is necessary, we emphasize the importance of maximizing muscle exposure to minimize resistance caused by the screw-inserting instrument. Additionally, when using muscle retractors during open procedures, minimizing retractor movement after registration is crucial to avoid introducing errors.

We also conducted a comparative analysis to identify the difference in offset and GRS between the PLIF and OLIF groups. However, we would like to clarify that these 2 different interbody fusion methods were conducted exclusively at different institutions. Additionally, although there may be differences in interbody cage insertion methods, it is important to note that both groups underwent pedicle screw insertion using the same prone position with robot-assisted technique. According to our results, there were statistically significant differences between the PLIF and OLIF groups in entry offset, angular offset, and GRS. But it should be noted that these differences may be attributed to variations in the surgical institutions and surgeons involved, rather than solely the interbody fusion method. Therefore, careful interpretation of these results is warranted.

The robotic system we used in our study has several unique features that contributed to our relatively better results in terms of offsets. One notable feature is the real-time force navigation and patient displacement information provided by the system. The force navigation capability allows the system to detect the orientation and degree of lateral force from the surrounding tissue exerted on the surgical instrument in real time as it contacts the bone surface. This information helps the surgeon en-
sure that the instruments are being inserted along the planned path, thereby increasing the accuracy of screw placement. Additionally, the system can detect patient displacement, such as movement due to breathing, during the surgical procedure, which further enhances the accuracy of screw placement.

The real-time alarm system in the robotic system enables the surgeon to promptly respond to any force or displacement beyond acceptable levels. If such an event is detected, the surgeon can make adjustments, such as re-planning the screw path, adjusting the entry point or insertion angle, or enlarging the pilot hole using a larger end mill drill, to avoid errors. The surgeon’s expertise and experience play a crucial role in minimizing errors during the procedure, and the haptic feedback provided by the system during screw insertion is another important element in avoiding errors. This feedback is based on the surgeon’s perception and experience, which complements the robotic system’s capabilities. Overall, the combination of the robotic system’s real-time force navigation and patient displacement information, along with the surgeon’s decision-making and haptic feedback, contributes to improved accuracy in pedicle screw placement and helps minimize errors during the surgical procedure.

In terms of real-time feedback on lateral repulsive forces, the CUVIS-spine distinguishes itself from other spine robots. However, it is worth noting that some disadvantages of the CUVIS-spine relative to other robotic systems exist. Unlike other robotic systems, CUVIS-spine does not provide a dedicated tool using proprietary screws, which could enhance convenience. In other words, this system offers an open platform that allows for the use of various screw options, albeit without the dedicated tool, which may be considered a minor inconvenience.

One of the most significant advantages of robot-assisted spine surgery is the lower radiation exposure, particularly for the surgeon. Previous studies have shown that spine surgeons can be exposed to radiation dose rates up to 12 times higher than otherspin musculoskeletal surgeons, which raises concerns about potential health risks associated with prolonged radiation exposure. For instance, Roguin et al. reported cases of brain and neck tumors occurring in physicians who performed interventional procedures, with a disproportionate occurrence of tumors on the left side of the brain (85% of cases) due to the differential dose distribution of radiation exposure in interventionists who routinely worked with the left side of the head in close proximity to the primary x-ray beam and scatter. Hyun et al. compared intraoperative radiation output recorded by C-arm mSv output and thermoluminescent dosimeters worn by surgeons between a robot-guided minimally invasive spine surgery group and a fluoroscopic-guided open spine surgery group. The results showed that the C-arm mSv output was significantly lower in the robot-guided group (0.13) compared to the fluoroscopic-guided group (0.27) (p = 0.015), and the average per-screw radiation recorded by thermoluminescent dosimeters demonstrated a mean reduction of 62.5% in the use of radiation in the robotic-guided spine surgery group.

In our study, we used an intraoperative O-arm navigation system, except for only 6 cases where C-arm was used, which resulted in minimal radiation exposure for the surgeon and the operating room staff during the robotic-assisted spine surgery. This lower radiation exposure is a significant advantage of using robotic assistance in spine surgery, contributing to the safety and well-being of the surgical team.

Another challenge associated with robotic technology is the steep learning curve involved in mastering its use. Previous study by Urakov et al. evaluated the feasibility of robot-assisted pedicle instrumentation involving residents and fellows in an academic environment, found no significant difference in the speed of pedicle instrumentation based on the operators’ years of experience or dedication to spine surgery. However, they noted a trend towards improved efficiency with more cases performed. Schatlo et al. reported that achieving satisfactory accuracy in robotic spine surgery may require around 25 cases per surgeon. In the first 10–20 cases, skilled supervision may be necessary to avoid complications during screw insertion, as inexperienced surgeons may face risks of inaccuracy.

Our results also showed a learning curve for robotic guidance, with a gradual decline in offsets and duration of the robot-assisted procedure over time. Based on the learning curves depicted in Figs. 5 and 6, it is evident that there is little significant change in accuracy and surgical time after the initial 10–20 surgeries. This suggests that robotic-assisted surgery in this context offers the advantage of standardization. Once surgeons become familiar with the instruments used for screw insertion and adapt to the surgical process, we believe that achieving proficiency can be accomplished within approximately 10–20 surgeries.

However, there were several limitations in the analysis of the learning curve in this study. One limitation was the inability to include graphs for all 113 cases in Figs. 5 and 6. This was attributed to the multicenter nature of the research, which involved surgeries conducted at different time points by different surgeons. As a result, we selected a subset of 65 cases that met the criteria for standardized surgical approaches, performed by the same surgeon, allowing us to assess the learning curve associated with
robot-assisted spinal surgery. Future studies with larger sample sizes and diverse surgical settings are warranted to further validate our findings and generalize them to a broader population of patients undergoing robot-assisted spinal surgery. Secondly, the learning curve represented the general trend of decreasing surgical time as experience accumulates, but it did not provide a specific threshold or number of cases for achieving proficiency. To determine the necessary number of cases to achieve proficiency in robotic-assisted spine surgery, multiple factors need to be considered, including individual surgeon skill, complexity of cases, and the desired level of proficiency. It is essential to combine the findings from this study with other factors such as clinical judgment, additional performance metrics, and guidelines from professional societies to estimate the appropriate number of cases for achieving proficiency. Therefore, future studies exploring the learning curve and feasibility aspects of the robot procedure are required to investigate the differences among spine surgeons with varying levels of expertise, including residents, fellows, and professors.

Robotic assistance also offers the potential to lower the risk of infection, neurovascular damage, or revision surgery, as demonstrated in previous studies. Kantelhardt et al. showed that only 1% of robotic procedures required revision surgery, compared to a reoperation rate of 12.2% for conventional techniques. The study also reported lower postoperative infection rates of 2.7% in robot-guided procedures compared to 10.7% in the conventional open surgery group. In our study, no patients required revision surgery, and there were no cases of neurovascular damage or infection. Late complications, such as pseudoarthrosis, screw loosening, screw pullout, screw breakage, or late spinal instability, will be evaluated with a long-term follow-up period in future studies.

The high cost of the instruments associated with spine robotic systems is a significant limitation that can reduce the possibility of wider use and development of this surgery. However, the application of robotic assistance in spine surgery can be cost-effective, resulting in decreased reoperation rates, decreased intraoperative and postoperative complication rates, and reduced length of hospital stays. Further investigations are warranted to thoroughly evaluate the cost effectiveness of robotic assistance in spine surgery.

There are several limitations to consider in this study. Firstly, the retrospective design of the study, rather than a RCT, is a notable limitation. Secondly, there is a lack of comparison with a group that underwent screw insertion using the conventional method. Instead, comparisons were made based on data from previous studies, focusing on numerical values. The absence of a direct comparison with a conventional method group limits our ability to assess the accuracy of the robot-guided system in relation to traditional techniques. Future research should consider including a control group that undergoes screw insertion using the conventional method to provide a more comprehensive evaluation of the robotic system's accuracy. Thirdly, long-term follow-up was not included, which limits our understanding of potential complications that may arise in the delayed postoperative period. While no immediate neurovascular complications were observed in our study, it is important to assess the occurrence of complications over a longer duration. Finally, the experience of surgeons using the robot-guided system could potentially impact the outcomes. Although the multicenter design helps to mitigate this confounding factor to some extent, future studies should aim to include surgeons with varying degrees of experience. Prospective studies evaluating the efficacy of this robotic system in more complex cases, with long-term follow-up, are warranted.

In contrast to previous studies that mainly focused on clinical outcomes and gross descriptions such as GRS, one of the strengths of our study lies in its precise implementation of 3D offset calculations. Very few studies have conducted a thorough evaluation of 3D offset calculations with such accuracy, specifically in the context of the novel robotic technology. This makes our manuscript highly relevant and significant, as it contributes to the growing body of literature on the accuracy of robotic-assisted spinal surgery. By providing detailed insights into the 3D quantification of screw accuracy, our study addresses a critical aspect of this emerging field and emphasizes the importance of accuracy-based reports in evaluating the effectiveness of new robotic technologies.

**CONCLUSION**

In conclusion, this study demonstrated the clinical safety and high accuracy of robot-assisted pedicle screw placement, as assessed with a novel spine surgery robot using 3D quantitative offset measurement methodology. However, prospective RCTs are needed to further investigate the potential benefits of this robot-assisted method compared to conventional techniques.

**NOTES**

Supplementary Materials: Supplementary Figs. 1-3 can be found via https://doi.org/10.14245/ns.2346552.276.
Accuracy Assessment of a New Robotic System in Spine Surgery

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Conflict of Interest: The authors Seungjae Ryu, Yongyeob Cha, Sungteac Hwang, and Donggi Woo are salaried employees of CUREXO Inc. The CUVIS-spine robot described in this manuscript is manufactured by CUREXO Inc., where authors Seungjae Ryu, Yongyeob Cha, Sungteac Hwang, and Donggi Woo are employees. Seong Yi is a paid consultant to CUREXO Inc. Byeong-Jin Ha, Jong-Min Lee, Seon-Jin Yoon, Byung-Kwan Kim, Jun-seok Lee, Suhun Lee, Chang Kyu Lee, Dong Ah Shin, Yoon Ha, Sung Uk Kuh, Keung Nyun Kim, and Dongwuk Son declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORCID

Byeong-Jin Ha: 0000-0003-3573-9449
Junseok Lee: 0000-0003-2488-6953
Su Hun Lee: 0000-0001-8952-5556
Dongwuk Son: 0000-0002-9154-1923
Seong Yi: 0000-0003-0700-4744

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Supplementary Fig. 1. The surgical robotic guidance system with image-guided navigation system. (A) The surgical instrument is guided by the manipulator. The surgical planning information (B) is represented in the reference coordinate system (C). (D) The optical tracking system supervises the robotic arm, the surgical instruments, and the reference markers in real-time. (E) All real-time information is drawn on the screen.
Supplementary Fig. 2. Three steps of registration with intraoperatively scanned O-arm image and postoperative CT image. (A) By image segmentation procedure, the instrumented vertebrae were obtained in the pre- and postoperative images. (B) Paired-point registration was performed using several anatomical markers on the vertebral surfaces. (C) Two different image sets went through the iterative closest point registration algorithm which minimize the difference between 2 clouds of points and used to reconstruct 2-dimensional or 3-dimensional surfaces from different scans.
Supplementary Fig. 3. Postoperative computed tomography scan shows misplaced right L4 pedicle screw which is classified as Gertzbein-Robbins grade E due to 6.1 mm of lateral cortical breach.
Lumbar Endoscopic Unilateral Laminotomy With Bilateral Decompression Surgery in Severe Lumbar Stenosis Under Electrophysiological Monitoring: Focused on Full-Visualized Trephine/Osteotome

Ning-Ning Dou, Hao-lin Wang, Shao-Zhen Hu, Zheng-Nan Huang, Jun Zhong, Shi-Ting Li
Department of Neurosurgery, Shanghai Jiao Tong University School of Medicine, Xinhua Hospital, Shanghai, China

Objective: Although endoscopic drill has the advantages in manipulation and hemostasis, whose low efficiency and blurred vision reduce the efficacy of lumbar endoscopic unilateral laminotomy with bilateral decompression (LE-ULBD). The present study was designed to evaluate the safety and efficacy of full-visualized trephine/osteotome in the LE-ULBD surgery for severe lumbar stenosis.

Methods: Fifty-seven severe lumbar stenosis patients who underwent LE-ULBD between January 2020 to January 2023 were enrolled, who were divided into drill and visualized trephine groups. The medical records including demographics, operative duration, intraoperative electrophysiological findings, postoperative hospital stay or hospital stay, postoperative outcomes and complications were retrospectively reviewed and analyzed.

Results: A total of 57 patients included 15 in drill and 42 in trephine group were enrolled in the study. There was significant difference in the pre- and postoperative visual analogue scale and Oswestry Disability Index scores in both groups (p < 0.05). The mean operative duration in the trephine group (101.05 ± 12.18 minutes) was shorter than that in the drill group (134.67 ± 9.68 minutes) (p < 0.05). There was no statistical difference between the 2 groups in electrophysiological monitoring, posthospital stays, postoperative outcomes and complications. Abnormal free-electromyography (EMG) were recorded in 2 (13.3%) and 5 patients (11.9%) in the drill and trephine group. Intraoperative somatosensory evoked potential changes occurred in 3 (20%) and 3 patients (7.1%) in the drill and trephine group and all patients recovered immediately when surgery ended. No serious complications and recurrence occurred in all the patients.

Conclusion: Full-visualized trephine/osteotome has been approved to be convenient, safe and efficient in our study, which combined with translaminar inside-out technique and EMG monitoring especially free-EMG may offer a new choice in LE-ULBD surgery for lumbar stenosis patients.

Keywords: LE-ULBD, Full visualized trephine/osteotome, Endoscopic drill, Translaminar inside-out technique, Intraoperative electrophysiological monitoring
INTRODUCTION

Degenerative lumbar stenosis is a common spinal disease in elderly patients,1,2 which is attributed to facet osteoarthritis, ligamentum flavum (LF) hypertrophy, disc pathology, and spondylolisthesis, either alone or in any combination leading to symptoms such as leg/back pain, numbness and lower extremity weakness. Although with confirmed efficacy, the traditional open surgery is always accompanied with many complications such as wound infection, spinal nonfusion and failed back surgery syndrome especially in elderly patients because of excessive destruction of muscle and bone structures.3-5 To reduce iatrogenic injury to normal anatomic structures during surgery, more minimally invasive techniques are introduced. Unilateral laminotomy with bilateral decompression (ULBD) in combination with the microscope has been regarded as standard minimally invasive treatment for the lumbar stenosis since reported by Spetzger et al.6 in 1994. Endoscopic spine surgery in lumbar disease has continuously evolved over the past 3 decades since several pioneers introduced.7-11 However, lumbar endoscopic ULBD (LE-ULBD) surgery have not be widely popularized due to the steep learning curve,9 high complication rates,12 low efficiency and inadequate decompression.13 The widely used endoscopic bone removal tool is high-speed drill, although which has the advantages in manipulation and hemostasis, its low efficiency, vibration and blurred vision influence the widespread of LE-ULBD.14 We performed full-visualized LE-ULBD surgery by a new designed full-visualized trephine/osteotome under general anesthesia and electrophysiological monitoring, which is rarely seen in previous reports. In this article, we shared our surgical experience focusing on the visualized trephine/osteotome and inside-out technique.

MATERIALS AND METHODS

This is a retrospective study. We retrospectively reviewed our patients from January 2020 to January 2023, who underwent full-visualized LE-ULBD procedures under electrophysiological monitoring and general anesthesia. All patients have undergone conservative treatment preoperatively and failed, who were divided into 2 groups according to bone removal by endoscopic drill or trephine/osteotome. All the patients were operated by Dr. Zhong. The research complies with the guidelines for human studies. Informed consent for surgery was obtained from the all participants in the study. This study was approved by Institutional Review Board (IRB) of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (IRB No. XHEC-D-2023-106).

All patients underwent pre- and postoperative clinical evaluation including lumbar/computed tomography (CT)/magnetic resonance imaging (MRI)/dynamic x-ray. The inclusion criteria are described as follows: (1) neurogenic intermittent claudication with or without radiculopathy; (2) preevaluation including lumbar CT/MRI/dynamic x-ray shows severe central lumbar spinal stenosis (grade C with or without lateral recess stenosis and grade D); (3) failed conservative treatments for at least 6 weeks. Patients are excluded with segmental instability, cauda equina syndrome or the patient with multiple responsible levels.

The medical records including demographics, intraoperative findings, operation time, length of hospital stay, postoperative outcomes and complications were reviewed. All patients were followed up by telephone or outpatient clinic interview. Both back and sciatic pain were assessed by visual analogue scale (VAS 0–10) and Oswestry Disability Index (ODI). All patients underwent a lumbosacral CT within 24 hours postoperatively to evaluate the change of cross-sectional area pre- and postoperatively.

1. Electromyography Monitoring

The sensory and motor function were monitored by somato-sensory evoked potential (SSEP) and free-electromyography (EMG) respectively. Motor activity of the operative level and below was monitored by free-EMG bilaterally, meanwhile, sensory activity was monitored by SSEP. The monopolar needle electrodes (20 mm/28G; 25 mm/27G or 37 mm/27G) were placed 5–10 mm apart into characteristic muscle groups that were physiologically innervated by the targeted nerve root. For recording, filters were set at 10 Hz to 10 kHz and sensitivity at 100 µV to 1 mV. The time base was 20 to 500 msec. A Nicolet Endeavor (Nicolet Healthcare/Nicolet Biomedical, Madison, WI, USA) was used for all examinations. EMG signals were continuously made audible by loudspeakers and displayed on a monitor screen. The free-EMG in the form of isolated spikes or phasic bursts recorded intraoperatively and the SSEP amplitude reduction of more than 50% were considered abnormal.

2. Surgical Technique (Fig. 1)

1) Entry point and incision

All procedures were performed via a translaminar rather interlaminar approach under general anesthesia with prone position on a radiolucent table. The upper laminar-medial facet junc-
tion was located by intraoperative fluoroscopy. After the skin incision was confirmed by the fluoroscopy and a 10-mm vertical skin incision was made, a stepwise-dilating cannulas and working cannula were introduced along the guiding rod. X-ray fluoroscopy was performed again to confirm the location.

2) Ipsilateral decompression

Endoscopic radiofrequency electrodes and forceps were used to clean all the soft tissue as much as possible to expose the facet joints and superior and inferior lamina, otherwise, it will take more time to hemostasis and identify the anatomic landmark. Fully exposure of the upper 1/2 lamina, medial border of facet, 1/3 lower lamina and spinolaminar junction before removal of bony structure is critical in the process. The laminectomy starts at the inferior border of the cranial hemilamina in the spinolaminar junction going cranially until the origin of the ligamentum flavum by visualized trephine with semiring technique. Medial laminotomy and early piecemeal removal of the detached ligamentum flavum border could guide the surgeon to reduce nerve and dural damage incidence and prevent undue facetectomy.

Fig. 1. The LE-ULBD surgical procedure by inside-out technique. The bilateral decompression process follows the sequence (1 to 6). Fully exposure of the upper 1/2 lamina, medial border of facet, 1/3 lower lamina and spinolaminar junction before removal of bony structure is critical in the process. The laminectomy starts at the inferior border of the cranial hemilamina in the spinolaminar junction going cranially until the origin of the ligamentum flavum by visualized trephine with semiring technique. Medial laminotomy and early piecemeal removal of the detached ligamentum flavum border could guide the surgeon to reduce nerve and dural damage incidence and may prevent undue facetectomy.

Fig. 2. The full-visualized endoscopic trephine and working cannula (Jianbo Medical Device Co., Hangzhou, China).

Fig. 3. (A, B) The magnetic resonance imaging in the upper row shows severe central and lateral spinal canal stenosis of the L4/5. (C, D) The lower row shows preoperative and postoperative computed tomography scans.

3) Bone removal of spinolaminar basement

Removal of spinolaminar basement is critical for contralateral decompression in PE-ULBD, which focused on undercutting the base of the spinous process and the contralateral lamina by visualized trephine (Fig. 2), osteotome and Kerrison punches until the small detachment of the cranial contralateral LF. The trephine was used to undercut the bone and the osteotome was
adopted to remove smaller obstacle. Once the water pressure created a window to make the epidural fat and neural structures visible, then rotate and tilt the endoscope to decompress the LF and view the contralateral side (Figs. 3, 4).

4) Contralateral decompression

Once the contralateral superior articular process (SAP) was visualized, blunt dissectors were used to carefully detach adhesions between the dura and LF, then remove it piecemeal by Kerrison. As the decompression progresses, the field of vision widen by manipulating the endoscope to maximize the angle of sight to fully decompress the contralateral dura and traversing nerve root (Figs. 3, 4).

3. Reaction to the Abnormal EMG

1) Abnormal free-EMG

Unlike the transforaminal approach, the cannulas insertion in the translaminar approach tends not to cause abnormal EMG changes because the cannulas aim at the upper lamina rather than the interlaminar space. It is easy to irritate the nerve root during intracanal especially lateral recess decompression process. Burst potentials always mean direct or indirect nerve root irritation. When abnormal free-EMG occurs, we should stop to react and deal with the abnormality immediately based on the abnormal EMG and intraoperative findings. During intracanal decompression process, the traversing nerve root may be compressed by the cannula or be irritated by the forceps, bipolar or Kerrison. If the abnormal free-EMG was caused by canula, it should be adjusted to be more dorsal. If the stimulation was caused by decompression manipulation, the free-EMG would stop when manipulation stops.

2) Abnormal SSEP

The SSEP is highly sensitive, but also has the highest false positive incidence, which could be affected by many factors. However, the amplitudes of SSEP in patients with severe spinal stenosis are always low or even cannot be detected. Although the determinization in significance of SSEP abnormality was always controversial, the manipulation should be stopped immediately especially during contralateral decompression and the judgment should be made based on free-EMG and SSEP findings when abnormal SSEP occurred intraoperatively.

4. Outcome Measures and Statistical Analysis

The pre- and postoperative VAS and ODI scores were assessed by questionnaire preoperatively, which were recorded and analyzed by IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). A p-value of < 0.05 is statistically significant.

Table 1. Patient demographics and characteristics of clinical manifestation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>75.5 ± 5.4</td>
<td>73.1 ± 6.9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>12:3</td>
<td>27:20</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
<td>15.1 ± 8.06</td>
<td>12.9 ± 9.7</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Surgical level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L5S1</td>
<td>5</td>
<td>25</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>L4/5</td>
<td>10</td>
<td>17</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>L3/4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L2/3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Operative duration (min)</td>
<td>127 ± 7.2</td>
<td>80 ± 12.7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Posthospital stay (day)</td>
<td>2.3 ± 0.7</td>
<td>2.2 ± 0.6</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number. Group 1, drill group; group 2, trephine/osteotome group.
RESULTS

1. Participants and Descriptive Data (Table 1)
A total of 57 patients were enrolled in the study, which included 15 and 42 patients in drill and trephine/osteotome group with an average age of 75.5 ± 5.4 and 73.1 ± 6.9 years old respectively (p > 0.05). The mean symptoms duration in drill group was 15.1 ± 8.06 months, compared with 12.9 ± 9.7 months in the trephine group (p > 0.05) (Table 1).

2. Outcomes and Complications (Tables 2, 3)
The preoperative and postoperative VAS and ODI scores in both the 2 groups were significantly different (p < 0.05), as was the operation duration, which was 134.67 ± 9.68 and 101.05 ± 12.18 minutes respectively in the drill and trephine/osteotome group (p < 0.05). There was no difference in the posthospital stay in the 2 groups, which was 2.3 ± 0.7 and 2.2 ± 0.6 days respectively in the drill and trephine/osteotome group (p > 0.05). All except 5 patients were followed up by telephone or interview. No recurrence occurred in the 2 groups during the follow-up (Tables 2, 3). During the follow-up, 3 patients including 1 in the drill and 2 in the trephine/osteotome group complained of postoperative back pain and all but 1 relieved 6 months later. No other complications happened in all the patients during the follow-up.

3. EMG Findings
There was no statistical difference between the 2 groups in electrophysiological monitoring. Abnormal free-EMG in the form of isolated spikes or phasic bursts were recorded in 2 (13.3%) and 5 patients (11.9%) in the drill and trephine/osteotome group during intracanal and foraminal decompression. Intraoperative SSEP changes occurred in 3 (20%) and 3 patients (7.1%) in the drill and trephine/osteotome group and all patients recovered to less than 50% reduction of SSEP amplitude immediately when surgery ended. No complications occurred in all the patients with electrophysiological abnormalities, which was attributed to the timely adjustment of manipulation intraoperatively.

DISCUSSION

Endoscopic spine surgery has been evolving rapidly in the past decades, starting from contraindications and eventually becomes feasible for lumbar stenosis. Due to the wide range of treatable lumbar stenosis and the reported favorable clinical outcomes, the endoscopic posterior approach has attracted more and more attention.17-22

As we all know, the outside-in technique was most accepted in the LE-ULBD surgery,23 whose procedure involves removal of bony structure including the lamina, articular facet joint first, then the entire LF en bloc or piecemeal to expose the dura and nerve root. However, the outside-in technique has disadvantages including uncertain removal border, dura tear and nerve injury. Lee reported 5% of excessive facet resection in his cases,13 which would lead to iatrogenic destabilization. Meanwhile, ligament flavum and dura are closely adhesive because of loss of epidural fat in severe lumbar spinal stenosis.

1. Translaminar Inside-Out Technique
The inside-out technique we described here is completely different from what is meant by the foraminal approach. The trans-
laminar inside-out technique involves exposure of the dura and nerve root priorly or concurrently with bony and LF removal, which could avoid excessive bony resection because of visualized dura and nerve structure. Full endoscopic surgery also can precisely decompress the nerve, during which bone and LF were resected piecemeal and no effort is made to remove it en bloc. In our cases, there was no dura and nerve root injury observed during decompression.

2. Full-Visualized Trephines/Osteotome

Although the drill has the advantages in manipulation and hemostasis, its low efficiency, vibration and blurred vision influence the widespread of LE-ULBD. Ahn reported the rate of postoperative dysesthesia was 6.1%,\(^{14}\) which might be due to the thermal or vibration injury by the drill postoperatively. Compared with endoscopic drill, fully endoscopic trephine is a time-saving and safe equipment to undercut the osteophyte, which has been approved in our research. Endoscopic osteotome can also be used to accurately remove small osteophytes especially the medial border of facet.

The newly designed full-visualized trephine applied in this study advanced with rotation under full vision instead of x-ray (Fig. 2). Unlike endoscopic drill, whose vision would be blurred because of abrasive powder and drill's direction that influences the progress of the operation, the full-visualized trephine could always be visualized clearly with semiring technique (Fig. 4). What we refer to as the semiring technique is that when the ring is applied, only half or less of the ring is filled with bone rather than the entire ring. The semiring technique could ensure the dura and nerve root visible during the bone removal, which could decrease the incidence of nerve injury. It can also speed up the bone removal process because the semiring's bone is much easier to remove than full-ring's.

3. Electrophysiological Monitoring

Besides the full-visualized in-outside technique, the intraoperative EMG monitoring was also performed to provide double protection of the nerve.

The combination of free-EMG and SSEP intraoperatively appears to have a high enough sensitivity to identify nerve structures irritation, which could help to remind the surgeon to avoid the nerve injury by adjusting the cannulas and manipulation timely based on intraoperative electrophysiological monitoring and findings. SSEP contains many inherent problems including high unreliability and false positive rate to moderate spinal cord dysfunction,\(^{24}\) which makes SSEP rarely useful in the lumbar surgery intraoperatively. However, SSEP could monitor the overall sensory conduction of the spinal cord, which is important in patients with severe spinal canal stenosis.

Since motor evoked potential techniques could only monitor conduction of approximately 1/25 motor axons in the motor nerve root.\(^{24}\) Therefore, free- and triggered-EMG techniques have been the best way to monitor the electrophysiological activity of the muscle fibers, which could provide the surgeon with real-time feedback information on the function of the motor nerve. The purpose of motor nerve root monitoring is to check their function and integrity during intraoperatively in order to avoid irreversible injury. Burst potentials always means direct nerve root contact. As long as the irritation is not heavy, there will be no serious sequelae with removal of harmful factors timely.

CONCLUSION

Full-visualized trephine/osteotome has been approved to be convenient, safe and efficient in our study, which combined with translaminar inside-out technique and EMG monitoring especially free-EMG may offer a new choice in LE-ULBD surgery for lumbar stenosis patients. However, this is an observational retrospective study within a single center, which may lead to the bias in the final results. A multcenter, prospective study with a large sample size should be performed.

NOTES

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Author Contribution: Conceptualization: JZ, STL; Data curation: ZNH; Formal analysis: HIW, SZH, ZNH; Methodology: NND, HIW; Project administration: JZ, STL; Writing - original draft: NND; Writing - review & editing: NND.

ORCID
Ning-Ning Dou: 0000-0002-8310-5953
Hao-lin Wang: 0009-0000-3318-7025
Shao-Zhen Hu: 0009-0008-1966-5690
Zheng-Nan Huang: 0009-0009-2630-3257
Jun Zhong: 0000-0003-4349-2431
Shi-Ting Li: 0000-0001-6106-8891
REFERENCES

Clinical Effectiveness of Artificial Disc Replacement in Comparison With Anterior Cervical Discectomy and Fusion in the Patients With Cervical Myelopathy: Systematic Review and Meta-analysis

Jung Hwan Lee¹, Youn Joo Lee², Min Cheol Chang³, Jun Ho Lee⁴

¹Department of Rehabilitation Medicine, Namdarun Rehabilitation Clinic, Yongin, Korea
²Chadwick International School, Incheon, Korea
³Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu, Korea
⁴Department of Neurosurgery, Kyung Hee University Medical Center, Seoul, Korea

Objective: Cervical myelopathy (CM) describes the compressive cervical spinal cord state, often accompanied by serious clinical condition, by herniated disc or hypertrophied spurs or ligament. Anterior cervical discectomy and fusion (ACDF) has been frequently employed as conventional surgical solution for this CM despite its inherent biomechanical handicap. Alternatively, an artificial disc replacement (ADR) preserves cervical motion while still de-compressing the spinal canal and neural foramen. This analysis elaborated to clarify the potential benefits of ADR application to CM over ACDF from the conglomerated results of the past references.

Methods: A literature search was performed using MEDLINE, Embase, Cochrane review, and KMbase databases from the studies published until March 2023. Six studies (3 randomized controlled study [RCTs] and 3 non-RCTs) were included in a qualitative and quantitative synthesis. Data were extracted and analyzed using a random effects model to obtain effect size and its statistical significance. Quality assessment and evidence level were established in accordance with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.

Results: Among 6 studies, 2 studies showed that ADR group achieved significantly better clinical improvement than the ACDF group, while the rest 4 studies revealed no significant difference. A meta-analysis showed better clinical outcomes with or without statistical significance. The level of evidence was low because of inconsistency and imprecision.

Conclusion: ADR was superior or at least, not inferior to ACDF in terms of functional recovery. However, its application to the CM patients is merely empowered with weak strength due to low level of evidence.

Keywords: Cervical myelopathy, Anterior cervical discectomy and fusion, Artificial disc replacement, Clinical outcome, Systematic review, Meta-analysis

INTRODUCTION

Cervical myelopathy (CM) is a condition where the cervical spinal cord is compressed either ventrally by herniated disc or dorsally by hypertrophied bony structures or ligament, frequently yielding the serious clinical manifestations ranging...
from neck and/or arm pain, functional deficits limited to upper limb involvement even to lower limb functional impairment including gait disturbance.\textsuperscript{1-3} Conservative managements are frequently fraught with failure during its treatment, subsequently requesting an early, surgically decompressive management when the patients manifest excessive intractable pain or progressive neurological deficits.

Anterior cervical disectomy and fusion (ACDF) has been playing its role as an effective solution for CM.\textsuperscript{4,5} It might provide the sufficient decompression as well as the solid stabilization to the affected cervical segment. However, few concerns that relate to its inherent potency such as fusing the mobile spinal segment as well as incurring subsequent adjacent segment degeneration (ASD)\textsuperscript{6-7} have brought up the artificial disc replacement (ADR) as an alternative. The ADR might offer both the mechanical advantage of segmental motion preservation with consequent stress reduction at the adjacent levels while fulfilling the sufficient cervical cord decompression as during the ACDF.\textsuperscript{8-10} But there have been some concerns whether this mobile ADR can yield compatible clinical outcome and eventually be a substitute to ACDF in the treatment of CM. Past references have noticed the existence of disparities in the application of ADR versus ACDF in terms of the socioeconomic aspect, that the subjects with greater median income or the possession of the private insurance preferred ADR.\textsuperscript{11} They also manifested the elaborations to minimize its application during the surgical treatment of multilevel CM by overlapping with laminoplasty.\textsuperscript{12} Taking into account that the majority of the CM subjects are tend to be senile, deformed populations with already progressed facet degeneration as well as decreased cervical lordosis from even spontaneous fusion, ACDF still comprises as a general surgical solution for CM over ADR.\textsuperscript{13}

There have been a few clinical studies that compare clinical results between ADR and ACDF in the CM treatment. Hereby, we conducted systemic review with meta-analysis by synthesizing published articles regarding this topic to clarify the clinical benefits of ADR over the ACDF and further to investigate its potential as a substitute to ACDF for the CM management.

**MATERIALS AND METHODS**

1. Study Selection Criteria

The authors have recruited articles described in Korean or English language that have primarily met the following criteria: patients aged from 18 to 70 years old, clinical manifestation of CM with no significant improvement or even aggravation after conservative treatment, and the confirmative diagnosis of 1 or 2 levels of mechanical cervical cord compression by computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria were a previous history of cervical spinal surgery, severe osteoporosis, cervical kyphosis, foraminal stenosis, severe facet joint spondylosis, cervical radiculopathy, ossification of the posterior longitudinal ligament, inflammatory cervical cord diseases, tumor, or infectious disease. Among the studies fulfilling these criteria, those that have included the contents regarding the clinical outcome after the ADR or ACDF and have provided the comparative results between the 2 surgical methods were finally selected.

2. Database Search and Study Extraction

The MEDLINE (PubMed), Embase, Cochrane review, and KMbase databases were searched for articles published until March 2023. We established individual search terms in each database's search engine (Supplementary Material). The search was not restricted to randomized controlled study (RCT) and was extended to original articles, including non–RCT. The decision for an article selection was primarily based on the title and abstract review, followed by full-text screening. The study screening and data extraction were independently performed by the 2 reviewers, and any discrepancies were resolved by discussion between the 2 reviewers or with the entire research group. Flow chart demonstrating the process of study selection was illustrated in Fig. 1.

3. Data Collection

Reference data such as the diagnosis and number of subjects in each surgical method group (ADR and ACDF groups), clinical evaluation tools, follow-up period, and comparative results of the clinical outcomes were extracted from the selected articles. Dichotomous variables such as the number of patients with pain and functional scores or adverse events were extracted for the estimation of relative risk ratio. Continuous variables such as mean and standard deviation of clinical scores were extracted for the estimation of mean differences. If the standard deviations were not reported, they were calculated from confidence interval (CI), mean, and the number of patients.

4. Quality Assessment of Selected Studies, Establishment of Level of Evidence, and Strength of Recommendation

Quality assessment of each study and level of evidence was established in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE)
methodology. The bias assessment for each RCT was conducted by method of risk of bias (ROB), which consisted of 7 domains: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The bias for each non-RCT was assessed with Risk of Bias Assessment tool for Nonrandomized Study (RoBANs); domains were selection of participants, confounding variables, measurement of intervention (exposure), blinding of outcome assessment, incomplete outcome data, and selective reporting. All the domains were evaluated as “low risk,” “high risk,” or “unclear.” These evaluations were performed by 2 independent reviewers and disagreements were resolved by discussion between 2 reviewers or with the entire research group.

Based on the comprehensive evaluation of inconsistency, indirectness, imprecision and publication bias in addition to ROB in all studies, the evidence level was determined as high, moderate, low, or very low grade. Besides, the strength of recommendation was determined as strong or weak by comprehensively assessing not only evidence level, but also other factors such as benefits, risks, burdens, and possibly cost. The level of evidence and strength of recommendation were determined by discussion involving the entire research group.

5. Meta-analysis
Review Manager software (RevMan ver. 5.4; Cochrane Collaboration, Oxford, UK) was used for meta-analysis to compare clinical outcome between the ADR and the ACDF group. Tests of heterogeneity were performed using $I^2$ statistics. The parameter with $I^2$ values of $p < 0.05$, which was considered to have significantly high degree of heterogeneity, was additionally validated by subgroup analysis or sensitivity analysis. A random effects model was applied to obtain effect size and its statistical significance because it was assumed that the subjects and methods of the included studies performed by independent researchers could not be entirely equivalent and, therefore, could not have a common effect size. A probability of $p < 0.05$ was considered statistically significant. The results were expressed as mean difference and 95% CI for continuous outcome data.
and in the form of relative risk ratio and 95% CI for dichotomous outcome data.

RESULTS

1. Search Results

Our database search has initially recruited 139 articles. After the exclusion of the 27 duplicates, 112 potentially eligible articles have remained. After the title and abstract screening, 59 articles were excluded due to the lack of the inclusion criteria fulfillment. Thus, the remaining 53 articles were retrieved for full-text analysis, of which 47 were subsequently excluded because of the irrelevance to the scheme of this analysis.

Ultimately, 3 RCTs and 3 non-RCTs were included in this study (Fig. 1).19-24 The pain intensity was measured in the selected studies using Numerical Rating Scale or visual analogue scale. The functional measurement tool used in the selected studies was the Neck Disability Index (NDI), Japanese Orthopaedic Association score (JOA), and 36-item Short Form health survey (SF-36). Odom criteria were used to evaluate the degree of patients’ satisfaction for treatment, which was divided into 4 grades including excellent, good, fair and poor grades. Excellent or good grade was regarded as satisfactory response. The follow-up period was variable across the studies ranging from 3 weeks to 7 years.

2. Quality Assessment

The ROB of all selected studies was illustrated in Fig. 2 (A: RCT, B: non-RCT). Three RCTs were assessed as unclear risk in random sequence generation domain because they did not describe the sequence generation process.19,22,24 The most frequently biased domain was blinding of outcome assessment, in which all 3 RCTs were rated as high risk or unclear because one RCT assessed the patients by nonblind staff,19 and the other 2 studies did not clarify whether the clinical evaluation was conducted by assessor who was blind or not involved in the process of patients selection and treatment.22,24 Sixteen domains among 21 (76.2%) were rated as low risk, thus, the overall ROB was considered low (Fig. 2A). Of 3 non-RCTs, one study was rated as high risk in selection of participants domain because they compared the group consisting of the patients recruited during different period.21 All 3 non-RCTs did not reveal whether clinical outcome was evaluated by the staff blind to treatment and thus were rated as unclear risk.20,21,23 Of 18 domains across all studies, 13 domains (72.2%) were determined as low risk; thus, the overall ROB was considered low (Fig. 2B). A discrepancy between reviewers was found in 6 of total 39 domains (15.4%) at first. After the discussion, all the discrepancies were resolved.

3. Clinical Outcome Analysis

All included studies have disclosed significant improvement of clinical results after 2 types of surgery. Among the 3 RCTs ul-

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Fig. 2. Quality assessment for extracted studies. (A) Risk of bias for randomized controlled study. (B) Risk of Bias Assessment tool for Nonrandomized Study for nonrandomized study. Green color, low risk of bias; red color, high risk; white color, unclear risk of bias.
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1 study showed that the ADR group achieved significant better clinical improvement than the ACDF group,19 while the other 2 studies revealed no significant difference between the 2 groups.22,24 Of 3 non-RCTs, 1 study found better clinical results in the ADR group than the ACDF group, whereas the other 2 studies found no significant different clinical outcomes between the 2 groups.21,23 Comprehensively, ADR was superior or at least noninferior surgical method to obtain favorable clinical outcomes in the patients with CM (Table 1).

4. Meta-analysis

Meta-analysis was mainly performed in terms of surgical time (minutes), blood loss (mL), number of reoperations, range of motion (ROM) of surgical level, functional scores, and patients’ satisfaction score, sufficiently provided for analysis across the studies. The study by Riew et al.22 divided the ADR group into Prestige ST and Bryan group according to prosthesis type and compared them with the 2 ACDF group respectively. Thus, 2 comparisons were extracted and analyzed respectively in this meta-analysis. Ultimately 6 studies and 7 comparisons were included in meta-analysis. Because the data regarding pain score was not provided sufficiently for a proper meta-analysis performance, this analysis was performed mainly as to the functional improvement after surgery. Since the preoperative baseline NDI and JOA were not consistent across the selected studies, the changes of mean and standard deviation between baseline and follow-up period was obtained and analyzed.

5. Surgical Time

Seven comparisons from 6 studies provided continuous data of surgical time for the analysis of effect size by the mean difference.18–24 The overall mean difference was estimated as 13.74 (95% CI, 0.71–26.76), which meant that ACDF required longer surgical time with statistical significance (p = 0.04). A high degree of heterogeneity was revealed (I^2 = 93%) (p < 0.01) (Fig. 3A). Sensitivity test revealed no specific study to significantly contribute to overall heterogeneity.

6. Blood Loss

Seven comparisons from 6 studies provided continuous data of blood loss for the analysis of effect size by the mean difference.18–24 The overall mean difference was estimated as -18.44

Table 1. Evidence table

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riew et al.</td>
<td>RCT</td>
<td>N = 106 ADR (N = 59, Prestige ST, N = 47, Bryan)</td>
<td>NDI, SF-36, neck and arm pain score at 6 weeks, 3, 6, 12, and 24 months</td>
<td>Both groups had significant improvement following surgery, which was not significantly different between the groups.</td>
</tr>
<tr>
<td>(2008)</td>
<td></td>
<td>N = 93 ACDF</td>
<td></td>
<td></td>
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<tr>
<td>Cheng et al.</td>
<td>RCT</td>
<td>N = 41 ADR (Bryan)</td>
<td>Modified Odom’s criteria, JOA scale, SF-36, and NDI at 3 years</td>
<td>The ADR group scored significantly better in JOA scale, SF-36, and NDI than the ACDF.</td>
</tr>
<tr>
<td>(2011)</td>
<td></td>
<td>N = 42 ACDF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al.</td>
<td>RCT</td>
<td>N = 30 ADR (Bryan)</td>
<td>NDI, VAS, JOA scale, and Odom’s criteria at 2 weeks, 3 months, 1 year, and 3 years</td>
<td>There were no significant differences in VAS, JOA, NDI, and satisfactory rates of Odom criteria between the 2 groups before or after the operation.</td>
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<tr>
<td>(2019)</td>
<td></td>
<td>N = 30 ACDF</td>
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<tr>
<td>Ding et al.</td>
<td>Retrospective study</td>
<td>N = 37 ADR (N = 25, Prestige ST, N = 12, Bryan)</td>
<td>SF-36 for PCS and MCS, JOA scale, NDI, Nurick grade at 1 week, 3 months, 6 months, 12 months, and 24 months</td>
<td>The ADR group achieved significant improvement in NDI, SF-36 for PCS and MCS than the ACDF group. Both group showed the significant improvement in JOA scale and Nurick grade, which was no significant difference between both groups.</td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td>N = 39 ACDF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gornet et al.</td>
<td>Retrospective study</td>
<td>N = 59 ADR (Prestige ST)</td>
<td>NDI, neck &amp; arm pain, SF-36, neurological status, at 2 and 7 years</td>
<td>No significant differences in clinical outcomes were found between the 2 groups.</td>
</tr>
<tr>
<td>(2018)</td>
<td></td>
<td>N = 51 ACDF</td>
<td></td>
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<tr>
<td>Shi et al.</td>
<td>Prospective cohort study</td>
<td>N = 60 ADR (Discover)</td>
<td>JOA scale and NDI until 24 months</td>
<td>Both treatments significantly improved all clinical parameters without statistically relevant differences between both groups.</td>
</tr>
<tr>
<td>(2016)</td>
<td></td>
<td>N = 68 ACDF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADR, artificial disc replacement; ACDF, anterior cervical discectomy and fusion; NDI, Neck Disability Index; SF-36, 36-item Short Form health survey; JOA, Japanese Orthopaedic Association; VAS, visual analogue scale; PCS, physical composite score; MCS, mental composite score.
Fig. 3. Forest plot of comparison. (A) Mean difference of surgical time. (B) Mean difference of blood loss (upper: subgroup analysis [< 100 mL vs. ≥ 100-mL blood loss], lower: total analysis). (C) Relative risk of reoperation. (D) Mean difference of range of motion (ROM) at surgical level (upper: total analysis, lower: sensitivity analysis after exclusion of the study of Ding et al.). Bryan, artificial disc replacement with Bryan prosthesis; Prestige ST, artificial disc replacement with Prestige ST; ADR, artificial disc replacement; ACDF, anterior cervical discectomy and fusion; SD, standard deviation; CI, confidence interval; df, degrees of freedom.
(95% CI, -42.79 to 5.9), meaning blood loss was smaller in ADR than ACDF, but without statistical significance (p = 0.14). A high degree of heterogeneity was revealed (I^2 = 95%) (p < 0.01) (Fig. 3B).

Subgroup analysis was conducted after division of the studies into 2 subgroups depending on whether blood loss was 100 mL or more and less than 100 mL. In the subgroup of 100 mL or more of blood loss, the mean difference was estimated as -70.25 (95% CI, -111.5 to -29.0), meaning blood loss was significantly smaller in ADR than ACDF (p < 0.01). But high degree of heterogeneity was also found, although its degree was somewhat decreased by subgroup analysis (I^2 = 89%) (p < 0.01). In the subgroup of less than 100 mL of blood loss, the mean difference was estimated as 2.28 (95% CI, -9.45 to 14.01), meaning blood loss was smaller in ACDF than ADR without statistical significance (p = 0.70). But high degree of heterogeneity was also observed despite its decrease after subgroup analysis (I^2 = 64%) (p = 0.02) (Fig. 3B).

7. Reoperation

Four comparisons from 3 studies provided the dichotomous data for measurement of effect size by relative risk ratio about reoperation rate. This suggested that a smaller number of reoperations were observed in ADR than ACDF with estimated risk ratio of 0.55 (95% CI, 0.29–1.05) without statistical significance (p = 0.07). No heterogeneity was found (I^2 = 0%) (p = 0.45) (Fig. 3C).

8. ROM at Surgical Level

Three studies were available in the analysis of effect size by the mean difference for ROM at surgical level. The estimated overall mean difference was calculated as 8.91 (95% CI, 5.82–12.01), which favored ADR with statistical significance (p < 0.01). The degree of heterogeneity was significant (I^2 = 99%) (p < 0.01).

Sensitivity test without Ding et al’s study revealed the low degree of heterogeneity (I^2 = 0%) (p = 0.76), which indicated that Ding et al’s study significantly contributed to heterogeneity of ROM at surgical level. After removal of this study, the estimated overall mean difference was calculated as 6.81 (95% CI, 6.65–6.96), which revealed also favor of ADR with statistical significance (p < 0.01) (Fig. 3D).

9. NDI at 3 Months

Five comparisons from 4 studies presented continuous data of NDI improvement at 3 months and were available in the analysis of effect size by the mean difference. The overall mean difference was estimated as -3.52 (95% CI, -6.80 to -0.23), favoring ADR, and this was the degree of statistical significance (p = 0.04). A high degree of heterogeneity was revealed (I^2 = 82%) (p < 0.01) (Fig. 4A). Sensitivity test revealed no specific study to significantly contribute to overall heterogeneity.

10. NDI at 6 Months

Three comparisons from 2 studies were available in the analysis of effect size by the mean difference for NDI improvement at 6 months. The estimated overall mean difference was calculated as -6.36 (95% CI, -12.26 to 0.46), which favored ADR with statistical significance (p = 0.03). The degree of heterogeneity was not significant (I^2 = 61%) (p = 0.08) (Fig. 4B).

11. NDI at 12 Months

Four comparisons from 2 studies were available in the measurement of effect size by the mean difference of successful NDI improvement at 12 months. The estimated overall mean difference was calculated as -5.27 (95% CI, -9.79 to 0.75), which meant significant superiority of ADR over ACDF (p = 0.02). The degree of heterogeneity was significantly high (I^2 = 74%) (p < 0.01).

Sensitivity test excluding Chen et al’s study revealed the low degree of heterogeneity (I^2 = 37%) (p = 0.20), which indicated that this study significantly contributed to heterogeneity of NDI at 12 months. After removal of this study, the estimated overall mean difference was calculated as -7.18 (95% CI, -11.72 to -2.64), which empowered the significant superiority of ADR over the ACDF (p < 0.01) (Fig. 4C).

12. NDI at 24 Months

Five comparative data from 4 studies provided the value of -5.26 (95% CI, -10.56 to 0.03), the effect size measured by the mean difference, which showed trends toward ADR without statistical significance (p = 0.05). Significant heterogeneity was found (I^2 = 89%) (p < 0.01).

Sensitivity test excluding Shi et al’s study revealed the low degree of heterogeneity (I^2 = 43%) (p = 0.15), which indicated that this study significantly contributed to heterogeneity of NDI at 24 months. The analysis after excluding this study obtained the statistical significance with the estimated overall mean difference of -7.09 (95% CI, -11.11 to -3.08), which favor ADR (p < 0.01) (Fig. 4D).
Fig. 4. Forest plot of comparison. (A) Mean difference of Neck Disability Score (NDI) change between the baseline and 3 months. (B) Mean difference of NDI change between the baseline and 6 months. (C) Mean difference of NDI change between the baseline and 12 months (upper: total analysis, lower: sensitivity analysis after exclusion of the study of Chen et al.). (D) Mean difference of NDI change between the baseline and 24 months (upper: total analysis, lower: sensitivity analysis after exclusion of the study of Shi et al.). Bryan, artificial disc replacement with Bryan prosthesis; Prestige ST, artificial disc replacement with Prestige ST; ADR, artificial disc replacement; ACDF, anterior cervical discectomy and fusion; SD, standard deviation; CI, confidence interval; df, degrees of freedom.
13. JOA at 3 Months
Two studies presented the continuous data for measurement of effect size by mean difference about JOA improvement at 3 months.\textsuperscript{23,24} The data showed no significance between ADR and ACDF with an estimated mean difference of 0.15 (95% CI, -0.27 to 0.57), despite slight supportiveness for ADR (p = 0.48). No heterogeneity was observed (I\(^2\) = 0%) (p = 0.63) (Fig. 5A).

14. JOA at 12 Months
Two studies were available in the measurement of effect size by mean difference of JOA improvement at 12 months.\textsuperscript{20,24} This analysis showed slightly favorable trends toward ADR with an estimated mean difference of 0.34 (95% CI, -0.78 to 1.46), but without statistical significance (p = 0.55). No significant heterogeneity was found (I\(^2\) = 67%) (p = 0.08) (Fig. 5B).

15. JOA at 24 Months
Two studies provided the value of 0.23 (95% CI, -0.18 to 0.64), the effect size measured by the mean difference, which slightly favored ADR without statistical significance (p = 0.28).\textsuperscript{20,22} No significant heterogeneity was found (I\(^2\) = 0%) (p = 0.67) (Fig. 5C).

16. Patients’ Satisfaction at 3 Years
Two studies provided the dichotomous data for measurement of effect size by relative risk ratio about JOA improvement at 3 years, which slightly favored ACDF with estimated risk ratio of 1.06 (95% CI, 0.91–1.23) without statistical significance (p = 0.47).\textsuperscript{19,24} No significant heterogeneity was found (I\(^2\) = 66%) (p = 0.09) (Fig. 5D).

Fig. 5. Forest plot of comparison. (A) Mean difference of Japanese Orthopedic Association scale (JOA) change between the baseline and 3 months. (B) Mean difference of JOA change between the baseline and 12 months. (C) Mean difference of JOA change between the baseline and 24 months. (D) Relative risk ratio of patients’ satisfaction at 3 years. ADR, artificial disc replacement; ACDF, anterior cervical discectomy and fusion; SD, standard deviation; CI, confidence interval; df, degrees of freedom.
17. Level of Evidence and Strength of Recommendation

The ROB was considered to be low (not-problematic or not serious) as previously mentioned. Directness was not considered as problematic because all included studies have directly compared ADR with ACDF. Publication bias was not assessed because fewer than 10 studies were included during each meta-analysis. The consistency was validated to be problematic due to clinical heterogeneity across the selected studies and statistical heterogeneity revealed by I² of some categories of meta-analysis. The degree of precision was also regarded as problematic or serious due to the small number of patients in the selected studies. Ultimately, evidence level determined by GRADE system is evaluated to be low.

Overall, synthetic results of selected studies and meta-analysis showed superior or at least, not inferior clinical outcomes of ADR over ACDF mainly in terms of the functional improvement during the treatment of CM. Although ADR might be costlier or demands more sophisticated surgical details, it might be superior over ACDF for the sake of cervical ROM preservation as well as ASD prevention in addition to the clinical benefits found in meta-analysis.

After all of these analyses and considerations, the authors have concluded that ADR could be recommended over ACDF for the surgical treatment of the patients with CM with weak strength.

DISCUSSION

CM is a form of myelopathy that involves compression of the spinal cord at the cervical level of the spinal column. The radiologically verified CM by MRI or CT scans often results in the clinical/symptomatic myelopathy of neurological deficit of spasticity (sustained muscle contractions), hyperreflexia, pathologic reflexes, loss of fine motor skills (digit/hand clumsiness), loss of balance, and/or subsequent gait disturbance. Usually, this condition prevails in the elderly population with the advanced cervical column degeneration after the repetitive wear-and-tear changes that inflicts over the cervical vertebrae as we age (cervical spondylotic myelopathy).

The benefits of ACDF during CM treatment would be its direct, cervical cord decompressing potential under less invasive operative field compared to the posterior approach, cervical alignment restorative capability, as well as stability provision. However, since the physiological curvature of the cervical spine mainly functions to reduce and buffer the external shock, the straightening or the reversal of the cervical lordosis combined with immobilization of the single or a couple of the functional cervical segments after the ACDF procedures might sometimes propagate the tension of the paravertebral muscles and ligament complex, accelerates the degeneration of the adjacent cervical levels, and consequently incur pains in the neck muscles.

In this regard, the ADR has been accepted as an alternative to ACDF even for the CM populations recently since the same surgical approach and neural decompression is carried out as per ACDF but the motion segment is effectively preserved as well as minimize degenerative changes at adjacent levels as seen in ACDF. Although CM patients have been actually treated with ADR in previous studies, their results are usually mixed in with radiculopathy patients, making it difficult to assess their exclusive outcomes within a specific cohort.

This meta-analysis showed that ADR achieved compatible or better functional outcomes in terms of NDI and JOA in the treatment of CM from 3- to 24-month follow-up compared to ACDF. The NDI assesses the degree of interference of neck pain during daily activities. Therefore, NDI, although this might be the functional score, rather preferentially reflects the neck and upper limb pain severity. JOA evaluates the severity of functional aspect of upper and lower limb, reflecting neurological deficits resulted not only from peripheral nervous system but also from spinal cord or central nervous system. Consequently, the clinical benefits of ADR implementation would be supported in the pain relief, cervical motion maintenance as well as upper or lower limb functional recovery aspect.

A meta-analysis recently published also showed positivity of ADR compared with ACDF, which compared clinical outcomes 2 surgical techniques in patients with CM, making it similar to the current study. But the current study has split the follow-up period from 3 to 24 months and has evaluated the clinical outcomes according to the differential time point, which might be the main differentiated aspect from the prior existing literature. The functional outcomes such as NDI and JOA between the 2 groups were compared after analyzing the improvement in terms of these functional scores rather than the final scores at the follow-up period. This helped to overcome the inconsistency of the preoperative baseline scores across selected studies and eventually further clarified the comparison. In addition, the current study has conducted the sensitivity test or subgroup analysis for the parameters with significantly high heterogeneity. If the outlier study was found, the authors have reanalyzed the parameter after the exclusion of that outlier, which might prompt the statistical robustness.

The few investigated parameters related to the operative pro-
procedure also added the superiority of ADR over the ACDF with or without statistical significance during this analysis. With these purported procedural simplicity as well as benefit such as shorter operative duration with less bleeding or reoperation rates, Hill et al.\textsuperscript{28} has even recommended for a 2-level ADR in the outpatient setting for properly selected patients without increasing the complication or readmission rates.

The ADR group lost less blood during surgery than the ACDF group in this study, of which 4 studies indicated less blood loss of the ADR group in comparison with the ACDF group. Gao et al.\textsuperscript{27} meta-analysis including the patients with radiculopathy, myelopathy, or disc herniation, which is the main difference from our study, showed the opposite results, explaining that increased blood loss was resulted from the keel cuts into cancellous bone required by arthroplasty technique. The main reason of opposite results observed in our study might be that ACDF required more extensive resection in association with large blood loss than ADR in case of myelopathy.

The longer surgical time of ADR than ACDF could be explained by that ADR required more skillful and exact placement of prosthesis to establish physiological axis of rotation, which was essential component of successful surgical results.\textsuperscript{28,29}

Reoperation rate revealed by 3 studies included in this analysis was about 6.67%. This was higher than the previously reported revision rate of 3.9% by another systemic review. This discrepancy might be incurred from lack of the clinical or radiological definition or indication on the prosthesis failure requesting the reoperation across the past references.\textsuperscript{30}

The main concern or controversy with ADR as the surgical choice for CM would be the feasible, repetitive microtrauma that might constantly inflict on the spinal cord after the ROM maintenance at the ADR switched cervical segment.\textsuperscript{31,32} Moreover, other concerns such as higher probability of the incomplete removal of compressive hypertrophied bony or ligament structures or the exaggeration of the cervical mal-alignment when the ADR prosthesis is placed within the kyphotic segment might still exist.\textsuperscript{33,34}

But ADR has been repeatedly acclaimed from its capability to achieve the favorable clinical outcomes while permitting the physiological ROM maintenance without recurrence of pain or functional deficits after surgery in the studies dealing with the ADR applications over the pathologies (such as degenerative spondylolisthesis, radiculopathy, or Modic change) other than CM.\textsuperscript{8,10,33,34} Long-term follow-up studies also showed comparable results with ACDF. A 48-month follow-up study of cervical radiculopathy (and/or myelopathy) has indicated the consistent, sustained significantly superior outcomes for ADR when compared with ACDF.\textsuperscript{35} The statistical superiority of ADR for overall success has persistently extended up to 7-year follow-up period that include biomechanical advantage of angular motion maintenance at the surgical level, less formation of the bridging bone, and lack of adjacent segment angulation increase either proximal or distal to the surgical level.\textsuperscript{36} Overall, these results suggested that biomechanically mobile property of ADR might rather contribute to the better clinical and functional outcomes achievements, dispelling the suspicions such as feared worsening of symptomatic or neurological impairment from keeping its mobility instead of a firm stabilization at the compromised cervical segment even for prolonged period after surgery.

The results of current meta-analysis, the superiority of ADR over ACDF in terms of NDI and JOA, despite statistical insignificance, could be properly interpreted from the fact that, even though the mechanically thorough decompression of compressed spinal cord should be prioritized, the anatomical or physiological preservation of spinal column itself could partly contribute to the functional improvement for the CM subjects instead. Tian et al. have asserted that the limited neck ROM and its subsequent neck stiffness was main cause of disability for those undergoing ACDF and, instead, ADR could solve this problem.\textsuperscript{37}

Another concern might be the segmental kyphosis development or exaggeration after the ADR switch. The Bryan (Sofamor Danek, Memphis, TN, USA) prosthesis previously showed the less capacity to restore the regional lordosis due to the lack of anterior column support.\textsuperscript{38,39} However, more proper patient selection and technical modifications such as over-milling of the endplate’s avoidance enabled the Bryan prosthesis to overcome this default.\textsuperscript{40} Even ACDF also has the concerns of segmental kyphotic change, further leading to worse clinical outcomes, associated with subsidence of intervertebral cages.\textsuperscript{41}

The patients in selected studies were mostly affected with single or 2 levels of CM and probably an extensive decompression was not mandated. This might have attributed to an excuse that the inadequate decompression from the incomplete removal of the neighboring structures compressing the spinal cord, one of the concerns after ADR for CM, was not brought up as a serious issue during this analysis. The multiple segment involvements caused more different pattern of biomechanical instability or substantial alignment change than single segment pathology.\textsuperscript{42,43} This analysis has supported that the ADR might be beneficial during the surgical management of few segments involved CM, whereas its clinical implication on the multilevel CM that is often fraught with extensive ligament hypertrophy is
still yet to be supported. It could be assumed that, while the multiple segments arthroplasty might be inferior in terms of inadequacy of decompression or insufficient removal, multilevel fusion surgery might be vulnerable to a significant destabilization after the extensive decompression or might prompt a more severe adjacent disc degenerative process.\(^7\,44,45\) Meanwhile, even in patients with nonlordotic alignment but without major kyphotic deformity, ADR had the potential to generate and maintain lordosis and improve patient-reported outcome measures in the short-term post-surgical results.\(^46\)

This study has several limitations. Firstly, the number of selected studies was small and available data was not sufficient for conducting meta-analysis in more extensive categories for a longer outcome period over 3 years. The primary distinction of this research from the existing literature might be the stepped follow-up points analysis. However, the inadequate number of studies at each follow-up point severely compromises the meta-analysis quality and caused serious statistical heterogeneity in some parameters. Secondly, there were differences in methodology across the studies, which might produce clinical heterogeneity. Thirdly, the restricted number of studies for each parameter was not enough to conduct subgroup analysis when there was significant heterogeneity. Fourthly, CIs in some categories were too widely ranged for achieving precision or accuracy. All these aspects lowered evidence level to low, consequently weaken the strength of meta-analysis. Further study with larger number of relevant articles in the future would be needed to provide the meta-analysis that would be more statistically powerful.

**CONCLUSION**

ADR was superior or at least, not inferior to ACDF in terms of functional recovery. However, its application to the CM patients is merely empowered with weak strength due to low level of evidence.

**NOTES**

Supplementary Material: Supplementary material can be found via https://doi.org/10.14245/ns.2346498.249.

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**ORCID**

Jung Hwan Lee: 0000-0003-2680-6953

Youn Joo Lee: 0000-0002-5818-9542

Min Cheol Chang: 0000-0002-7629-7213

Jun Ho Lee: 0000-0001-6246-8053

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Traditional Dual Growing Rods With 2 Different Apical Control Techniques in the Treatment of Early-Onset Scoliosis

Shengru Wang*, Yiwei Zhao*, Guanfeng Lin, You Du, Yang Yang, Jianguo Zhang
Department of Orthopedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Objective: Based on traditional dual growing rods (TDGR), apical control techniques (ACTs) were introduced as adjuvant procedures to improve deformity correction at the apex segment in the treatment of early-onset scoliosis (EOS). We aimed to explore whether TDGR+ACTs have different indications, attain more deformity correction, have negative effects on spinal growth, and have different complications.

Methods: Between 2004 and 2019, a retrospective study of EOS patients treated with TDGR with or without ACTs was conducted and divided into 3 groups: TDGR group; hybrid technique (HT) group: Vertebrectomy/hemivertebrectomy with short fusion and TDGR; ACPS group: apical convex control pedicle screws (ACPS) and TDGR. Demographic, radiographic parameters, clinical outcomes, complications, and revisions were analyzed and compared.

Results: Seventy-eight EOS patients were enrolled. The preoperative main curve was the largest in the HT group. ACPS group had the smallest residual curve (19° ± 8.9°) and apical vertebral translation (12.0 ± 9.0 mm) at the latest follow-up, followed by the HT group (30° ± 17.4°, 22.1 ± 13.4 mm) and TDGR group (30° ± 13.2°, 32.8 ± 17.1 mm). ACPS group had the largest T1–12 height and T1–S1 height after index surgery. Complications and revisions in the ACTs groups was lower than the TDGR group. Scoliosis Research Society-22 self-image questionnaire was superior in the ACPS group.

Conclusion: According to our intermediate results, TDGR+ACTs could improve correction ability of apex deformity. ACTs had little deleterious effects on spinal height during the lengthening procedures, with a lower complication rate than TDGR. TDGR+ACTs might be a supplemental option for suitable EOS patients.

Keywords: Apical convex control pedicle screws, Apical control technique, Complications, Hybrid technique, Spine growth, Traditional dual growing rods

INTRODUCTION

Early-onset scoliosis (EOS) is one of the most challenging deformity in spine surgery, as patients with EOS still have great and important growth potential of the lung, thorax and spine.¹ Surgeons must consider the growth of these important structures when treating these children. Early long fusion for EOS patients who are far from bone mature should be avoided to prevent iatrogenic thoracic insufficiency syndrome.² Many growth-friendly techniques have been introduced to correct the deformity while allowing growth of the spine and thorax,³ ⁸ and traditional dual growing rods (TDGR) are the most widely used procedures.

The clinical outcomes of TDGR have been well described.⁹ ¹² However, there are still some challenges for TDGR, including repeated anesthesia and surgeries, large residual deformities, limited apex control, and a high risk of complications (Fig. 1).⁵ ⁹ ¹³ ¹⁶ Large residual deformities and limited apex control due to the
biomechanical limitations of TDGR may contribute to the 3-dimensional chest and spinal deformity, especially narrowing and rigidity of the convex hemithorax as the spine penetrates into the convex chest because of coronal translation, axial rotation and lordosis. To address this issue, surgeons reported several techniques to improve apical control of the curve when using growth-friendly techniques, including Luque-Trolley technique,17 Shilla technique18,19 and TDGR combined with apical control techniques (ACTs). Wang et al.20 and Johnston21 building on the experience of TDGR, introduced 2 different ACTs, hybrid technique (HT, apical vertebrectomy/hemivertebrectomy and short fusion) and apical control pedicle screws (ACPS), aiming to improve correction of the apical deformity and decrease complications. As a relatively new technique, the results of TDGR+

ACTs remain unclear. A prior study conducted a comparative study of HT and TDGR techniques on congenital EOS (CEOS) patients,21 and the preliminary results showed better deformity correction and fewer complications in the HT group. However, CEOS were different from EOS caused by other etiologies, some type of CEOS may progress quickly at a very young age, which is prone to result in a more severe and rigid deformity than other etiologies.22,23 Besides, congenital scoliosis is often associated with abnormalities in other systems derived from mesoderm, among which spinal cord, cardiac and genitourinary tract abnormalities are commonly concomitant,24 which may also cause a potential impact on clinical outcomes.

We therefore compared HT, ACPS and TDGR in EOS patients, and asked whether apical control technique (1) have different indication, (2) attain more deformity correction, (3) have negative effects on spinal growth, and (4) have different complications?

MATERIALS AND METHODS

1. Participants and Demographics

Following Institutional Review Board approval of Peking Union Medical College Hospital (K2138), a single-center, retrospective study was conducted. Patients diagnosed with EOS and underwent growing rod technique between March 2004 and December 2019 were considered potentially eligible for recruitment in this study. A total of 186 EOS patients treated with growing rod technique, 10.22% (19 of 186) of patients treated with single growing rod were excluded. Based on the surgical method used, the patients were divided in the TDGR (n = 119), HT (n = 29), and ACPS (n = 19) group. A flowchart showed the recruitment process of the current study (Fig. 2).

In the TDGR group, 21.01% (25 of 119) patients short of 3-year follow-up was excluded, 12.61% (15 of 119) patients without regular follow-up were excluded, and 25.21% (30 of 119) patients lack of preoperative and/or postoperative radiographic data were excluded, leaving 41.18% (49 of 119) for analysis.

In the HT group, 13.79% (4 of 29) patients short of 3-years follow-up was excluded, 17.24% (5 of 29) patients without regular follow-up were excluded, and 3.45% (1 of 29) patients lack of preoperative and/or postoperative radiographic data were excluded, leaving 65.52% (19 of 29) for analysis.

In the ACPS group, 26.32% (5 of 19) patients short of 3-years follow-up was excluded, 21.05% (4 of 19) patients without regular follow-up were excluded, leaving 52.63% (10 of 19) for analysis.

Fig. 1. A case of traditional dual growing rods (TDGR) to treat early-onset scoliosis. (A) A 3-year-old girl with severe congenital deformities caused by multiple segmentation failures in the thoracic spine. (B) TDGR was applied to correct the deformity while allowing for the growth of the spine and thorax. (C, D) However, the residual spine and chest deformities were large, and a “Windswept” thorax causing by apical coronal translation, axial rotation and along lordosis still existed during lengthening procedures at 6 years. High-grade osteotomy such as a 3-column osteotomy with increased complications in a stiff spine may be mandatory to correct residual spine and chest deformities.
Fig. 2. A flowchart showed the recruitment process of the current study. EOS, early-onset scoliosis; HT, hybrid technique; TDGR, traditional dual growing rods; ACPS, apical control pedicle screws.

Fig. 3. A case of hybrid technique (HT) to treat early-onset scoliosis. (A–D) A 7-year-old boy with severe congenital early-onset scoliosis due to multiple formation and segmentation failures. HT was applied. T9 vertebral column resection and short fusion were performed. Growing rods were implanted with a 6-rod technique from T2–L3. (E, F) The correction of the main curve was good after index surgery and was well maintained. (G, H) Significant growth of the spine and thorax was observed after 3 lengthening procedures. T1–T12 height: 12.1 cm to 14.2 cm to 17.7 cm; T1–S1 height: 21.3 cm to 26.6 cm to 33.1 cm (pre- to post- to follow-up).
2. Treatment Algorithm and Reference

Both TDGR and TDGR+ACTs were used to treat EOS patients in our institution. In principle and practice, most TDGR was indicated for: (1) failure of treatment with bracing or casting, (2) curve more than 60°, (3) ages younger than 10 years old, (4) diagnose with all etiology. ACTs were introduced in recent years, as relatively novel technologies, no clear indication has been proposed or confirmed. We used HT as ACT in patients with rigid and severe curves (most were congenital formation or segmentation failures at apex segment) (Fig. 3) while using ACPS described by Johnston in relatively flexible curves (mostly had flexible discs at apex segments, such as idiopathic, syndromic or neuromuscular scoliosis) (Fig. 4). The convex spine bending film was also used to evaluate the curve flexibility in all patients and as a reference for choosing the ACTs.

3. Measurement of Study Outcomes

Data for all patients were reported at the preoperative, postoperative, and latest follow-up visits within the study period. To answer our question, data included demographic information, radiographic parameters (corrective parameters of scoliosis, spinal growth parameters), complications and revision procedures was measured. All radiographs were evaluated blindly by 2 well-trained attending spine surgery surgeons. A Scoliosis Re-

Fig. 4. A case of ACPS to treat early-onset scoliosis. (A–D) A 3-year-old girl with idiopathic scoliosis with severe rotation and mild kyphosis. ACPS was used at the apex, and growing rods were implanted with a 4-rod technique from T6–L4. (E, F) Good correction was obtained immediately after the index surgery. (G, H) The residual spine and chest deformities were mild, and significant growth of the spine and thorax was observed after 8 lengthening procedures in 8 years. The T1–T12 height: 15.1 cm to 17.5 cm to 21.2 cm; T1–S1 height: 23.0 cm to 28.0 cm to 34.4 cm (pre- to post- to follow-up).
search Society (SRS)-22 questionnaire was used as an outcome measure at the latest follow-up in patients who were old enough to complete the questionnaire.

4. Statistical Analyses
Analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation. All continuous variables were tested for normal distribution, using t-test for data that conformed to normal distribution and nonparametric test for data that did not conform to normal distribution (Kruskal-Wallis test for comparison among 3 groups and Mann-Whitney U-test for comparison between the 2 groups). For categorical variables, the chi-square test and Fisher exact test were used. Comparisons at different time points were analyzed. A p-value of < 0.05 was considered as statistically significant.

Table 1. Demographic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT group (n = 19)</th>
<th>TDGR group (n = 49)</th>
<th>ACPS group (n = 10)</th>
<th>p-value†</th>
<th>p-value‡</th>
<th>p-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>49</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology, CS:non-CS</td>
<td>15:4</td>
<td>40:9</td>
<td>5:5</td>
<td>0.094</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classification of CS</td>
<td>0.102</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Failure of formation</td>
<td>6</td>
<td>16</td>
<td>3</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Failure of segmentation</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>7</td>
<td>13</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>4:15</td>
<td>13:36</td>
<td>6:4</td>
<td>0.069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at index surgery (yr)</td>
<td>6.9 ± 2.5</td>
<td>7.2 ± 2.1</td>
<td>7.6 ± 2.6</td>
<td>0.642</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of lengthenings</td>
<td>5.1 ± 2.5</td>
<td>5.9 ± 2.3</td>
<td>4.9 ± 1.6</td>
<td>0.248</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration (yr)</td>
<td>6.6 ± 2.1</td>
<td>5.8 ± 2.3</td>
<td>5.2 ± 2.7</td>
<td>0.399</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduation</td>
<td>5</td>
<td>11</td>
<td>3</td>
<td>0.105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final fusion</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retained and observation</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± standard deviation.
HT, hybrid technique; TDGR, traditional dual growing rods; ACPS, apical control pedicle screws; CS, congenital scoliosis.
† p-value refers to statistic value among 3 groups.

Table 2. Comparison of the coronal radiographic parameters of deformity

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT group</th>
<th>TDGR group</th>
<th>ACPS group</th>
<th>p-value†</th>
<th>p-value‡</th>
<th>p-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main curve (°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>80 ± 21.1</td>
<td>62 ± 16.6</td>
<td>62 ± 11.2</td>
<td>0.000</td>
<td>0.016</td>
<td>0.968</td>
</tr>
<tr>
<td>Flexibility (%)</td>
<td>21.3 ± 7.6</td>
<td>30.7 ± 14.4</td>
<td>52.4 ± 10.7</td>
<td>0.136</td>
<td>0.005</td>
<td>0.012</td>
</tr>
<tr>
<td>Post</td>
<td>29 ± 14.9</td>
<td>29 ± 13.5</td>
<td>21 ± 9.5</td>
<td>0.994</td>
<td>0.116</td>
<td>0.064</td>
</tr>
<tr>
<td>F/U</td>
<td>30 ± 17.4</td>
<td>30 ± 13.2</td>
<td>19 ± 8.9</td>
<td>0.972</td>
<td>0.067</td>
<td>0.014</td>
</tr>
<tr>
<td>Primary correction rate</td>
<td>0.65 ± 0.13</td>
<td>0.54 ± 0.15</td>
<td>0.65 ± 0.13</td>
<td>0.005</td>
<td>0.652</td>
<td>0.010</td>
</tr>
<tr>
<td>Total correction rate</td>
<td>0.64 ± 0.18</td>
<td>0.50 ± 0.23</td>
<td>0.64 ± 0.18</td>
<td>0.020</td>
<td>0.428</td>
<td>0.013</td>
</tr>
<tr>
<td>ΔMCa</td>
<td>51 ± 11.4</td>
<td>33 ± 10.4</td>
<td>41 ± 7.1</td>
<td>0.000</td>
<td>0.02</td>
<td>0.025</td>
</tr>
<tr>
<td>ΔMCb</td>
<td>50 ± 14.5</td>
<td>32 ± 15.2</td>
<td>43 ± 12.2</td>
<td>0.000</td>
<td>0.198</td>
<td>0.038</td>
</tr>
<tr>
<td>AVT (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>44.1 ± 15.3</td>
<td>40.2 ± 14.9</td>
<td>55.1 ± 10.2</td>
<td>0.323</td>
<td>0.180</td>
<td>0.002</td>
</tr>
<tr>
<td>Post</td>
<td>23.3 ± 13.0</td>
<td>24.4 ± 14.1</td>
<td>17.0 ± 9.5</td>
<td>0.778</td>
<td>0.188</td>
<td>0.122</td>
</tr>
<tr>
<td>F/U</td>
<td>22.1 ± 13.4</td>
<td>32.8 ± 17.1</td>
<td>12.0 ± 9.0</td>
<td>0.017</td>
<td>0.042</td>
<td>0.000</td>
</tr>
<tr>
<td>ΔAVTa</td>
<td>20.8 ± 13.0</td>
<td>15.9 ± 13.4</td>
<td>38.1 ± 11.9</td>
<td>0.172</td>
<td>0.002</td>
<td>0.000</td>
</tr>
<tr>
<td>ΔAVTb</td>
<td>22.1 ± 16.1</td>
<td>7.5 ± 16.7</td>
<td>43.11 ± 17.2</td>
<td>0.002</td>
<td>0.003</td>
<td>0.000</td>
</tr>
<tr>
<td>TS (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>25.1 ± 15.2</td>
<td>20.5 ± 19.7</td>
<td>16.6 ± 15.1</td>
<td>0.104</td>
<td>0.090</td>
<td>0.524</td>
</tr>
<tr>
<td>Post</td>
<td>19.5 ± 13.1</td>
<td>15.0 ± 10.2</td>
<td>17.3 ± 9.3</td>
<td>0.226</td>
<td>0.663</td>
<td>0.467</td>
</tr>
<tr>
<td>F/U</td>
<td>18.0 ± 14.7</td>
<td>18.8 ± 16.0</td>
<td>18.3 ± 10.4</td>
<td>0.989</td>
<td>0.696</td>
<td>0.716</td>
</tr>
<tr>
<td>ΔTSa</td>
<td>5.6 ± 19.2</td>
<td>5.5 ± 17.6</td>
<td>-0.7 ± 13.8</td>
<td>0.707</td>
<td>0.302</td>
<td>0.262</td>
</tr>
<tr>
<td>ΔTSb</td>
<td>7.1 ± 19.7</td>
<td>1.7 ± 17.0</td>
<td>-1.7 ± 15.9</td>
<td>0.267</td>
<td>0.237</td>
<td>0.564</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
HT, hybrid technique; TDGR, traditional dual growing rods; ACPS, apical control pedicle screws; AVT, apical vertebral translation; TS, trunk shift; F/U, follow-up; Δa, postindex minus preindex parameters; Δb, F/U minus preindex parameters.
† p-value: † comparison between HT and TDGR groups. ‡ comparison between HT and ACPS groups. § comparison between ACPS and TDGR groups.

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RESULTS

Seventy-eight patients were finally enrolled, including 49 patients in the TDGR group, 19 patients in the HT group and 10 patients in the ACPS group. The etiology of congenital scoliosis was 15 of 19 in the HT group (6 with formation failure, 2 with segmentation failure, 7 with mixed type), 40 of 49 in the TDGR group (16 with formation failure, 11 with segmentation failure, 13 with mixed type) and 5 of 10 in the ACPS group (3 with formation failure, 1 with segmentation failure, 1 with mixed type). The curve flexibility in convex bending film was 52.4% ± 10.7% in the ACPS group, 30.7% ± 14.4% in the TDGR group, and 21.3% ± 7.6% in the HT group. There were no differences in the mean age, number of lengthening or lengthening treatment duration (Table 1). Nineteen patients graduated from lengthening procedures, 10 of them received final fusion surgery and 9 just retained growing rods under regular follow-up.

Table 3. Comparisons of the growth of spine and the chest

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT group</th>
<th>TDGR group</th>
<th>ACPS group</th>
<th>p-value †</th>
<th>p-value ‡</th>
<th>p-value §</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1–T12 height (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>14.9 ± 3.6</td>
<td>15.4 ± 3.9</td>
<td>17.6 ± 1.8</td>
<td>0.660</td>
<td>0.035</td>
<td>0.009</td>
</tr>
<tr>
<td>Post</td>
<td>16.9 ± 3.9</td>
<td>16.6 ± 3.7</td>
<td>19.9 ± 1.8</td>
<td>0.784</td>
<td>0.029</td>
<td>0.008</td>
</tr>
<tr>
<td>F/U</td>
<td>20.4 ± 3.7</td>
<td>20.7 ± 4.5</td>
<td>23.2 ± 2.6</td>
<td>0.788</td>
<td>0.039</td>
<td>0.085</td>
</tr>
<tr>
<td>ΔT1–T12a</td>
<td>2.0 ± 1.3</td>
<td>1.2 ± 2.2</td>
<td>2.3 ± 1.2</td>
<td>0.183</td>
<td>0.493</td>
<td>0.144</td>
</tr>
<tr>
<td>ΔT1–T12b</td>
<td>3.5 ± 2.3</td>
<td>4.1 ± 2.7</td>
<td>3.3 ± 1.9</td>
<td>0.400</td>
<td>0.838</td>
<td>0.397</td>
</tr>
<tr>
<td>Annual growth</td>
<td>0.6 ± 0.5</td>
<td>0.8 ± 0.7</td>
<td>0.7 ± 0.4</td>
<td>0.322</td>
<td>0.632</td>
<td>0.724</td>
</tr>
<tr>
<td>T1–S1 height (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>25.5 ± 4.8</td>
<td>25.2 ± 5.9</td>
<td>28.9 ± 3.2</td>
<td>0.811</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Post</td>
<td>29.4 ± 5.1</td>
<td>27.9 ± 5.8</td>
<td>32.7 ± 3.1</td>
<td>0.316</td>
<td>0.078</td>
<td>0.014</td>
</tr>
<tr>
<td>F/U</td>
<td>34.5 ± 4.3</td>
<td>35.1 ± 5.7</td>
<td>37.7 ± 3.3</td>
<td>0.687</td>
<td>0.051</td>
<td>0.169</td>
</tr>
<tr>
<td>ΔT1–S1a</td>
<td>3.9 ± 1.7</td>
<td>2.8 ± 2.7</td>
<td>3.8 ± 1.1</td>
<td>0.084</td>
<td>0.887</td>
<td>0.22</td>
</tr>
<tr>
<td>ΔT1–S1b</td>
<td>5.0 ± 3.5</td>
<td>7.1 ± 4.0</td>
<td>4.9 ± 2.4</td>
<td>0.081</td>
<td>0.971</td>
<td>0.104</td>
</tr>
<tr>
<td>Annual growth</td>
<td>1.1 ± 1.1</td>
<td>1.4 ± 1.1</td>
<td>1.1 ± 0.6</td>
<td>0.443</td>
<td>0.953</td>
<td>0.481</td>
</tr>
<tr>
<td>SAL ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.8 ± 0.10</td>
<td>0.9 ± 0.09</td>
<td>0.9 ± 0.06</td>
<td>0.031</td>
<td>0.029</td>
<td>0.432</td>
</tr>
<tr>
<td>Post</td>
<td>1.0 ± 0.07</td>
<td>1.0 ± 0.06</td>
<td>1.0 ± 0.04</td>
<td>0.852</td>
<td>0.787</td>
<td>0.885</td>
</tr>
<tr>
<td>F/U</td>
<td>1.0 ± 0.05</td>
<td>1.0 ± 0.06</td>
<td>1.0 ± 0.04</td>
<td>0.443</td>
<td>0.024</td>
<td>0.130</td>
</tr>
<tr>
<td>ΔSAL1</td>
<td>0.1 ± 0.12</td>
<td>0.1 ± 0.06</td>
<td>0.1 ± 0.04</td>
<td>0.031</td>
<td>0.059</td>
<td>0.197</td>
</tr>
<tr>
<td>ΔSAL2</td>
<td>0.2 ± 0.11</td>
<td>0.1 ± 0.09</td>
<td>0.1 ± 0.08</td>
<td>0.157</td>
<td>0.310</td>
<td>0.940</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
HT, hybrid technique; TDGR, traditional dual growing rods; ACPS, apical control pedicle screws; SAL, space available for lung; F/U, follow-up; Δa, postindex minus preindex parameters; Δb, F/U minus postindex parameters; Δ1, postindex minus preindex parameters; Δ2, F/U minus preindex parameters.
p-value: † comparison between HT and TDGR groups. ‡ comparison between HT and ACPS groups. § comparison between ACPS and TDGR groups.

1. Correction of the Deformity

The preoperative main curve was the largest in the HT group among 3 groups, while the preoperative apical vertebral translation (AVT) was larger in the ACPS group. Patients in the ACPS group had the smallest residual curve (19° ± 8.9°) and AVT (12.0 ± 9.0 mm) at the latest follow-up, followed by the HT group (30° ± 17.4°, 22.1 ± 13.4 mm) and TDGR group (30° ± 13.2°, 32.8 ± 17.1 mm). The correction rate of the main curve at the latest follow-up was comparable between the HT (64%) and ACPS (64%) groups and was higher than that of the TDGR group (50%) (Table 2). No differences were found in sagittal parameters among the 3 groups after index surgery and during follow-up (Table 3).

2. Gain of Spinal Height

Patients in the ACPS group had the largest T1–12 height and T1–S1 height before and after index surgery, while the parame-
ters in the other 2 groups were comparable at any observation time. No significant differences were found in the annual growth of T1–12 height and T1–S1 height during the lengthening procedures in the 3 groups. Preoperative space available for lung (SAL) was smallest in the HT group. However, no differences were found in SAL among the 3 groups at either the postindex surgery or latest follow-up time points (Table 4).

3. Complications and Patient-Reported Clinical Outcomes

Sixteen complications occurred in 10 patients in the HT group (12 mechanical-related complications, 2 wound problems, 1 dural tear, and 1 neurological deficit; Fig. 5), 71 complications occurred in 32 patients in the TDGR group (65 mechanical-related complications, 5 wound problems, and 1 dural tear), and 5 complications occurred in 4 patients in the ACPS group (4 mechanical-related complications and 1 wound problem). The mean number of total complications, mechanical-related complications and unanticipated revision surgeries was comparable between the HT group and the ACPS group and was lower than that of the TDGR group. Thirty-eight patients could complete the SRS-22 questionnaire at the latest follow-up, and SRS-22 self-image score was superior in ACPS group among the 3 group at the latest follow-up, while the other 2 group were comparable (Table 5).

Table 4. Comparison of the sagittal radiographic parameters of deformity

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT group</th>
<th>TDGR group</th>
<th>ACPS group</th>
<th>p-value</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TK (°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>34 ± 16.9</td>
<td>27 ± 19.6</td>
<td>25 ± 8.1</td>
<td>0.169</td>
<td>0.119</td>
<td>0.741</td>
</tr>
<tr>
<td>Post</td>
<td>20 ± 9.5</td>
<td>16 ± 11</td>
<td>15 ± 8.4</td>
<td>0.152</td>
<td>0.186</td>
<td>0.849</td>
</tr>
<tr>
<td>F/U</td>
<td>25 ± 9.4</td>
<td>21 ± 14.1</td>
<td>19 ± 12.8</td>
<td>0.248</td>
<td>0.163</td>
<td>0.701</td>
</tr>
<tr>
<td>TLC (°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>6 ± 18.3</td>
<td>9 ± 13.4</td>
<td>14 ± 11.0</td>
<td>0.467</td>
<td>0.208</td>
<td>0.25</td>
</tr>
<tr>
<td>Post</td>
<td>4 ± 6.7</td>
<td>6 ± 6.1</td>
<td>5 ± 4.9</td>
<td>0.352</td>
<td>0.818</td>
<td>0.62</td>
</tr>
<tr>
<td>F/U</td>
<td>6 ± 12.0</td>
<td>10 ± 8.8</td>
<td>10 ± 5.7</td>
<td>0.103</td>
<td>0.301</td>
<td>0.102</td>
</tr>
<tr>
<td>LL (°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>50 ± 14.6</td>
<td>45 ± 15.2</td>
<td>47 ± 11.6</td>
<td>0.263</td>
<td>0.518</td>
<td>0.831</td>
</tr>
<tr>
<td>Post</td>
<td>45 ± 10.8</td>
<td>40 ± 11.6</td>
<td>43 ± 9.8</td>
<td>0.091</td>
<td>0.577</td>
<td>0.453</td>
</tr>
<tr>
<td>F/U</td>
<td>47 ± 12.2</td>
<td>45 ± 13.1</td>
<td>51 ± 14.2</td>
<td>0.655</td>
<td>0.582</td>
<td>0.247</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. HT, hybrid technique; TDGR, traditional dual growing rods; ACPS, apical control pedicle screws; TK, thoracic kyphosis; TLC, thoraco-lumbar junction curve; LL, lumbar lordosis; F/U, follow-up. p-value: †comparison between HT and TDGR groups. ‡comparison between HT and ACPS groups. §comparison between ACPS and TDGR groups.

4. Outcomes of Surgical Variables

The mean surgical time of index surgery was 216.32 ± 27.73 minutes in the HT group, 148.16 ± 24.30 minutes in the TDGR group and 158.10 ± 32.93 minutes in the ACPS group. The estimated blood loss was 276.32 ± 96.62 mL in the HT group, 91.22 ± 76.28 mL in the TDGR group and 106.01 ± 42.99 mL in the ACPS group. The length of stay was 15.00 ± 2.21 days in the HT group, 11.20 ± 2.10 days in the TDGR group and 11.80 ± 1.93 days in the ACPS group. One positive intraoperative neurological monitoring event occurred in the HT group (Table 6).

DISCUSSION

TDGR is the most widely used distraction-based growth-friend-ly technique for EOS.29 Due to biomechanical limitations of simple distraction through end-vertebral anchors, it may only partially control the 3-dimensional spinal and chest deformity.29 Therefore, ACTs were introduced to improve the control of the apical deformity when TDGR was applied. Different ACTs were applied in different EOS patients, and evaluation of apical deformity flexibility should be the key consideration when choosing ACT. Johnston used convex control pedicle screws to improve deformity correction by direct apex derotation and translation while allowing for concave growth.14,15 They enrolled patients for the ACPS technique included: Large curves and short T1–12 segments (range, 8.5–14.4 cm) in patients 5 years of age or less, with significant axial plane deformity. However, direct apex derotation and translation with ACPS could only be used in relatively flexible curves, as this technique could hardly work in patients with angular and rigid deformity, such as CEOS with multiple formation and segmentation failures. ACPS might be best indicated for patients whose apical deformity is flexible with relatively normal discs, without multiple formation or segmentation failures. The ACPS group is treated with a more flexible curve in our institution, with an average flexibility of 52.4%. Therefore, we propose the indication for the ACPS technique: (1) failure of treatment with bracing or casting, (2) ages younger than 10 years old, (3) degree of curvature of more than 60° with large AVT and AVR at the apical segment, (4) flexible disc at the apical segment. However, based on the current results, we are unable to quantify AVT and AVR. Furthermore, as previously reported, the TDGR results for CEOS were not as good as those caused by other etiologies.12,30 HT technique was first reported by Wang et al.28 in 2014, and by apical vertebrectomy/hemivertebrectomy and short fusion, the apical rigid, severe deformity at apex segment could be better addressed. The indi-

https://doi.org/10.14245/ns.2346406.203
cition was also based on the TDGR technique, and the ideal candidate for the HT technique was: severe and rigid EOS at the apical segment with a long sweeping curve, which has pronounced asymmetric growth potential around the apex. In this study, we also followed and standardized the indication as follows: (1) failure of treatment with bracing or casting, (2) ages younger than 10 years old, (3) severe and rigid deformity at the apical segment with a long sweeping curve. As the high-grade osteotomy needed advanced technique and increased surgical difficulty, we only used the HT technique to treat severe and rigid EOS patients (most of them were CEOS). We have developed a preliminary workflow of ACT choice for the treatment of EOS (Fig. 6), and further study by setting flexibility thresholds may help to develop indications for different ACTs.

Attaining a better deformity correction was a major surgical goal for EOS treatment. Alanay et al. and Demirkiran et al. reported the effectiveness of posterior convex growth arrest with pedicle screws and concave distraction with traditional growing rods or magnetically controlled growing rods for the treatment of patients with long sweeping congenital curves. The correction of the main curve at the latest follow-up was about 41.3% (60.5° to 35.5°), and spine growth was achieved during concave

Fig. 5. Patients with a complication of neurological deficits. (A, B) A 9-year-old girl with severe and rigid congenital early-onset scoliosis without preoperative neurological deficits. She underwent HT surgery. The motor-evoked potential loss (more than 80%) was shown when we performed T11 hemivertebrectomy. We chose to complete the osteotomy quickly to control bleeding, raised mean arterial pressure and used methylprednisolone. After that, the signal partially recovered from the lowest point. The patient showed transient motor function deficits of the left lower limbs, and recovered to preoperative status at 6 months. The correction of the main curve was good after index surgery (C, D) and was well maintained (E–H).
Table 5. SRS-22 scores and complications in 3 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT group</th>
<th>TDGR group</th>
<th>ACPS group</th>
<th>p-value†</th>
<th>p-value‡</th>
<th>p-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-reported outcomes (n)</td>
<td>9</td>
<td>23</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS-22 total</td>
<td>4.0 ± 0.28</td>
<td>4.0 ± 0.24</td>
<td>4.1 ± 0.18</td>
<td>0.779</td>
<td>0.57</td>
<td>0.318</td>
</tr>
<tr>
<td>SRS-22 function</td>
<td>3.8 ± 0.24</td>
<td>3.9 ± 0.27</td>
<td>4.0 ± 0.43</td>
<td>0.576</td>
<td>0.45</td>
<td>0.593</td>
</tr>
<tr>
<td>SRS-22 pain</td>
<td>4.4 ± 0.41</td>
<td>4.3 ± 0.36</td>
<td>4.3 ± 0.51</td>
<td>0.604</td>
<td>0.618</td>
<td>0.775</td>
</tr>
<tr>
<td>SRS-22 self-image</td>
<td>3.6 ± 0.57</td>
<td>3.6 ± 0.63</td>
<td>4.1 ± 0.37</td>
<td>0.905</td>
<td>0.059</td>
<td>0.033</td>
</tr>
<tr>
<td>SRS-22 mental-health</td>
<td>4.0 ± 0.40</td>
<td>3.9 ± 0.42</td>
<td>4.0 ± 0.26</td>
<td>0.81</td>
<td>0.836</td>
<td>0.67</td>
</tr>
<tr>
<td>SRS-22 satisfaction</td>
<td>4.2 ± 0.66</td>
<td>4.0 ± 0.67</td>
<td>4.0 ± 0.62</td>
<td>0.644</td>
<td>0.632</td>
<td>0.887</td>
</tr>
<tr>
<td>Total No. of complications</td>
<td>16</td>
<td>71</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients had complications</td>
<td>10</td>
<td>32</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of complications/per patient</td>
<td>0.79 ± 0.92</td>
<td>1.43 ± 1.14</td>
<td>0.50 ± 0.71</td>
<td>0.055</td>
<td>0.439</td>
<td>0.018</td>
</tr>
<tr>
<td>No. of mechanical-related</td>
<td>0.63 ± 0.68</td>
<td>1.33 ± 1.05</td>
<td>0.40 ± 0.52</td>
<td>0.032</td>
<td>0.59</td>
<td>0.023</td>
</tr>
<tr>
<td>Total no. of revision surgeries</td>
<td>5</td>
<td>30</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of revision surgeries/per patient</td>
<td>0.26 ± 0.56</td>
<td>0.61 ± 0.57</td>
<td>0.10 ± 0.32</td>
<td>0.035</td>
<td>0.431</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Types of complications

| Mechanical-related                | 12       | 65         | 4          |          |          |          |
| Rod breakage                     | 0        | 3          | 1          |          |          |          |
| Hook dislodgement                | 1        | 20         | 0          |          |          |          |
| Screw loosening                  | 3        | 13         | 1          |          |          |          |
| Cap dislodgement                 | 1        | 2          | 0          |          |          |          |
| Proximal junctional kyphosis     | 2        | 9          | 2          |          |          |          |
| Distal junctional kyphosis       | 0        | 1          | 0          |          |          |          |
| Coronal imbalance                | 5        | 17         | 0          |          |          |          |
| Wound problems                   | 2        | 5          | 1          |          |          |          |
| Delayed healing                  | 1        | 4          | 0          |          |          |          |
| Infection                        | 1        | 1          | 1          |          |          |          |
| Dural tear                       | 1        | 1          | 0          |          |          |          |
| Neurological deficits            | 1        | 0          | 0          |          |          |          |

Values are presented as mean ± standard deviation or number.
HT, hybrid technique; TDGR, traditional dual growing rods; ACPS, apical control pedicle screws; SRS, Scoliosis Research Society.
p-value: †comparison between HT and TDGR groups. ‡comparison between HT and ACPS groups. §comparison between ACPS and TDGR groups.

Table 6. Surgical variables among 3 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT group</th>
<th>ACPS group</th>
<th>TDGR group</th>
<th>p-value†</th>
<th>p-value‡</th>
<th>p-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBL</td>
<td>276.32 ± 96.62</td>
<td>91.22 ± 76.28</td>
<td>106.01 ± 42.99</td>
<td>0.000</td>
<td>0.000</td>
<td>0.557</td>
</tr>
<tr>
<td>Surgical time</td>
<td>216.32 ± 27.73</td>
<td>148.16 ± 24.30</td>
<td>158.10 ± 32.93</td>
<td>0.000</td>
<td>0.000</td>
<td>0.277</td>
</tr>
<tr>
<td>Length of stay</td>
<td>15.00 ± 2.21</td>
<td>11.20 ± 2.10</td>
<td>11.80 ± 1.93</td>
<td>0.000</td>
<td>0.000</td>
<td>0.411</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
HT, hybrid technique; ACPS, apical control pedicle screws; TDGR, traditional dual growing rods; EBL, Estimated blood loss.
p-value: †comparison between HT and TDGR groups. ‡comparison between HT and ACPS groups. §comparison between ACPS and TDGR groups.

distraction. Three column osteotomies may be needed for patients with severe and rigid EOS to gain mobility for correction. Wang et al.20 introduced HT of apical vertebrectomy/hemivertebrectomy and TDGR for more severe, non-flexible deformity.
In Wang’s cohort of 7 patients treated with HT, the mean curve improved from 81.4° to 41°. Their preliminary results were supported by Bas et al. and Sun et al. Our study found that HT had the best curve magnitude correction in patients with the most severe and rigid preoperative main curve. The correction rate of the main curve was comparable in the HT group and ACPS group immediately after index surgery and at the latest follow-up. Patients in the ACPS group had the smallest residual curve and AVT at the latest follow-up.

Another major concern is whether ACT, especially the HT technique, which needs apical vertebrectomy/hemivertebrectomy and fusion, has negative effects on spine growth. Thompson found that apical segmental fusion within growing rods could exert a negative influence on spine growth. Wang et al. and Sun et al. reported that the growth of T1–S1 height in their cohort of patients treated with HT was similar to that reported of patients treated with TGR only. In the current study, the gain of T1–12 and T1–S1 height after index surgery was greater in the ACPS and HT groups, while T1–12 and T1–S1 height gain was greater during the lengthening procedures in the TDGR group. Although there were no significant differences, the mean annual growth of T1–12 and T1–S1 height was lower in patients in the HT and ACT groups than in those in the TDGR group. Both HT and ACPS may have slightly negative effects on spine growth during lengthening procedures, but these negative effects could be countered by more spine height gain during index surgeries in both groups. No significant differences were found in the T1–12 and T1–S1 heights among the 3 groups at the latest follow-up.

TGR is inherently prone to complications due to biomechanical limitations. The complication rate of TGR could be more than 50%. Mechanical failures are the most common complications. Helenius et al. found that severe EOS was associated with larger residual deformity and more complications than moderate EOS when treated with TGR. Patients with a severe and rigid apical curve may have large residual deformities when treated with TDGR. The enormous asymmetric growth potential around the residual deformities may contribute to an increased risk of complications of the TGR for patients with CEOS. HT was introduced to address these issues. During the index surgery of HT, apical vertebrectomy/hemivertebrectomy and short segmental fusion could powerfully improve the correction of the major curve while eliminating the asymmetric growth potential around the apex. Furthermore, additional pedicle screws used in patients treated with HT and ACPS could provide more fixation points to improve the stability of TDGR. Wang et al. found that the correction of the main curve was 50.7%, and no complications occurred. In the study of Sun et al., the correction of the main curve after the index surgery was 57.2%, and 2 of 13 patients developed 2 complications. In the current study, patients in the HT and ACPS groups had fewer complications, mechanical failures, and anticipated revision surgeries. TDGR+ ACTs may help to decrease the risk of complications, especially mechanical failures.

There were several limitations in this study. First, this was a retrospective study and suffered from treatment selection bias; Second, the etiology of EOS was not unified in this study; Third, ACT was relatively more aggressive and not widely used, so the patient samples in the ACT groups were relatively small, and most patients in both groups were still skeletally immature and still in the treatment period. Larger studies of such patients who graduate from lengthening procedures will be critical in fully understanding the strengths, weaknesses, and indications of the procedures. However, understanding the intermediate follow-up period offers valuable information on the advantages of TDGR+ACTs for surgeons and patients who may be candidates for
these techniques.

**CONCLUSION**

In summary, ACTs, including HT and ACPS, could improve the correction of TDGR while decreasing the risk of complications and unanticipated revision surgeries. HT and ACPS did not have deleterious effects on the gain of T1–T12 and T1–S1 height during the lengthening procedures. TDGR+ACTs may be a supplemental option for patients with EOS, especially those with a large apical deformity. HT is indicated for severe and rigid curve, while ACPS is indicated for flexible curve. Long-term follow-up is mandatory to evaluate the final results of ACTs.

**NOTES**

**Conflict of Interest:** The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: SW, JZ; Formal Analysis: SW, YZ, YD; Investigation: YZ, SW; Methodology: SW, GL; Project Administration: JZ, JS; Writing – Original Draft: SW, YZ; Writing – Review & Editing: NW, YY, JZ.

**ORCID**

Shengru Wang: 0009-0004-3749-4267
Yiwei Zhao: 0000-0003-3935-5637
Guanfeng Lin: 0000-0002-6741-6321
You Du: 0009-0007-2041-0786
Yang Yang: 0000-0002-3971-6474
Jianguo Zhang: 0000-0003-3129-5190

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The Role of Exercise in the Amelioration of Neuropathic Pain Following Traumatic Spinal Cord Injuries: A Systematic Review and Meta-analysis

Amirmohammad Toloui1, Hamzah Adel Ramawad2, Pantea Gharin1, Alexander R. Vaccaro3, Hamed Zarei1, Mostafa Hosseini4, Mahmoud Yousefifard1, Vafa Rahimi-Movaghar5,6

1Physiology Research Center, Iran University of Medical Sciences, Tehran, Iran
2Department of Emergency Medicine, NYC Health + Hospitals, Coney Island, New York, NY, USA
3Department of Orthopedics and Neurosurgery, Rothman Institute, Thomas Jefferson University, Philadelphia, PA, USA
4Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
5Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran
6Brain and Spinal Injuries Research Center (BASIR), Neuroscience Institute, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

Objective: The objective of this systematic review and meta-analysis was to assess the efficacy of exercise in neuropathic pain following traumatic spinal cord injuries.

Methods: The search was conducted in MEDLINE, Embase, Scopus, and Web of Science by the end of 2022. Two independent researchers included the articles based on the inclusion and exclusion criteria. A standardized mean difference was calculated for each data and they were pooled to calculate an overall effect size. To assess the heterogeneity between studies, I2 and chi-square tests were utilized. In the case of heterogeneity, meta-regression was performed to identify the potential source.

Results: Fifteen preclinical studies were included. Meta-analysis demonstrated that exercise significantly improves mechanical allodynia (standardized mean difference [SMD], -1.59; 95% confidence interval [CI], -2.16 to -1.02; p < 0.001; I2 = 90.37%), thermal hyperalgesia (SMD, 1.95; 95% CI, 0.96–2.94; p < 0.001), and cold allodynia (SMD, -2.92; 95% CI, -4.4 to -1.43; p < 0.001). The improvement in mechanical allodynia is significantly more in animals with a compression model of SCI (meta-regression coefficient, -1.33; 95% CI, -1.84 to -0.57; p < 0.001) and in mild SCI (p < 0.001). Additionally, the improvement was more prominent if the training was started 7 to 8 days postinjury (coefficient, -2.54; 95% CI, -3.85 to -1.23; p < 0.001) and was continued every day (coefficient, -1.99; 95% CI, -3.07 to -0.9; p < 0.001). Likewise, voluntary exercise demonstrated a significantly more effect size (coefficient, -1.45; 95% CI, -2.67 to -0.23; p = 0.02).

Conclusion: Exercise is effective in the amelioration of neuropathic pain. This effect in mechanical allodynia is more prominent if voluntary, continuous training is initiated in the subacute phase of mild SCI.

Keywords: Exercise therapy, Neuropathic pain, Allodynia

INTRODUCTION

Injuries or functional disorders of the nervous system can lead to neuropathic pain, causing a persistent hypersensitivity to innocuous stimuli (allodynia) or an exaggerated response to noxious stimuli (hyperalgesia). Depending on the site of injury, neuropathic pain can have a central or a peripheral origin.1 Spinal cord injury (SCI) is a pathological condition in which
Exercise in Neuropathic Pain Following SCI

Toloui A, et al.

MATERIALS AND METHODS

1. Study Design

The objective of this systematic review and meta-analysis was to assess the efficacy of exercise as a therapeutic intervention for neuropathic pain following traumatic SCI. The present study employed 3 strategies for selecting keywords, including the use of MeSH (in the MEDLINE database) and Emtree (in the Embase database) to find related entries, consultation with experts in the field, and a review of the related articles. Based on the selected keywords, an exhaustive search was conducted in the electronic databases of MEDLINE, Embase, Scopus, and Web of Science by the end of 2022 to identify relevant articles. Search strategies were based on keywords related to exercise, SCI, and pain (Supplementary Material 1).

2. Inclusion Criteria

The definition of PICO was as follows: The population (P) of the included articles were humans or animals (rats or mice) with compression, transection, hemisection, or contusion models of SCI. The intervention (I) was the use of any active exercise technique to alleviate neuropathic pain. The comparison (C) was made with a control group that did not receive the intervention or received standard treatment. The outcomes (O) were the reported rating scales of pain perception in humans and alldynia and hyperalgesia in animals. Accordingly, we excluded studies that did not execute an active exercise program as the intervention, incorporated only assisted or combinative exercise programs, case reports, case series, studies without a control group, human studies that were not designed as randomized clinical trials, pre- posttest studies, studies without an SCI model, studies on transgenic animals, protocols, studies not reporting a desired outcome or lacking the sufficient data, studies that evaluated nonneuropathic pain, follow-up studies, and reviews.

3. Data Gathering

The results of the systematic search in electronic databases were collected in the 20th version of the Endnote program. In the initial screening process, 2 independent researchers assessed the titles and abstracts of the obtained articles and selected the potentially relevant studies. Then, the full text of the selected articles was reviewed, the inclusion and exclusion criteria were applied, and articles meeting the criteria were included. A search in the grey literature (Google, Google Scholar, and the thesis section of the ProQuest database) was conducted to avoid any
missing articles. Data were summarized in a checklist based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The obtained data included information regarding the study design, the sample size and characteristics, the SCI injury model and severity, the interval from SCI to the initiation of exercise, the exercise protocol, the interval to outcome assessment, and the outcome measurement test. If multiple articles were based on the same data, we included the article with the largest sample size or the longest follow-up interval. For data that were not presented in the article, we contacted the corresponding author. For articles in languages other than English, the data were extracted with the help of a translator fluent in both languages. Any disagreements were resolved through discussions with the third reviewer.

4. Quality Control and Certainty of Evidence

The risk of bias in animal studies was evaluated using SYRCLE’s risk of bias assessment tool and a traffic light plot with a summary figure was created using the Robvis visualization tool (Supplementary Material 2). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to evaluate the certainty of evidence (Supplementary Material 3). In the case of a disagreement, the conflict was resolved through discussions with a third researcher.

5. Statistical Analyses

The statistical analyses were conducted using Stata 17.0 (StataCorp LLC, College Station, TX, USA). The included studies were classified and summarized according to the classification of the reported neuropathic pain. A standardized mean difference (SMD) with a 95% confidence interval (95% CI) was calculated for each sample and they were pooled to calculate an overall effect size. It should be noted that meta-analysis was only performed if data were reported by at least 3 separate analyses. If a study used a scale in which a higher efficacy was observed with a lower score on the index scale, the absolute SMD value was inserted into the analysis. In this study, a random or fixed effect model was chosen based on the presence or absence of heterogeneity. To assess the heterogeneity between studies, I² and chi-square tests were utilized. In the case of heterogeneity, subgroup analyses, and meta-regression were performed to identify the potential source. Subgroup analyses were performed on different animal species, levels of SCI, models of SCI, severities of SCI, SCI to exercise timing, the duration of exercise protocol, number of days in the week that the animals were trained, and whether exercise was conducted voluntarily. Sensitivity analyses were performed to evaluate the robustness of the findings. Additionally, publication bias was reported with a funnel plot using the modified Egger’s test proposed by Doleman et al.

Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of the screening process.

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6. Ethic’s approval
This research has been approved by Tehran University of Medical Sciences and Health Services and Iran Ministry of Health and Medical Education.

RESULTS

1. Preclinical Studies
1) Characteristics of the included studies
The systematic search resulted in 2,656 nonduplicate records, of which the full text of 167 was reviewed in detail. Finally, 15 animal interventional studies met the inclusion criteria (Fig. 1).31-45 Notably, the search in human studies resulted in no eligible articles. In the included preclinical studies, 11 wielded strains of rats and 4 wielded mice. Eleven studies used the contusion model of SCI (9 moderate and 2 severe) and 4 used the compression model (1 mild and 3 moderate). The time interval between the induction of SCI and the initiation of exercise varied from 1 to 42 days postinjury; in 2 studies exercise was initiated in the first 5 days postinjury, 4 initiated the exercise protocol in 7 to 8 days postinjury, and in 6 studies exercise was initiated after the first 14 days. In 3 articles the interval from SCI to training was a combination of the aforementioned timelines. Twelve studies used a quadrupedal training program (running wheel, treadmill, exercise ball), 1 study used a bipedal gait training exercise and 2 studies used both quadrupedal and bipedal training. Apart from 1 study that continued the intervention for 2 years, the duration of exercise varied between 2 to 12 weeks. All exercise protocols were carried out 5–7 days per week. In 3 studies, animals were allowed to move freely during the exercise protocol, while in others each session lasted between 20 to 58 minutes. The last follow-up was immediately postintervention in all articles, except for one, that reported the outcome in 1 week and 2 weeks postintervention. All articles evaluated mechanical allodynia, 10 evaluated thermal hyperalgesia, and 4 evaluated cold allodynia. The results were separately reported for the contralateral or ipsilateral side of the injury in 3 articles (Table 1).

2. Meta-analysis
1) The effect of exercise on mechanical allodynia
Categorizing the effect of exercise on mechanical allodynia into ipsilateral, contralateral, and bilateral mechanical allodynia, 31 separate analyses were included in this meta-analysis. Pooled data analysis demonstrated that exercise significantly improves bilateral mechanical allodynia (SMD, -1.43; 95% CI, -2.17 to -0.7; p < 0.001; I² = 89.86%). Moreover, pooled data analyses in the contralateral side exhibited meaningful improvement in mechanical allodynia following exercise (SMD, -1.9; 95% CI, -3.42 to -0.39; p = 0.014; I² = 92.53%). The results were similar on the ipsilateral side (SMD, -1.76; 95% CI, -3.03 to -0.49; p = 0.007; I² = 91.39%). In total, exercise therapy significantly improves mechanical allodynia in animals (SMD, -1.59; 95% CI, -2.16 to -1.02; p < 0.001; I² = 90.37%) (Fig. 2).

2) Subgroup analyses for mechanical allodynia
Subgroup analyses and meta-regressions were performed to detect sources of heterogeneity. The improvement in mechanical allodynia was significant in almost all subgroups, except for animals with thoracolumbar SCI, which was investigated only in 3 distinct experiments. Performing a subgroup analysis was not methodologically feasible due to the low number of included experiments for animals that were trained 6 days per week. In the next step, meta-regressions demonstrated that the extent of improvement is significantly more in animals with a compression model of SCI (meta-regression coefficient, -1.33; 95% CI, -1.84 to -0.57; p < 0.001), while less improvement was evident in both moderate SCI (meta-regression coefficient, 2.95; 95% CI, 1.61–4.29; p < 0.001) and severe SCI (meta-regression coefficient, 3.67; 95% CI, 2.24–5.11; p < 0.001). Moreover, meta-regression showed a meaningful relationship between the effect size of improvement in mechanical allodynia and the SCI to training interval of 7 to 8 days (coefficient, -2.54; 95% CI, -3.85 to -1.23; p < 0.001) and also with animals that were trained every day (coefficient, -1.99; 95% CI, -3.07 to -0.9; p < 0.001). The improvement in mechanical allodynia was significantly more in animals that were in a voluntary exercise setting (meta-regression coefficient, -1.45; 95% CI, -2.67 to -0.23; p = 0.02) (Table 2). Determining the level of evidence in the pain-ameliorating effects of exercise on mechanical allodynia revealed a moderate level of evidence using the GRADE framework (Supplementary Material 3).

3) The effect of exercise on thermal hyperalgesia
In thermal hyperalgesia, 17 separate analyses were included. Pooled data analysis showed a significant improvement of thermal hyperalgesia reported on both sides following exercise (SMD, 1.95; 95% CI, 0.96–2.94; p < 0.001; I² = 91.37%). Meta-analysis also demonstrated a meaningful improvement of thermal hyperalgesia on the contralateral (SMD, 3.03; 95% CI, 2.3–3.77; p < 0.001; I² = 0%) and ipsilateral side (SMD, 2.38; 95% CI, 1.73–3.03; p < 0.001; I² = 0%). In total, exercise therapy had a mean-
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Animal</th>
<th>Species</th>
<th>Sex</th>
<th>Age (day)</th>
<th>Weight (g)</th>
<th>Sample size</th>
<th>SCI level</th>
<th>SCI model</th>
<th>SCI severity</th>
<th>Antibiotic</th>
<th>Injury to training</th>
<th>Exercise</th>
<th>Exercise protocol</th>
<th>Trained limbs</th>
<th>F/U (day)</th>
<th>Assessed limb</th>
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<td>Brown et al.</td>
<td>2011</td>
<td>Rat</td>
<td>SD</td>
<td>M</td>
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<td>350–400</td>
<td>18</td>
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<td>Contusion</td>
<td>Moderate</td>
<td>Penicillin/G</td>
<td>1 &amp; 8 Days</td>
<td>Exercise ball</td>
<td>Free, every day, 14 days</td>
<td>All</td>
<td>7 &amp; 14</td>
<td>Both hindpaws</td>
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<tr>
<td>Cheng et al.</td>
<td>2022</td>
<td>Rat</td>
<td>SD</td>
<td>F</td>
<td>Adult</td>
<td>250–300</td>
<td>84</td>
<td>Cervical</td>
<td>Compression</td>
<td>Mild</td>
<td>Ampicillin</td>
<td>7 Days</td>
<td>Running wheel</td>
<td>Free, every day, 21 days</td>
<td>All</td>
<td>Imme</td>
<td>Contra/ipsilateral hindpaws</td>
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<td>Cheng et al.</td>
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<td>Mice</td>
<td>C57BL/6</td>
<td>F</td>
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<td>19–20</td>
<td>95</td>
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<td>Contusion</td>
<td>Moderate</td>
<td>Ampicillin</td>
<td>7 Days</td>
<td>Running wheel</td>
<td>Free, every day, 21 days</td>
<td>All</td>
<td>Imme</td>
<td>Both hindpaws</td>
</tr>
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<td>Chhya et al.</td>
<td>2019</td>
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<td>SD</td>
<td>F</td>
<td>Adult</td>
<td>225–250</td>
<td>23</td>
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<td>Contusion</td>
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<td>Cefazolin</td>
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<td>Imme</td>
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<td>F</td>
<td>Adult</td>
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<td>Ampicillin</td>
<td>14 &amp; 28 Days</td>
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<td>Imme</td>
<td>Contra/ipsilateral hindpaws</td>
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<tr>
<td>Dugan and Sagen.</td>
<td>2015</td>
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<td>M</td>
<td>N/R</td>
<td>150–200</td>
<td>72</td>
<td>48</td>
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<td>Contusion</td>
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<td>N/R</td>
<td>5 &amp; 21 Days</td>
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<td>Both hindpaws</td>
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<td>M</td>
<td>Adult</td>
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<td>48</td>
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<td>N/R</td>
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<td>Stand, swim, treadmill</td>
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<td>Treadmill</td>
<td>40 min, 5 days a week, 28 days</td>
<td>All</td>
<td>Imme</td>
<td>Both hindpaws</td>
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<tr>
<td>Nees et al.</td>
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<td>C57BL/6</td>
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<td>56–70</td>
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<td>Contusion</td>
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<td>Ampicillin</td>
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<td>Wistar</td>
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<td>14 Days</td>
<td>Treadmill</td>
<td>30 min, 6 days a week, 42 days</td>
<td>All &amp; forepaws</td>
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<td>Bilateral trunk</td>
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SCI, spinal cord injury; F/U, follow-up; SD, Sprague-Dawley; N/R, not reported.
Exercise in Neuropathic Pain Following SCI

Toloui A, et al.

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Fig. 2. The forest plot for the efficacy of exercise in mechanical allodynia. SD, standard deviation; CI, confidence interval; REML, random-effects meta-analysis.

Fig. 3. A meaningful effect on the amelioration of thermal hyperalgesia in animals (SMD, 2.38; 95% CI, 1.73–3.03; p < 0.001; I² = 88.72%)
Table 2. Subgroup analyses and meta-regressions for different variables in mechanical allodynia and thermal hyperalgesia

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of experiments</th>
<th>Subgroup analysis</th>
<th>Meta-regression</th>
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<td>SMD (95% CI)</td>
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<td>≥ 14 Days</td>
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<td>No. of days in week</td>
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<td>Contusion</td>
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(Continued)
Table 2. Subgroup analyses and meta-regressions for different variables in mechanical allodynia and thermal hyperalgesia (Continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of experiments</th>
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<th>Meta-regression</th>
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<td></td>
<td></td>
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<td>7 Days</td>
<td>5</td>
<td>2.29 (1.43–3.16)</td>
<td>&lt; 0.001</td>
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<tr>
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SMD, standardize mean difference; CI, confidence interval; SCI, spinal cord injury; NA, not applicable since the data was included as continuous variable in the analysis.

4) Subgroup analyses for thermal hyperalgesia

Subgroup analyses demonstrated that exercise improved thermal hyperalgesia in rats, different levels of SCI, models of SCI, severities of SCI, intervals between SCI to exercise, and different groups of training durations in a week. However, meta-regressions showed that there were no significant differences in the effect sizes of different subgroups (Table 2). The level of evidence was demonstrated moderate using the GRADE framework (Supplementary Material 3).

5) The effect of exercise on cold allodynia

Cold allodynia was reported bilaterally in all included articles. Pooled data analysis on 6 separate analyses from 4 articles revealed that exercise significantly affected the improvement of cold allodynia (SMD, -2.92; 95% CI, -4.4 to -1.43; p < 0.001; I² = 87.3%) (Fig. 4). The level of evidence was determined as moderate in the pain-ameliorating effect of exercise on cold allodynia (Supplementary Material 3).

6) Sensitivity analyses

We performed sensitivity analyses for mechanical allodynia and thermal hyperalgesia due to the sufficient number of included experiments to evaluate the robustness of our results. The findings of these analyses demonstrated that the efficacy of exercise in the amelioration of mechanical allodynia and thermal hyperalgesia is evident in all different sets of experiments (Supplementary Material 4).

3. Clinical Studies

1) Characteristics of the included studies

Even though our search resulted in no eligible studies on the human population for the aforementioned outcome, we summarized the obtained randomized controlled trials (RCTs) that evaluated the amelioration of chronic pain in SCI patients following active exercise protocols. In this regard, shoulder pain and generally perceived pain were the 2 reported outcomes and were subsequently included in separate meta-analyses. Two articles evaluated the WUSPI (wheelchair user shoulder pain index), 2 reported the 36-item Short-Form survey (SF-36), and 1 reported both. All articles included chronic SCI patients. Three studies conducted a home-based exercise program whereas 2 articles conducted the exercise protocol in rehabilitation centers. All exercise protocols were for the upper extremities except for 1 study that exercised all limbs. The exercise duration ranged between 6 to 36 weeks, 2 to 4 days a week. Except for 1 article that only included resistance training, others included aerobic, stretching, and resistance training in their exercise protocol (Table 3).
4. Meta-analysis

1) The effect of active exercise on chronic pain following traumatic SCI

Pooled data analysis on 3 different samples demonstrated that exercise therapy significantly improved the general perception of pain in chronic SCI patients (SMD, -0.76; 95% CI, -1.14 to -0.37; p < 0.001; I² = 0%). Conversely, the meta-analysis exhibited no significant improvement in shoulder pain following exercise (SMD, -0.43; 95% CI, -1.04 to 0.17; p = 0.159) (Fig. 5).

2) Quality control

In the included preclinical studies, all studies adjusted the experiment and the control groups at baseline for confounders. Randomization and its proper concealment were adequately applied. The risk of bias was unclear in the domain of random housing in all included articles. Drop-out animals were not adequately mentioned and imported in analyses of 4 studies (Supplementary Material 2).

In RCTs, the allocation concealment and the blinding of the participants were not adequately addressed in any of the included articles. The blinding of the study team and the outcome assessor were unclear in 3 articles. One article had incomplete outcome data. In total, the risk of bias in all RCTs was considered high (Supplementary Material 5).

3) Publication bias

No publication bias was observed in the articles reporting mechanical allodynia (p = 0.288), thermal hyperalgesia (p = 0.163), and cold allodynia (p = 0.686) (Supplementary Material 6). Due to the low number of included RCTs, publication bias assessment
The purpose of the present systematic review and meta-analysis was to gather current literature regarding the efficacy of exercise in the amelioration of neuropathic pain following traumatic SCIs. We demonstrated that exercise significantly improves mechanical allodynia, thermal hyperalgesia, and cold allodynia in rodent models of SCI. Meta-regressions showed a significantly more effect size for the amelioration of mechanical allodynia in compression models of SCI and mild SCIs. Likewise, the extent of this improvement was substantially more if the exercise protocol began in the subacute phase of SCI, continued every day, and was voluntary.

The development of neuropathic pain is a consequence of nerve injury, either in the periphery or the CNS. Even though a multitude of factors have been suggested to provoke the pathological pathways that lead to neuropathic pain, the distinct molecular and cellular alterations involved in the process remain understudied. The underlying mechanisms of neuropathic pain can be categorized into the alterations of pain threshold in the primary afferent nociceptive neurons, activation of non-nociceptive receptors, changes in neurotransmitter transduction, and rewiring of neurons in the pain perception pathways of the CNS.

As the resident immune cells in the CNS and the main modulators of neuroinflammation, microglia play an important role...
in both central and peripheral mechanisms of mechanical allodynia. Following an injury to the nervous system, microglia undergo activation and morphologic changes, exerting both beneficial and detrimental effects on the tissue healing process. One way the activation of these cells could contribute to the development of neuropathic pain is the activation of the ionotropic adenosine triphosphate receptor P2X4 which eventually leads to the release of brain-derived neurotrophic factor (BDNF), altering the pattern of excitability in the sensory and dorsal horn neurons.

Physical activity has been shown to exert an anti-inflammatory effect that suppresses microglia activation and thus improves neuro-inflammation. With the role of BDNF being controversial in the pain perception pathways, the relationship between exercise and subsequent alterations in BDNF levels should be addressed in future studies.

Furthermore, recent literature argues that high-intensity and interval training programs could promote oxidative stress and neuroinflammation, whereas low- to moderate-intensity and continuous exercises would exert more anti-inflammatory and neuroprotective properties. In rodent models, it was previously reported that forced treadmill exercise contributed more to the production of proinflammatory molecules in comparison with voluntary wheel running. Considering that different exercise programs influence the neuroplasticity of distinctive brain regions, the present systematic review along with previous studies exhibited that continuous and voluntary exercise protocols are more beneficial in the amelioration of neuropathic pain.

We demonstrated that exercise—regardless of the timing of commencement after SCI—is effective for the amelioration of mechanical allodynia. However, the extent of this improvement is more if exercise is started in the subacute phase, and similar for both acute and chronic phases. As reported previously, early therapeutic approaches in the management of SCI lead to better outcomes and fewer postoperative complications, both in clinical and preclinical evidence.

Even though we aimed at summarizing the evidence from both animal and human populations, our search resulted in no clinical research that would meet our inclusion criteria. The chronic shoulder pain and generally perceived pain that was evaluated in previous RCTs could have etiologies other than neuropathic pain, and their inclusion is considered an ancillary analysis in this meta-analysis. Evidence with a high risk of bias showed a significant improvement in generally perceived pain in chronic SCI patients following exercise, but no such effect was observed in the amelioration of chronic shoulder pain (Supplementary Material 5).

We considered the level of evidence for our included preclinical articles to be moderate, due to serious risks of bias. Con-
versely, it is recently argued that the current guidelines for the evaluation of the risk of bias in preclinical studies are not in compliance with the guidelines on how to conduct them; therefore, the risk of bias could be overestimated due to the lack of reporting in some domains of risk of bias assessment, simply because the authors did not document them in their manuscripts. Since our results demonstrated an acceptable efficacy for exercise in the management of neuropathic pain, we prominently recommend further clinical research with robust methodologies in this field. In order to have more reliable findings, it should be emphasized that the blinding of participants and caregivers in studies that involve active physical activity is an important cause for bias; active exercise requires the patient's cooperation with the assessor, and the lack of blinding is inevitable. Therefore, we recommend more attention to proper blinding in future studies.

In addition, our analyses for the detection of publication bias demonstrated no bias. However, in order to address the asymmetry in our funnel plots, it is noteworthy that according to the study by Egger et al., asymmetric funnel plots could be due to different reasons: publication bias, selective outcome reporting, poor methodological quality, the presence of substantial heterogeneity, sampling variations, and by chance. Therefore, the observed asymmetry could be due to the aforementioned reasons.

As an inevitable limitation of review articles, it is important to draw attention to the low number of included experiments for some subgroups, and the importance of cautious interpretation of findings. For instance, even though we found a significantly more effect size in compression models of SCIs and in mild SCIs, only 1 article with 4 experiments was included in mild SCI, and 4 articles out of the included 15 executed a compression model of SCI. Notably, all compression SCIs were mild to moderate in severity, and contusion SCIs were all moderate to severe. Nevertheless, sensitivity analyses demonstrated a similar level of difference in the effect sizes of different subgroups, omitting the possible role of the observed heterogeneity in our findings.

At last, we would like to acknowledge that the protocol of this systematic review was not registered on an open-access database. The design and methodology of the present study validate the robustness of our results, but it is important to mention that protocol registration contributes to a better evaluation of outcomes and prevents duplicate efforts.

CONCLUSION

Continuous voluntary exercise initiated in the subacute phase of moderate to severe SCI is strongly associated with the amelioration of neuropathic pain in rodents. Although physical activity improves the general perception of pain in chronic SCI patients, its efficacy in the amelioration of shoulder pain should be further evaluated in further studies.

NOTES

Supplementary Materials: Supplementary Materials 1-6 can be found via https://doi.org/10.14245/ns.2346588.294.
Conflict of Interest: The authors have nothing to disclose.
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Author Contribution: Conceptualization: HAR, ARV, MH, MY, VRM; Data curation: AT, HAR, PG, ARV, HZ, MH, MY, VRM; Formal analysis: AT, ARV, MH, MY, VRM; Funding acquisition: VRM; Methodology: AT, HAR, PG, ARV, HZ, MH, MY, VRM; Project administration: ARV, MH, MY, VRM; Visualization: MH; Writing - original draft: AT, HAR, PG, ARV, HZ, MH, MY, VRM; Writing - review & editing: AT, HAR, PG, ARV, HZ, MH, MY, VRM.

ORCID
Amirmohammad Toloui: 0000-0002-9809-0985
Hamzah Adel Ramawad: 0000-0002-9687-3599
Pantea Gharin: 0000-0002-7500-9144
Alexander R. Vaccaro: 0000-0002-8073-0796
Hamed Zarei: 0000-0002-2170-079X
Mostafa Hosseini: 0000-0002-1334-246X
Mahmoud Yousefiard: 0000-0001-5181-4985
Vafa Rahimi-Movaghar: 0000-0001-7347-8767

REFERENCES

Supplementary Material 1. Search strategies

**MEDLINE (PubMed)**

```
```

**Embase**

```
#1 'spinal cord injury'/exp OR 'spinal cord injury' OR 'spinal cord contusion'/exp OR 'spinal cord contusion' OR 'spinal cord hemisection'/exp OR 'spinal cord hemisection' OR 'spinal cord transection'/exp OR 'spinal cord transection' OR 'cervical spine injury'/exp OR 'cervical spine injury' OR 'spinal cord lesion'/exp OR 'spinal cord lesion' OR 'injured spinal cord'/exp OR 'injured spinal cord' OR 'nerve transection'/exp OR 'nerve transection' OR 'nerve transaction'/exp OR 'nerve transaction'

#2 'neuropathic pain'/exp OR 'neuropathic pain' OR 'chronic pain'/exp OR 'chronic pain' OR 'pain'/exp OR 'pain'

#3 'exercise'/exp OR 'aerobic exercise'/exp OR 'isometric exercise'/exp OR 'cool down'/exp OR 'warm up'/exp OR 'kinesiotherapy'/exp OR 'gait'/exp

#1 AND #2 AND #3
```

**Scopus**

```
#1 ("spinal cord injury") OR ("Spinal cord injuries") OR ("spinal cord contusion") OR ("spinal cord hemisection") OR ("spinal cord transection") OR ("cervical spine injury") OR ("Spinal compression") OR ("spinal cord trauma") OR ("injured spinal cord") OR ("spinal cord injured") OR ("nerve transaction")

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```

www.e-neurospine.org
Exercise in Neuropathic Pain Following SCI

Toloui A, et al.

#1 AND #2 AND #3

Web of Science

#1 TS = (“spinal cord injury” OR “Spinal cord injuries” OR “spinal cord contusion” OR “spinal cord hemisection” OR “spinal cord transection” OR “cervical spine injury” OR “Spinal compression” OR “spinal cord trauma” OR “injured spinal cord” OR “spinal cord injured” OR “nerve transection”)

#2 TS = (“Pain” OR “Chronic Pain” OR “Chronic Pains” OR “Neuropathic pain” OR “Neuropathic Pains” OR “allodynia” OR “hyperalgesia” OR “Nerve Pain” OR “Nerve Pains”)

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#1 AND #2 AND #3
## Supplementary Material 2

Risk of bias assessment of the included preclinical studies according to the SYRCLE's risk of bias assessment tool.

### Risk of bias

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- **D1:** Item 1: Was the allocation sequence adequately generated and applied?
- **D2:** Item 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?
- **D3:** Item 3: Was the allocation adequately concealed?
- **D4:** Item 4: Were the animals randomly housed during the experiment?
- **D5:** Item 5: Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?
- **D6:** Item 6: Were animals selected at random for outcome assessment?
- **D7:** Item 7: Was the outcome assessor blinded?
- **D8:** Item 8: Were incomplete outcome data adequately addressed?
- **D9:** Item 9: Are reports of the study free of selective outcome reporting?
- **D10:** Item 10: Was the study apparently free of other problems that could result in high risk of bias?

### Supplementary Material 3

[Link to additional information](https://doi.org/10.14245/ns.2346588.294)
### Supplementary Material 3. The certainty of evidence

<table>
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<tr>
<th>Outcome</th>
<th>No. of experiments</th>
<th>Risk of bias</th>
<th>Imprecision</th>
<th>Inconsistency (I² range)</th>
<th>Indirectness</th>
<th>Publication bias</th>
<th>Judgment</th>
<th>Level of evidence</th>
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<td>Serious</td>
<td>No serious imprecision</td>
<td>No serious inconsistency*</td>
<td>No serious indirectness</td>
<td>No publication bias</td>
<td>Level of evidence was down rated one grade due to possible risk of bias</td>
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<tr>
<td>Thermal hyperalgesia</td>
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</table>

*There is no serious inconsistency since the sources of heterogeneity were identified.*
### Supplementary Material 4. Sensitivity analyses on mechanical allodynia and thermal hyperalgesia

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of experiments</th>
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<td>Both sides</td>
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<td>-1.35 (-2.2 to -0.49)</td>
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<td>-1.75 (-3.02 to -0.48)</td>
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<td>91.39 (&lt;0.001)</td>
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<tr>
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<td>-1.43 (-2.16 to -0.7)</td>
<td>&lt;0.001</td>
<td>89.86 (&lt;0.001)</td>
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<td>Moderate to severe injuries</td>
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<tr>
<td>Both sides</td>
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<td>-1.43 (-2.16 to -0.7)</td>
<td>&lt;0.001</td>
<td>89.86 (&lt;0.001)</td>
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<td>Both sides</td>
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<td>89.86 (&lt;0.001)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>16</td>
<td>-1.63 (-2.41 to -0.86)</td>
<td>&lt;0.001</td>
<td>89.21 (&lt;0.001)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>6</td>
<td>-1.9 (-3.41 to -0.38)</td>
<td>0.014</td>
<td>92.53 (&lt;0.001)</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>7</td>
<td>-1.75 (-3.02 to -0.48)</td>
<td>0.007</td>
<td>91.39 (&lt;0.001)</td>
</tr>
<tr>
<td>Bipedal/quadrupedal gait training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>16</td>
<td>-1.58 (-2.39 to -0.77)</td>
<td>&lt;0.001</td>
<td>90.59 (&lt;0.001)</td>
</tr>
<tr>
<td>Thermal hyperalgesia</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>10</td>
<td>2.35 (1.14–3.56)</td>
<td>&lt;0.001</td>
<td>91.37 (&lt;0.001)</td>
</tr>
<tr>
<td>Thoracic/thoracolumbar injuries</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>13</td>
<td>1.94 (0.95–2.93)</td>
<td>&lt;0.001</td>
<td>91.37 (&lt;0.001)</td>
</tr>
<tr>
<td>Moderate to severe injuries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>13</td>
<td>1.94 (0.95–2.93)</td>
<td>&lt;0.001</td>
<td>91.37 (&lt;0.001)</td>
</tr>
<tr>
<td>No stratifications were made for the development of alldynia prior to exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>13</td>
<td>1.94 (0.95–2.93)</td>
<td>&lt;0.001</td>
<td>91.37 (&lt;0.001)</td>
</tr>
<tr>
<td>Only limbs were evaluated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>13</td>
<td>1.94 (0.95–2.93)</td>
<td>&lt;0.001</td>
<td>91.37 (&lt;0.001)</td>
</tr>
<tr>
<td>Bipedal/quadrupedal gait training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both sides</td>
<td>11</td>
<td>2.02 (0.82–3.23)</td>
<td>0.001</td>
<td>93.24 (&lt;0.001)</td>
</tr>
</tbody>
</table>

SMD, standardized mean difference; CI, confidence interval.

*Sensitivity analyses were performed only if a with sufficient number of experiments were included.
Supplementary Material 5. Risk of bias assessment for the randomized clinical trials

| Study                  | Year | Selection bias | Performance bias | Detection bias | Attrition bias | Reporting bias | Other bias | Overall |
|------------------------|------|---------------|------------------|----------------|----------------|----------------|------------|
|                        |      | Random sequence Allocation concealment Blinding of participants Blinding of study team Random outcome assessment Blinding of outcome assessor Incomplete outcome data Selective outcome data | | | | | | |
| Cardenas et al. 46     | 2020 | Low           | High             | High           | Low            | Low            | Low        | Low      | Low       | High      |
| Ginis et al. 47        | 2003 | Low           | High             | High           | High           | High           | Low        | Low      | Low       | High      |
| Hicks et al. 48        | 2003 | Low           | High             | High           | Low            | High           | High       | Low      | Low       | High      |
| Nightingale et al. 49  | 2018 | Low           | High             | High           | High           | High           | Low        | Low      | Low       | High      |
| Mulroy et al. 21       | 2011 | Low           | High             | High           | Low            | Low            | Low        | Low      | Low       | High      |
Supplementary Material 6. Publication bias for mechanical allodynia (A), thermal hyperalgesia (B), and cold allodynia (C). s.e., standard error.
Advancing the Adoption of Robot-Assisted Surgery as the Routine Minimally Invasive Approach in Spinal Procedures: Commentary on “Floor-Mounted Robotic Pedicle Screw Placement in Lumbar Spine Surgery: An Analysis of 1,050 Screws”

Lu-Ping Zhou\textsuperscript{1,2}, Ren-Jie Zhang\textsuperscript{1,2}, Cai-Liang Shen\textsuperscript{1,2}

\textsuperscript{1}Department of Orthopedics and Spine Surgery, the First Affiliated Hospital of Anhui Medical University, Hefei, China
\textsuperscript{2}Laboratory of Spinal and Spinal Cord Injury Regeneration and Repair, the First Affiliated Hospital of Anhui Medical University, Hefei, China

The development of artificial intelligence and communications technology has revolutionized the field of healthcare, particularly in the realm of spinal procedures. One notable advancement in this area is the utilization of robot-assisted (RA) techniques in spinal surgery, which provide enhanced safety, accuracy, and minimal invasion compared to conventional surgical techniques.\textsuperscript{1}

Shahi et al.\textsuperscript{2} investigated the application of floor-mounted robot (ExcelsiusGPS, Globus Medical, Inc., Audubon, PA, USA) in minimally invasive lumbar fusion. They included a large sample size of 229 patients with 1,050 pedicle screws, and found that the accuracy of pedicle screw placement in RA methods was 96.4\%, and the proximal facet and proximal endplate violation rates were 0.4\% and 0.9\%, respectively, indicating that RA techniques contributed to excellent accuracy, large screw size, and negligible screw-related complications.

However, RA systems are currently in its early stages, mainly used for the pedicle and translaminar screw instrumentation, and the conventional percutaneous and open free-hand techniques still dominate in clinical practice. Consequently, significant progress remains for RA spinal surgery to become a routine minimally invasive approach in spinal procedures, which is an inevitable trend in the field.

To facilitate the routine implementation of RA techniques in minimally invasive surgeries, we proposed the following methodologies.

First, the most fundamental approach is to promote the innovation and upgrade of robot systems to satisfy the diverse requirements: (1) Achieving safe screw placement throughout the entire spinal segments. RA techniques have been widely investigated in thoracolumbar spine surgery, the feasibility and safety of which have been confirmed in many randomized
controlled trials, demonstrating promising clinical and radiographic results. However, the implementation of RA techniques in cervical spinal surgery is still limited due to the complexed cervical anatomy and vulnerability to catastrophic complications from malposition. Although the RA cervical screw placement has been determined to be safe and feasible in our previous study, with optimal and clinically acceptable accuracies of 88.0% and 98.4% respectively, it is essential to improve precision and accuracy, as well as enhance real-time visualization and tracking systems. These enhancements are necessary to addressing surgeons’ reluctance when considering RA cervical spinal surgery, and to foster their confidence during surgical procedures. Overcoming the challenges presented by RA cervical spinal surgery is a crucial aspect for the successful integration of RA techniques into routine practice.

(2) Achieving safe screw placement for different types of screws and screw placement techniques. On the one hand, it is necessary to integrate RA techniques with the currently available screw types and surgery procedures. Recently, RA techniques have been applied in the midline lumbar interbody fusion using cortical bone trajectory screw, oblique lumbar interbody fusion, and percutaneous kyphoplasty. On the other hand, there are only several percutaneous cervical screw systems available. Presently, posterior C1–2 screw insertions are frequently conducted, but there is a need to develop innovative percutaneous cervical screw systems specifically tailored for RA procedures.

(3) Achieving safe screw placement in various malformed and degenerative vertebral bodies. The robot systems can preplan the optimal entry point and trajectory for accurate screw placement based on the 3-dimensional images displaying the abnormal and degenerative structures. The systems require further upgrading in order to ensure safe operations for severe malformed and degenerative diseases, including basilar invagination, kyphosis deformity resulting from ankylosing spondylitis, and severe fractures.

(4) Achieving safe screw placement during remote interactions and improving related policies and regulations. Utilizing robotic technology and mutual telecommunication networks, medical information, including images, audio, and video, can be digitally transmitted over long distances to facilitate real-time remote surgery. The fifth generation mobile communication technology, commonly referred to as 5G, enables high-speed, low-latency, and high-capacity wireless communication, extensive connectivity, and seamless integration of industrial networks, thereby facilitating remote RA cervical spinal surgery. However, there is a lack of detailed rules for determining liability in cases of Internet medical accidents, and the ownership of medical data on cloud storage has not been clearly determined under the curly legislation. Thus, the legal supervision systems for the Internet medical service industry need further improvement, and the standards for 5G remote surgery and specific requirements with details are urgently needed.

Second, the RA training of surgeons is crucial for the promotion of orthopedic surgical robots. Pennington et al. found evidence of a learning curve in spinal robotics, with the typical minimum experience threshold ranging from 20 to 30 cases. The effective training empowers surgeons to enhance technical skills, develop surgical strategies, and master management of safety and risk during the use of orthopedic robots. This ensures standardized surgical procedures and promotes teamwork, thereby enhancing the quality and safety of RA surgery.

Third, economic and policy support plays a crucial role in promoting the widespread adoption of RA surgery. It is imperative to increase investment in technological innovation and upgrades of robotics to reduce the costs associated with purchasing and maintaining these robots. Meanwhile, reforms to healthcare insurance institutions and government policies are necessary, which should include the addition of RA surgery to the scope of reimbursement, as well as the supervision of Internet medical services.

Fourth, it is crucial to raise patient awareness and acceptance of RA surgery. Patients can be educated about the advantages and potential benefits of robotic surgery, including minimized invasiveness, surgical precision, and accelerated recovery. Moreover, it is possible to establish a communication channel with patients, to answer their questions and explain the RA surgical process.

Finally, the organization of large-scale data, conduction of rigorous clinical research, and systematic accumulation of evidence on RA surgery is essential. These data will provide strong support for the widespread application of RA surgery and help us further upgrade RA systems and improve surgical techniques.

The routine implementation of RA techniques as the minimally invasive approach in spinal procedures is an inevitable trend in the future. With the incorporation of artificial intelligence and communications technology, spinal robots have the potential to serve as either main or independent surgical operators. As Dr. Theodore, the inventor of the ExcelsiusGPS robot, pointed out, the future of robotics is bright.

- **Conflict of Interest:** The authors have nothing to disclose.
REFERENCES


Erratum

Erratum: Correction of Figure 1

Erratum: Reciprocal Changes Following Cervical Realignment Surgery

Jae-Koo Lee, Seung-Jae Hyun, Seung Heon Yang, Ki-Jeong Kim
Department of Neurosurgery, Spine Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

To the editor,
I hope this letter finds you well. I am writing to submit an erratum to our recently published manuscript titled “Reciprocal Changes Following Cervical Realignment Surgery,” which was published in *Neurospine*.

Upon careful review of our published article, my co-authors and I have identified errors in Fig. 1 that require correction. Specifically, the figure was missing crucial markers and an incorrect label was assigned to the depicted motion. We sincerely apologize for these oversights and any inconvenience they may have caused.

Here are the specific errors identified in Fig. 1:
1. Missing markers: Several essential markers representing relevant information were inadvertently omitted from the original figure, affecting the clarity and accuracy of the data presentation.
2. Incorrect labeling: The motion described in the figure was mistakenly labeled as “extension” instead of the correct term, “dorsiflexion.” This mislabeling inaccurately represents the nature of the movement observed in our study.

To address these errors, we have prepared a corrected version of Fig. 1 (see attached). The revised figure includes the missing markers and accurately labels the motion as “dorsiflexion.” We believe these corrections will significantly enhance the accuracy and clarity of our findings.

We understand the importance of maintaining the integrity of the scientific record and are committed to rectifying any inaccuracies promptly. We kindly request that you consider publishing this erratum to ensure that readers have access to the correct information.

We would be grateful for your guidance on the appropriate steps to proceed in updating the published version of our article. We are committed to cooperating fully with the journal to ensure the dissemination of accurate information to the scientific community.

Thank you for your attention to this matter. Should you require any additional information or further clarification, please do not hesitate to contact me.

We sincerely appreciate your assistance in resolving this matter promptly.
The corrected Figure 1 is as follows: