Featured Articles

Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury
Lahanya Guha, Nidhi Singh, Hemant Kumar

Three-Dimensional-Printed Titanium Versus Polyetheretherketone Cages for Lumbar Interbody Fusion: A Systematic Review of Comparative In Vitro, Animal, and Human Studies
Neal A. Patel, Sinead O’Bryant … Martin H. Pham

Intra-articular Distraction Versus Decompression to Treat Basilar Invagination Without Atlantoaxial Dislocation: A Retrospective Cohort Study of 54 Patients
Boyan Zhang, Maoyang Qi … Zan Chen

Mini-Open Intercostal Retroperitoneal Approach for Upper Lumbar Spine Lateral Interbody Fusion
Su Hun Lee, Dong Wuk Son … Geun Sung Song

METTL3 Affects Spinal Cord Neuronal Apoptosis by Regulating Bcl-2 m6A Modifications After Spinal Cord Injury
Shengyu Guo, Tao Tao Lin … Wenge Liu
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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From the Editor-in-Chief: Featured Articles in the June 2023 Issue

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

“Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury” by Guha et al.¹

This paper reviews the complex processes of cell death, integral to cell replacement, and potentially inciting inflammation in cases of spinal cord injury. It emphasizes the impact of these pathways on neuronal cells, especially following acute or chronic injury, given the restricted regenerative and recuperative abilities of neurons. These process malfunctions are correlated with spinal cord injuries, leading to disrupted motor activity and axonal degeneration. A deeper understanding of these processes could enhance neuronal survival and mitigate neurological deficits, offering new avenues for therapeutic strategies in spinal cord injury treatment.

“Three-Dimensional-Printed Titanium Versus Polyetheretherketone Cages for Lumbar Interbody Fusion: A Systematic Review of Comparative In Vitro, Animal, and Human Studies” by Patel et al.²

The paper conducts a systematic review comparing outcomes of interbody spinal cages made of polyetheretherketone (PEEK) and 3-dimensional printed porous titanium (3D-pTi), focusing on fusion results and subsidence rates. Across 7 studies involving human and ovine subjects, most showed 3D-pTi to have superior fusion outcomes and osseointegration without increased risk of subsidence or reoperation compared to PEEK. Despite limited data, the paper suggests that 3D-pTi interbodies might offer superior results due to their osteoinductive properties, warranting further clinical investigation.

“Intra-Articular Distraction Versus Decompression to Treat Basilar Invagination Without Atlanto-Axial Dislocation: A Retrospective Cohort Study of 54 Patients” by Zhang et al.³

This retrospective cohort study compares 2 surgical treatments for type B basilar invagination: posterior intra-articular C1–2 facet distraction, fixation, and cantilever reduction versus foramen magnum decompression. Results from 54 patients suggest the former technique results in better basilar invagination reduction, improved nerve pressure relief, and superior patient outcomes as assessed by Japanese Orthopedic Association and 12-item Short Form health survey scores. A preoperative craniovertebral junction triangle area cut-
off value of 2.00 cm² is proposed as a surgical indication. Despite positive results, the study recommends investigating alternative treatment strategies due to the multifactorial nature of the condition.

**“Mini-Open Intercostal Retroperitoneal Approach for Upper Lumbar Spine Lateral Interbody Fusion” by Lee et al.*

This study compares 2 surgical methods: conventional oblique lumbar interbody fusion (OLIF) and the proposed intercostal retroperitoneal (ICRP) approach for upper lumbar spine access. Results from 121 patients show a significantly lower incidence of endplate injury with the ICRP approach (9.1% vs. 34.3% in conventional OLIF). This is particularly evident in patients with a lower rib line. The ICRP approach offers these benefits without requiring pleural exposure or rib resection. The use of ICRP has increased nearly threefold since 2022.

**“METTL3 Affects Spinal Cord Neuronal Apoptosis by Regulating Bcl-2 m6A Modifications After Spinal Cord Injury” by Guo et al.**

The study investigates the role of methyltransferase METTL3, a key enzyme in the m6A RNA modification, in spinal cord injury (SCI). In both oxygen-glucose deprivation models of PC12 cells and rat spinal cord hemisection models, METTL3 expression and overall m6A modification levels increased significantly. Inhibiting METTL3 activity or expression raised Bcl-2 mRNA and protein levels, reduced neuronal apoptosis, and improved viability in the spinal cord post-SCI. This suggests that inhibiting METTL3 could potentially protect spinal cord neurons following injury via the m6A/Bcl-2 signaling pathway.

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

**REFERENCES**

Cervical Spondylotic Myelopathy: From the World Federation of Neurosurgical Societies (WFNS) to the Italian Neurosurgical Society (SINCh) Recommendations

Cervical spondylotic myelopathy (CSM) is a progressively growing pathology to afford by a spinal surgeon due to the aging of the population, associated with better treatment management and the best diagnosis and treatment solutions are greatly discussed. Nowadays that scientific literature is progressively increasing to identify the gold standard in diagnosis and treatment can be very challenging. This is particularly evident in spinal surgery with many different indications not only in different countries but also in the same local reality. In this scenario, many neurosurgical societies work to identify some guideline or recommendations to help spinal surgeons in daily practice. Furthermore, in an era in which legal issues are increasingly present in clinical practice to have some indications globally accepted can be very useful. World Federation of Neurosurgical Societies (WFNS) few years ago starts this process creating a list of recommendations originating from a worldwide steering committee to respect all the local reality. The spinal section of Italian Neurosurgical Society decides to adopt the WFNS recommendations with some revision basing on Italian scenario. The steering committee of the Spinal Section of Italian Neurosurgical Society identify 7 groups to review the literature of the last 10 years about different topics on CSM and to analyses the WFNS recommendations to adapt it to the Italian daily practice. The statements were discussed and voted in 2 sessions to obtain the final version. A list of recommendations on natural course and clinical presentation; diagnostic tests; conservative and surgical treatment; anterior, posterior and combined surgical treatment; role of neurophysiological monitoring and follow-up and outcome was created with only few new or revised statements respect the ones of WFNS. The Spine Section of Italian Neurosurgical Society create a list of recommendations that represent the more contemporary treatment concepts for CSM as presented in the highest quality clinical literature and best clinical practices available on this subject.

Keywords: Cervical spondylotic myelopathy, Recommendations, Guidelines, Evidence-based medicine

INTRODUCTION

Cervical spondylotic myelopathy (CSM) is a degenerative pathology, known to be the most common cause of spinal cord dysfunction. Due to an aging population and superior treatment management for elderly patients, both neurosurgeons and orthopedic surgeons have to manage this pathology more frequently. However, guidelines are advocated to better define clinical management due to the potentially high social impact of this condition, regarding daily activity as well as a medical-legal standpoint. The World Federation of Neurosurgical Societies (WFNS) start few years ago the definition of recommendations on different topics of spine surgery with the aim of standardize daily clinical practice. These recommendations are intended to reflect contemporary treatment concepts for CSM as presented in the highest quality clinical literature and best clinical practices available on this subject.

Aim of WFNS is to provide practical indication for the management of spine pathologies that can be applied by the different Neurosurgical Societies worldwide, including also middle and low-income countries. However, this process may not reflect exactly the standard of care of the different countries. For this reason, with the aim of standardizing the diagnosis and treatment of the spine pathologies as done before in the case of lumbar stenosis (LS) as much as possible, the spinal section of the Italian Society of Neurosurgeon (SINch) analyzed and proposed their own recommendations for the management of CSM in accordance with the recommendations published by the spine committee of the WFNS. In this paper, we present the standardized protocol of revision, the methodology and as well the results.

MATERIALS AND METHODS

Following the criteria and methodology adopted by the spinal section for the recommendations of degenerative lumbar spine stenosis 1 the results of the WFNS consensus conference, were carefully and critically analyzed. All the statements of the WFNS were presented to the Spinal Section of the SINch. The literature review was presented by each group to all the members of the Spine Section and all the WFNS recommendations were voted for consensus with Delphi Method. After the first voting session, some recommendations were proposed for revision and each group proposed some new statements; after the
Steering Committee validation all the revised and new statements were voted again. This process had the purpose to critically review the best literature indication on the topic according to the personal experience and the local daily practice specific for our country.

In detail, the committee of the Spine Section of the SINch was divided into 7 groups to perform this critical revision, and each group revisited a specific topic of the recommendation of CSM: (1) natural course and clinical presentation, (2) diagnostic tests, (3) conservative treatment versus surgical treatment, (4) anterior surgical treatment, (5) posterior and combined surgical treatment, (6) role of neurophysiological monitoring; (7) follow-up and outcome.

Each group was composed by at least 4–5 active members of the Spinal Section of the SINch and comprise 1 senior surgeon (> 60 years-old), 2 experienced (> 40, < 60 years-old), and at least 1 young (< 40 years-old).

A literature review was conducted using the Cochrane Database of systematic reviews and MEDLINE/PubMed, including papers from a 10-year span (2011–2021). A secondary search of the listed citations was performed on the identified articles, to ensure that all relevant publications were included.

The literature review and the analysis of the WFNS recommendations were discussed during regular Zoom meetings, while the final results were presented and voted (via an electronic survey among only the members of the spinal section of the SINch) during the Spine Section Congress of SINch (Mestre -September 17–18, 2021) (Fig. 1).

The Delphi method was applied to administer a questionnaire and obtain a consensus on the topics. To establish a consensus, the levels of agreement or disagreement for each item were voted independently in a blind-manner using a Likert-type scale from 1 to 5 (1, strongly disagree; 2, disagree; 3, somewhat agree; 4, agree; 5, strongly agree). Results were expressed as a percentage of respondents who scored each item as 1 or 2 (disagreement) or as 3, 4, or 5 (agreement). Consensus was achieved when the sum for disagreement or agreement was ≥ 66%. Each consensus point was clearly defined with evidence strength, recommendation grade, and consensus level provided.

To obtain the final version of the Italian Recommendations on CSM each group proposed a list of statements, the modified or the new ones were drafted by all the group and the senior member provide the final version to propose to the Steering Committee first (for revision) and finally to all the members (for the vote). We explain in detail in the authors contributions who provide the drafted version of statement and the final one (all the members write the original draft of the statements and the discussion of the literature review; the senior members write the final version of the statements). Furthermore, the authors provided the draft, the correction and the final version of the papers.

RESULTS

Following the literature review performed by each study group, the Spinal Section accepted 62 of the 68 recommendations (89.4%) proposed by the WFNS, while 6 statements were suggested for revision. Moreover, based on national clinical practice, the committee considered further indications appropriate and accordingly proposed 13 new statements. This led to a total of 19 statements (6 revisions and 13 new) being proposed for a vote and added to the recommendations. The results are presented in specifics for each group.

1. Group 1: Natural Course and Clinical Presentation

All the 8 statements of the WFNS were accepted without revision (Table 1) and 2 new statements were proposed to be added. The statement proposed for the vote and consequent re-
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Table 1. Recommendations for natural course and clinical presentation of cervical spondylotic myelopathy (CSM)

<table>
<thead>
<tr>
<th>Recommendations for natural course and clinical presentation of CSM</th>
<th>WFNS</th>
<th>SINch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelopathic signs (hyperreflexia, inverted brachioradialis reflex, Hoffmann sign, Babinski and clonus) are an integral component of clinical diagnosis of cervical myelopathy. However, they are not very sensitive and may be absent in about 20% of myelopathic patients.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Individual myelopathic signs taken alone cannot diagnose cervical myelopathy in all patients but at least one is present in severe myelopathy.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Clinical diagnosis of CSM relies heavily on characteristic symptoms and signs elicited during history and physical exam which prompt further investigation with cervical spine imaging.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>In severe myelopathic patients, after laminoplasty, major recovery in myelopathic signs occurs during the first 6 months and there after it plateaus.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>In patients with myelopathic signs, if there are no alternative explanations, a combination of clinical symptoms and imaging studies must form the basis of our treatment decisions. The absence of myelopathic signs does not preclude the diagnosis of CSM nor its successful surgical treatment.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Natural course of patients with cervical stenosis and signs of myelopathy greatly varies.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Progression of the disease is possible, but prediction of those patients is not well known. Some patients may remain static for lengthy periods, and some patients with severe disability can improve without treatment.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>For patients with no symptoms but having significant stenosis (premyelopathic), risk of developing myelopathy with cervical stenosis is approximately 3% per year.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Patients should be warned about the increased susceptibility to acute spinal cord injury and that they should avoid hazardous activities and environments.</td>
<td>New</td>
<td></td>
</tr>
<tr>
<td>Patients without clear sign of myelopathy but clinical and/or electrophysiological evidence of cervical radicular dysfunction should be counselled on the risk of developing myelopathy.</td>
<td>New</td>
<td></td>
</tr>
</tbody>
</table>

WFNS, World Federation of Neurosurgical Societies; SINch, Italian Neurosurgical Society.

results are:

(1) Patients should be warned about the increased susceptibility to acute spinal cord injury and that they should avoid hazardous activities and environments. This statement reached a strong positive consensus with total of 96.1% of positive votes (the detail of the vote was: 1.32% grade 1 of Linkert scale, 2.63% grade 2, 25% grade 3, 18.42% grade 4, and 52.63% grade 5).

(2) Patients without clear sign of myelopathy but clinical and/or electrophysiological evidence of cervical radicular dysfunction should be counselled on the risk of developing myelopathy. This statement reached a strong positive vote with an agreement of 86.4% (2.67% grade 1, 10.67% grade 2, 33.33% grade 3, 20% grade 4, 33.33% grade 5).

2. Group 2: Diagnostic Tests

Twelve statements of the WFNS were accepted without revision and one was suggested for revision (Table 2), with one new statement proposed to be added. The statements suggested for the vote and consequent results are:

(3) Electrophysiological tests may have better outcome predictions than magnetic resonance (MR) changes. To date, one of the most important roles of neurophysiological assessment is to monitor the progression of cervical myelopathy, which can add to the surgical decision-making. This statement reached a strong positive consensus with an agreement of 84.0% (2.67% grade 1, 13.33% grade 2, 37.33% grade 3, 18.67% grade 4, 28% grade 5).

(4) Preoperative somatosensory evoked potential/motor evoked potential (SEP/MEP) may be useful to better analyze radiological CSM associated with normal/subclinical signs of myelopathy and can be added to the surgical decision-making tool. This statement reached a strong positive consensus with a total of 93.3% of positive votes (none voted grade 1, 6.67% grade 2, 29.33% grade 3, 24% grade 4, 40% grade 5).

3. Group 3: Conservative Treatment Versus Surgical Treatment

Nine statements were accepted without revision while one was suggested for revision (Table 3) and 3 new statements were proposed. The statements suggested for the vote and consequent results are:

(5) When counselling patients with mild CSM, quality of life (QoL) assessment should be part of the examination and physical function in day-to-day activities as social functioning should be carefully investigated while taking in consideration the patient’s reported performance status. This statement reached a
Italian Recommendations for CSM

Costa F, et al.

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Table 2. Recommendations for diagnostic tests for cervical spondylotic myelopathy (CSM)

<table>
<thead>
<tr>
<th>Recommendations for diagnostic tests</th>
<th>WFNS</th>
<th>SINch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Value of electrophysiology</strong></td>
<td></td>
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</tr>
<tr>
<td>Electrophysiological tests to be used in CSM patients are (in order of benefits): motor evoked potential (MEP), spinal cord evoked potential, somatosensory evoked potential (SEP), and electromyography.</td>
<td>√</td>
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</tr>
<tr>
<td>Routine electrophysiological tests are useful in differential diagnosis of CSM from other neurological conditions. However, especially during the early course of the disease differential diagnosis is very difficult, specific tests are necessary and mild forms of amiotrophic lateral sclerosis and polyneuropathy may not be differentiated easily. Although MEP and SEP have been found as valuable tests to predict outcomes of CSM surgery, there is no evidence that they are more valuable than clinical parameters.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Electrophysiological tests may have better outcome predictions than magnetic resonance (MR) changes. To date, one of the most important roles of neurophysiological assessment is to monitor the progression of cervical myelopathy, which can add to the surgical decision-making.</td>
<td>×</td>
<td>Rev</td>
</tr>
<tr>
<td>Preoperative SEP/MEP may be useful to better analyze radiological CSM associated with normal/subclinical signs of myelopathy and can be added to the surgical decision-making tool.</td>
<td></td>
<td>New</td>
</tr>
<tr>
<td><strong>Recommendations for value of canal diameters in CT and MRI</strong></td>
<td></td>
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</tr>
<tr>
<td>In spite of conflicting evidence, MRI morphometric analysis of the spine has a significant role in evaluation and prognostication of CSM and it should be included in the preoperative workup.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Among the many variables assessed using MRI – compression ratio, maximum canal compromise and transverse area are most importantly correlated with functional outcomes following surgery in patients with CSM. Each parameter has its own strength and limitation, therefore a combined assessment of MR parameters has a greater predictive yield.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Intense spinal cord T2 hyperintensity on cervical MRI may be correlated with a worse outcome in CSM.</td>
<td>√</td>
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</tr>
<tr>
<td>Patients with lighter signal changes in T2 on cervical MRI should not be excluded from surgical treatment of CSM.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>More studies are needed to validate proposed grading systems, or to create new ones.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>T1 hyposignal should be considered as a sign of more advanced disease, with worse outcome.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>More studies are needed to assess the effect of sagittal and axial extension of T1 signal changes on outcome.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td><strong>Recommendations for new imaging techniques for CSM</strong></td>
<td></td>
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</tr>
<tr>
<td>Diffusion MRI, MR spectroscopy and dynamic MRI may be a part of MR examinations for CSM protocol apart from conventional MRI. We suggest their usage for outcome studies. With data pooling of clinical and imaging findings, we will be able to prognosticate better and identify patients earlier before the changes and permanent damage sets in.</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

WFNS, World Federation of Neurosurgical Societies; SINch, Italian Neurosurgical Society; CT, computed tomography; MRI, magnetic resonance imaging.

strong positive consensus with 92% of agreement (1.33% grade 1, 6.67% grade 2, 34.67% grade 3, 32% grade 4, 25.33% grade 5).

(6) We suggest to propose surgical intervention to patients with substantial reduction of QoL and greater neck pain and motor impairment at presentation or serious SEP abnormality. This statement reached a strong positive consensus with an agreement of 98.7% (none voted grade 1, 1.33% grade 2, 24% grade 3, 20% grade 4, 54.67% grade 5).

(7) A supervised trial of structured rehabilitation should be offered to patients with mild CSM with better QoL and less physical/mental dysfunction. This statement reached a positive consensus with 88.9% (1.39% grade 1, 9.72% grade 2, 41.67% grade 3, 23.61% grade 4, 23.61% grade 5).

(8) If initial nonoperative management is pursued, we recommend operative intervention if there is neurological deterioration or appearance of SEP abnormality and suggest operative intervention if the patient fails to improve. This statement reached a strong positive consensus with 100% of positive votes (none voted grade 1 or 2, 24.32% voted grade 3, 20.27% grade 4, 55.41% grade 5).

4. Group 4: Anterior Surgical Treatment

All 9 statements were accepted without revision, none was suggested for revision (Table 4) and no new statements were proposed.

5. Group 5: Posterior and Combined Surgical Treatment

All the 10 statements were accepted without revision (Table
Table 3. Recommendations for value of surgical and nonsurgical treatment for cervical spondylotic myelopathy (CSM)

<table>
<thead>
<tr>
<th>Recommendations for value of surgical and nonsurgical treatment for CSM</th>
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<th>SINch</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with moderate and severe CSM surgical intervention is recommended. We recommend using modified Japanese Orthopedic Association scale or its regional modifications to classify CSM as severe, moderate or mild. When counselling patients with mild CSM, QoL assessment should be part of the examination and physical function in day-to-day activities as social functioning should be carefully investigated while taking in consideration the patient's reported performance status. We suggest offering surgical intervention to patients with substantial reduction of QoL and greater neck pain and motors impairment at presentation or serious SEP abnormality. Nonmyelopathic patients with radiologic evidence of cord compression but without signs and symptoms of radiculopathy should not be offered a prophylactic surgery. These patients should be counselled about the potential risk of worsening, educated about the signs and symptoms of progression and followed up clinically regularly. An informed consent should be obtained about neurological deficits that may follow trivial injury. More studies are needed to validate proposed grading systems, or to create new ones. Nonmyelopathic patients with radiologic evidence of cord compression and with clinical evidence of radiculopathy are potential candidates who may deteriorate thus carrying high risk and hence need to be counselled about it. These patients are recommended to undergo surgery or close observation with rehabilitation if the patient refuse to undergo surgery. In the event of developing myelopathic signs they are advised to go for surgery at the earliest. An informed consent should be obtained about neurological deficits that may follow trivial injury. There is a consistent lack of evidence regarding the value of nonoperative treatment of cervical myelopathy in the literature. Hence nonoperative treatment may not be the final decision in most cases. A supervised trial of structured rehabilitation should be offered to patients with mild CSM with better QoL and less physical/mental disfunction. If initial nonoperative management is pursued, we recommend operative intervention if there is neurological deterioration or appearance of SEP abnormality and suggest operative intervention if the patient fails to improve. Predicting factors that indicate a possible deterioration during nonoperative management are: circumferential cord compression in axial MRI, reduced diameter of CSF space, hypermobility of spinal segment, angular edged deformity, instability, greater angle of vertebral slip, lower segmental lordotic angle, and presence of OPLL. Important predictors of myelopathy development include the presence of symptomatic radiculopathy, prolonged MEPs and SEPs and electromyography signs of anterior horn cell lesions (low evidence). Duration of symptoms has a greater impact on outcomes. Substantial delay in surgical management leads to suboptimal outcome. In other words, patients are likely to achieve a better result after surgery if they have a shorter duration of symptoms (low evidence). As there is still clinical equipoise between surgery and conservative treatment in mild CSM, the WFNS Spine Committee strongly encourages randomized controlled trials comparing surgical versus nonsurgical interventions in mild CSM. There is also a need to analyze the cost effectiveness, standardized methodology and costs of long-term follow-up in mild CSM. In patients with CSM, the indications for surgery include persistent or recurrent radiculopathy nonresponsive to conservative treatment (3 years); progressive neurological deficit; static neurological deficit with severe radicular pain when associated with confirmatory imaging (CT, MRI) and clinical-radiological correlation. The indications of anterior surgery for patients with CSM include straightened spine or kyphotic spine with a compression level below three.</td>
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</tr>
</tbody>
</table>

WFNS, World Federation of Neurosurgical Societies; SINch, Italian Neurosurgical Society; QoL, quality of life; SEP, somatosensory evoked potential; MRI, magnetic resonance imaging; CSF, cerebral spinal fluid; OPLL, ossification of the posterior longitudinal ligament; MEP, motor evoked potential; CT, computed tomography.

5) and 2 new statements were proposed. The statements suggested for the vote and consequent results are:

(9) Stand-alone laminectomy, in absence of superiority/inferiority study respect to the different posterior techniques, may be considered a valuable surgical option. This statement reached a positive consensus with an agreement of 79.5% (more than 40% voted grade 3 of Linkert Scale).

(10) Stand-alone laminectomy is advisable in cases with preserved cervical lordosis and in patients with low risk to develop late instability. This statement reached a positive consensus with 84.61% of positive votes (5.13% voted grade 1, 15.38% voted grade 2, 41.03% grade 3, 17.96% grade 4, 20.51% grade 5).
Table 4. Recommendations for anterior surgical approach for cervical spondylotic myelopathy (CSM)

<table>
<thead>
<tr>
<th>Recommendations for anterior surgical approach</th>
<th>WFNS</th>
<th>SINch</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are many options for anterior decompression such as anterior cervical discectomy and fusion (ACDF), anterior cervical corpectomy and fusion (ACCF), oblique corpectomy, skip corpectomy and hybrid surgery.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>A corpectomy is a good option for a ventral compression of less than 3 vertebral segments where a single level disc and osteophyte excision are inadequate to decompress the cord in patients with CSM. In cases with a kyphotic deformity of the cervical spine, corpectomy can restore the normal lordotic curvature alignment.</td>
<td>√</td>
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</tr>
<tr>
<td>In cases of a multisegment disease with contiguous multisegment compression, alternate segment discectomy/osteophyte removal while keeping the body of the intervening vertebra intact is biomechanically more stable than a complete corpectomy with contiguous segment discectomy.</td>
<td>√</td>
<td></td>
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<tr>
<td>An oblique partial corpectomy can improve the sagittal canal diameter substantially. However, this procedure may be difficult to perform in cases with bilateral radiculopathy. If there is significant instability, oblique corpectomy should not be chosen.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>The incidence of the Horner syndrome due to unilateral disruption of the sympathetic chain has been decreased to less than 5% by some modifications in surgical technique.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>In the elderly age groups with bony ankylosis due to osteophytes at C5–6–7, CSM may manifest at higher levels where motion segments are preserved, especially the C3-4 level and also at lower levels such as the C7-T1 level.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Improvement after anterior surgery for CSM has been reported in 70% to 80% of patients. Japanese Orthopedic Association recovery rates are around 60% to 70%.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>There is no significant difference of success rates with ACDF, ACCF, and oblique corpectomy.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Reported complications resulting from anterior surgeries for CSM are quite variable.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Approach-related complications (dysphagia, dysphonia, esophageal injury, respiratory distress etc.) are more often than neurologic, and implant-related complications. With appropriate choice of implants and meticulous surgical technique, the surgical complications should be seen only rarely.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Selection of surgical approach</td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

There are several factors that should be considered for selection of surgical approach in patients with CSM: sagittal curvature, locations of the compressive pathology, number of levels involved, and patient comorbidities.

WFNS, World Federation of Neurosurgical Societies; SINch, Italian Neurosurgical Society.

6. Group 6: Role of Neurophysiological Monitoring

One out of 3 statements was accepted without revision with 2 being modified (Table 6), 4 new statements were proposed. The statements suggested for the vote and consequent results are:

(11) The value of monitoring during anterior cervical discectomy and fusion surgery is questionable due to high rate of false positive. This statement reached a positive consensus with 79.5% of positive votes (4.11% grade 1, 16.44% grade 2, 38.36% grade 3, 15.07% grade 4, 26% grade 5).

(12) It is preferable to use both intraoperative MEP/SEP during posterior approaches for CSM surgery, as they may be useful to change some surgical choices. This statement reached a positive consensus, although with a percentage of 67.13%, at the limit with nonconsensus (4.11% grade 1, 28.77% grade 2, 38.36% grade 3, 12.33% grade 4, 16.44% grade 5).

(13) Intraoperative MEP/SEP worsening is specific, but it does not show clinical worsening in every incidence. This statement reached a strong positive consensus with 93.25% of positive votes (none voted grade 1, 6.76% grade 2, 45.95% grade 3, 20.27% grade 4, 27.03% grade 5).

(14) Preoperative MEP have a significant and linear correlation with clinical presentation (modified Japanese Orthopedic Association scale, mJOA) and are particular helpful for early diagnosis in “silent” or subclinical CSM form. This statement reached a positive consensus with an agreement of 82.1% (2.56% grade 1, 15.39% grade 2, 43.59% grade 3, 17.96% grade 4, 20.51% grade 5).

(15) Preoperative SEP seems useful to predict development of CSM in case of cervical stenosis, and has a good correlation with the prognosis of the disease. This statement reached a positive consensus with an agreement of 71.8% (5.13% grade 1, 23.08% grade 2, 38.46% grade 3, 10.26% grade 4, 23.08% grade 5).

(16) MEP/SEP may be performed at 6 months follow-up after surgery in case of absence of clinical changes or in persistent compression at magnetic resonance imaging (MRI). This statement reached a positive consensus with 71.8% of positive votes.
Table 5. Recommendations for posterior and combined surgical approaches

<table>
<thead>
<tr>
<th>Recommendations for posterior and combined surgical approached</th>
<th>WFNS</th>
<th>SINch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior surgical decompression is an effective technique in improving the neurological function of patients with CSM.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Posterior surgical techniques for CSM consist of laminectomy alone, laminectomy with fusion, and laminoplasty.</td>
<td>√</td>
<td></td>
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<tr>
<td>These techniques are often used if there are 3 or more levels anterior compressions. But, in cases with significant posterior compression at 1 or 2 levels, posterior decompressive surgeries are mandatory.</td>
<td></td>
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</tr>
<tr>
<td>The relative merit of different posterior decompression techniques has not been well determined. In kypotic cases, especially if it is a flexible kyphosis, laminectomy and posterior fixation with fusion should be chosen. However, in rigid kyphosis, an anterior surgery combined with a posterior decompression should be preferred. In cases with preserved lordosis, laminoplasty is a good option. Cases with severe axial neck pain should not be a candidate for laminoplasty. However, there are always gray zone cases such as straightened cervical spine that we do not know for sure which approach is better.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Combined approach should be chosen in patients with significant ventral and dorsal osteophytic compression which cannot be handled holistically with a single anterior or posterior surgery.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Multiple factors must be taken into account when deciding on the appropriate operation for a particular patient. Surgeons need to tailor their preoperative discussion to alert patients about these facts.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Complications resulting from posterior surgeries for CSM include injury to spinal cord and nerve roots, implant-related complications, C5 palsy, spring-back closure of lamina after laminoplasty, post-laminectomy kyphosis.</td>
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</tr>
<tr>
<td>In comparing laminectomy to laminoplasty, there is a trend towards laminoplasty being better than traditional laminectomy but relatively equivalent to newer techniques of minimally invasive skip laminectomies.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Future directions about surgical approaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current knowledge is deficient, especially considering the cost to benefit analysis of various surgical approaches, comparative efficacy of surgical approaches using various techniques, and long-term follow-up to determine outcomes. Therefore, continued research into outcomes of cervical spine surgery is essential.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Since randomized controlled studies are very difficult to conduct in spine surgery, prospective registries with long-term follow-up will be important for our future decisions.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Stand-alone laminectomy, in absence of superiority/inferiority study respect the different posterior techniques, may be considered a valuable surgical option.</td>
<td>New</td>
<td></td>
</tr>
<tr>
<td>Stand-alone laminectomy is advisable in cases with preserved cervical lordosis and in patients with low risk to develop late instability.</td>
<td>New</td>
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</tbody>
</table>

WFNS, World Federation of Neurosurgical Societies; SINch, Italian Neurosurgical Society; CSM, cervical spondylotic myelopathy.

Table 6. Recommendations for value of electrophysiology for cervical spondylotic myelopathy (CSM)

<table>
<thead>
<tr>
<th>Recommendations for value of electrophysiology during surgery</th>
<th>WFNS</th>
<th>SINch</th>
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</thead>
<tbody>
<tr>
<td>The value of monitoring during ACDF surgery is questionable due to high rate of false positive.</td>
<td>×</td>
<td>Rev</td>
</tr>
<tr>
<td>EMG and MEP monitoring have been found to be useful to decrease C5 root palsy during CSM surgery.</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Intraoperative MEP/SEP worsening is specific, but it does not show clinical worsening in every incidence.</td>
<td>×</td>
<td>Rev</td>
</tr>
<tr>
<td>Is preferable to use both intraoperative MEP/SEP during posterior approaches for CSM surgery, as they may be useful to change some surgical choice.</td>
<td>New</td>
<td></td>
</tr>
<tr>
<td>Preoperative MEP have a significant and linear correlation with clinical presentation (mJOA) and are particular helpful for early diagnosis in “silent” or subclinical CSM form.</td>
<td>New</td>
<td></td>
</tr>
<tr>
<td>Preoperative SEP seems useful to predict development of CSM in case of cervical stenosis, and have a good correlation with the prognosis of the disease.</td>
<td>New</td>
<td></td>
</tr>
<tr>
<td>MEP/SEP may be performed at 6 months follow-up after surgery in case of absence of clinical changes or in persistent compression at MRI.</td>
<td>New</td>
<td></td>
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</tbody>
</table>

WFNS, World Federation of Neurosurgical Societies; SINch, Italian Neurosurgical Society; ACDF, anterior cervical discectomy and fusion; EMG, electromyography; MEP, motor evoked potential; SEP, somatosensory evoked potential; mJOA, modified Japanese Orthopedic Association; MRI, magnetic resonance imaging.
Table 7. Recommendations for follow-up and outcome for cervical spondylotic myelopathy (CSM)

<table>
<thead>
<tr>
<th>Recommendations for follow-up and outcome for CSM</th>
<th>WFNS</th>
<th>SINch</th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome measures</strong></td>
<td></td>
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<tr>
<td>There is a variety of outcome measures used for CSM. As functional measures we recommend modified Japanese Orthopedic Association scale (mJOA), Nurick grade and myelopathy disability index.</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Walking tests can be used for quantitative measurements although is not a standardize tool. 36-item Short Form health survey is a good functional quality life measure.</td>
<td>×</td>
<td>Rev</td>
</tr>
<tr>
<td><strong>Clinical variables affecting outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three clinical variables that are most commonly related with CSM are age, duration of symptoms and severity of the myelopathy at presentation. Greater the age, the longer the duration of symptoms and the more severe symptoms at presentation, the more adverse outcomes can be expected after surgery.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>However, examination findings require more detailed study to validate their effect on the outcomes of surgery. The predictive variables which were studied and seemed to affect the outcomes in CSM are hand atrophy, leg spasticity, clonus and Babinski sign.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Radiological variables affecting outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical alignment parameters are correlated with general health scores and myelopathy severity. The curvature of the cervical spine seems as one of the most important variables.</td>
<td>×</td>
<td>Rev</td>
</tr>
<tr>
<td>Cervical spine kyphosis predicts worse outcomes. Neurological improvement is significant in patients with normal cervical lordosis.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Instability of the cervical spine is predictive for outcomes. In patients with single segmental CSM with instability, longer duration of symptoms, lower preoperative JOA score, and more preoperative physical signs are highly predictive of a poor surgical outcome.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Spinal cord compression ratio is a critical factor for prognosis of CSM. However, anteroposterior diameter of the spinal canal has no clinical significance.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Spinal cord atrophy cannot predict outcomes.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>High signal intensity on T2-weighted magnetic resonance (MR) images is a negative predictor for prognosis.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical variables affecting outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery should be done from anterior or posterior if the disease is focal (1 or 2 levels).</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>If the anterior compression is more than 2 levels or if it is a diffuse narrowing, posterior decompression should better be chosen.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>The most important factor on decision-making in cases with multilevel (more than 2) CSM is cervical sagittal vertical axis.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Diffusion tensor imaging sequences on MR images have good capacity to predict outcome in CSM.</td>
<td>✓</td>
<td>New</td>
</tr>
</tbody>
</table>

WFNS, World Federation of Neurosurgical Societies; SINch, Italian Neurosurgical Society.

(10.26% grade 1, 17.95% grade 2, 38.46% grade 3, 17.95% grade 4, 15.38% grade 5).

7. Group 7: Follow-up and Outcome

Eleven statements were accepted without revision, 2 were suggested for revision (Table 7) and 1 new statement was proposed. The statements suggested for the vote and consequent results are:

(17) Walking tests can be used for quantitative measurements although are not a standardize tool. 36-Item Short Form Survey (SF-36) is a good functional quality life measure. This statement reached a positive consensus with an agreement of 86.5% (none voted grade 1, 13.51% grade 2, 50% grade 3, 24.32% grade 4, 12.16% grade 5).

(18) Cervical alignment parameters are correlated with general health scores and myelopathy severity. The curvature of the cervical spine seems one of the most important variables. This statement reached a positive consensus with 79.7% of positive votes (2.7% grade 1, 17.57% grade 2, 48.66% grade 3, 13.51% grade 4, 17.57% grade 5).

(19) Diffusion tensor imaging (DTI) sequences on MR images have good capacity to predict outcome in CSM. This statement reached a positive consensus with an agreement of 80.8% 1.37% grade 1, 17.81% grade 2, 45.21% grade 3, 17.81% grade 4, 17.81% grade 5).
DISCUSSION

Although the recommendations of WFNS are useful and provide well balanced indications for the management of spine pathologies in some points may not reflect the current national necessity.

Following we discuss critically the single revision works of each group.

1. Group 1: Natural Course and Clinical Presentation

The literature prior to 2019 seems to be consistent with the statements regarding the natural history of CSM and there are no relevant articles after that year.

However, little is known about the spontaneous course and prognosis of clinically “silent” presymptomatic spondylotic cervical cord compression. In this scenario, patients should be counselled on the risk of developing myelopathy and the option of surgery; if nonoperative management is chosen, frequent reassessment is warranted.8,9

Similar considerations are advised in the clinical guidelines for the management of CSM proposed by Badhiwala et al.10 Also in the Italian reality the warning for future neurological deficits development is considered important in relationship to the good QoL and life expectancy and may be considered as part of a preventive attitude of our Health Care System.

2. Group 2: Diagnostic Tests

The analysis of the literature did not result in substantial innovations with respect to almost all the statements of this section except for one. The statement “Electrophysiological tests may have better outcome predictions than MR changes.” appears limited in this form.

In our country the use of electrophysiology in all the phases of study for this pathology (preop-, intraop-, and postoperation) is important. On one side for its predictive value, especially in preoperative evaluation for subclinical myelopathy presence/evolution, and on the other hands as prediction of postoperative outcome.

In particular preoperative SEP/MEP may be useful to better analyze radiological CSM associated with normal/subclinical signs of myelopathy and can be added to the surgical decision-making tools. In fact, electromyography, sensory-evoked potential abnormalities and clinical radiculopathy, when present in patients with subclinical cord compression, predicted the development of CSM.11 Patients with significant cervical cord compression on MRI, but having symptomatic spondylotic cervical stenosis (i.e., with no clinical myelopathy signs), risk of early progression into symptomatic CMS (< 1 year) was predicted by the presence of symptomatic radiculopathy and abnormal SEPs and MEPs.11,12

3. Group 3: Conservative Treatment Versus Surgical Treatment

The analysis of the literature, especially after 2019 did not bring substantial innovations with respect to all of the statements in this section, except for one.

The statement “We suggest offering surgical intervention or rehabilitation for patients with mild CSM (mJOA score 15–17). If at the beginning nonoperative management was followed, we recommend operative intervention when rapid progression of symptoms appear. Nonoperative management may be considered for slowly progressive disease” required revision. In fact, in 2018, shortly before the publication of the WFNS guidelines, Koyanagi13 defined “mild myelopathy” with a score of 11 or greater on the neurosurgical cervical spine scale and did not use mJOA. In their series of 84 surgically treated patients, 9 met these criteria and the indication for surgical treatment depended on various factors; in fact, they concluded by stating that patients with mild myelopathy often show preserved QoL. Similar considerations appeared in a work published in 202014: the authors stated that mild CSM represents a heterogeneous population with some patients who would benefit from surgical intervention.

Furthermore, in the same year, a Canadian group published a work,15 in which they analyzed the characteristics and the clinical outcome in 122 patients with mild myelopathy according to the mJOA criteria, and found that patients selected for nonoperative management had higher QoL and less physical/mental function at baseline than those treated surgically, while they noticed that the cord signal intensity does not appear to correlate with severity of clinical symptoms or progression. Again, the Fehlings group in 201916 raised the problem of the sensitivity of the various scales, in particular the mJOA, in correctly differentiating between patients with “mild” forms those most disabled by their morbid condition. Finally, Feng et al.17 proposed the predictive role SEP classification in identifying progressive myelopathy in patients with mild CSM.

Therefore, in consideration of the above, the group proposed to reformulated the statement as follows: “When counselling patients with mild CSM, QoL assessment should be part of the examination and physical function in day-to-day activities as social functioning should be carefully investigated while taking

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in consideration the patient’s reported performance status. We suggest offering surgical intervention to patients with substantial reduction of QoL and greater neck pain and motor impairment at presentation or serious SEP abnormality. A supervised trial of structured rehabilitation should be offered to patients with mild CSM with better QoL and less physical/mental dysfunction. If initial nonoperative management is pursued, we recommend operative intervention if there is neurological deterioration or appearance of SEP abnormality and suggest operative intervention if the patient fails to improve.” For an easier clinical application this statement was divided and proposed in 4 different recommendations.

In general, we can conclude that in our country, basing on literature review and expert opinion, there is a more interventional behavior also in aged patients if the QoL and functional status are good or in case of progressive worsening. Also, in this case a fundamental role is played by the QoL guarantee and life expectancy.

The surgical treatment by anterior or posterior approach is nowadays worldwide well stated and this is reflected by the fact that any of the statement proposed by WFNS was revised. The Italian committee added 2 statements in favor of decompressive surgery without fusion in absence of present or delayed instability.

4. Group 4: Anterior Surgical Treatment

The analysis of the literature, especially after 2019 did not bring substantial innovations with respect to all the statements of this section.

5. Group 5: Posterior and Combined Surgical Treatment

The analysis of the literature did not underline substantial new data with respect to the statement of this section. Regarding the role of cervical laminectomy with or without posterior fusion, literature remains uncertain regarding the better choice. Kim and Dhillon in a comparative study published in 2019 concluded that in carefully selected patients with normal preoperative cervical sagittal alignment stand-alone laminectomy may offer acceptable results. And although the risk to develop postoperative kyphosis is higher this is partially compensated by the higher risk correlated with posterior instrumentation itself. Kotter et al. stated that globally cervical laminectomy with instrumented fusion is more effective, with a similar rate of preoperative complications. However, the authors stress the limitation of the study due to the bias of patient selection more unbalanced in favor of laminectomy and fixation. A similar conclusion was also presented by McAllister et al.: In particular, they found short-term results similar, with better results in the long-term period in favor of laminectomy and fixation. For these reasons and based on expert opinion, the group proposed 2 further statements: “Stand-alone laminectomy, in absence of superiority/inferiority study respect to the different posterior techniques, may be considered a valuable surgical option” and “Stand-alone laminectomy is advisable in cases with preserved cervical lordosis and in patients with low risk to develop late instability.”

At the end of the literature revision process for the different surgical approach the group underlined that in literature analysis the recommendations are mainly based on patients without Parkinson Disease (PD). We acknowledge the lack of available evidence on surgical indications and outcomes of cervical approaches in these patients. The group think that this pathological condition cannot be ignored related to progressively aging of the population with CSM that is eligible for surgery especially in our local reality. Thus, clinical and surgical recommendations have to rely on the biomechanical and physio pathological features of PD and on anterior approaches indications and drawbacks for non-PD patients. Therefore, recommendation for the different approaches in PD patients should rely on the ones made for non-PD patients and on nonspecific considerations about instrumented surgery in PD patients. Future studies may analyze this subpopulation in order to better assess these aspects.

6. Group 6: Role of Neurophysiological Monitoring

In this group, the analysis of literature, as well as daily practice and expert opinion, found the more relevant modification. In fact, out of the 3 recommendations proposed by WFNS Spine Committee 2 statements were modified and 4 new were proposed.

The role of neurophysiological monitoring in the preoperative phase was discussed in detail in group 2. Severino et al. tried to analyze the definition of patient selection and detection of best responders for surgical treatment in CSM. The authors suggest a multidisciplinary evaluation, especially in silent form, including the preoperative evaluation MEP/SEP and in this study, MEP notably appears to correlate with mJOA. According to different studies MEP seems to be more sensitive in detecting the chronic form of CSM. Instead, preoperative SEP seems useful in predicting the development of CSM in cases of cervical stenosis, and show a good correlation with the prognosis of the disease. The role of EMG in CSM is limited only in
cases associated with radiculopathy.\textsuperscript{23}

 Numerous studies have been published recently regarding the role of intraoperative monitoring (IOM) during surgery for CSM.\textsuperscript{24,25} However, clear scientific evidence is still lacking. One of the most common drawbacks is the bias of alert criteria adopted during surgery. In particular, the role of IOM during anterior surgery remains unclear, while when a posterior approach is performed in cases of multilevel myelopathy, a combination of MEP and SEP may predict clinical worsening, allowing the modification of some surgical choices during surgery. Moreover, intraoperative MEP/SEP worsening is specific, but it does not show clinical worsening in every incidence.

 The role of MEP/SEP in postoperative care and follow-up have still not been analyzed well. SEP are described as more sensitive with respect to preoperative data, especially when improvement is achieved. Based on the previous discussion and role of MEP and SEP, these evaluations may be suggested at 6-month follow-up after surgery in case of the absence of clinical changes or in persistent compression at MRI.

7. Group 7: Follow-up and Outcome

 Literature analysis did not result in substantial innovations with respect to almost all the statements of this section, except for two. Their adjunct is mainly due to easy regional access to MRI studies for both preoperative evaluation and postoperative follow-up.

 In the outcome measures section, the second statement was revised after literature review: in fact, though simple to apply in clinical practice, walking test is administered in such different ways that it is hard to obtain any universal validation. As for the JOA scale, it may easily reflect other pathological conditions, such as hip or knee osteoarthritis. On the other hand, the SF-36 seems to us an excellent tool in ascertaining the degree of QoL; however, it is too generic to evaluate CSM, which is a disease with several, and different, clinical and radiological aspects.

 Literature review regarding the radiological variables affecting outcome showed new interesting studies. The growing interest toward sagittal balance of the spine led to the development and validation of several parameters for assessing the correct alignment of cervical elements. Several studies investigated the correlation between sagittal parameters and mJOA score. The multicenter AOSpine North America Cervical Spondylotic Myelopathy Study found that mJOA scores correlated negatively with C2–7 sagittal vertical axis (SVA), C2 tilt, C2 slope. The mJOA score correlated weakly with T1 slope minus C2–7 Cobb angle. It was not detected to correlate significantly with center of gravity-C7 SVA, C2–7 Cobb angle, or the posterior or anterior length of the spinal column (level of evidence III). These findings have been the pillars of the AOSpine North America study group statements regarding cervical radiographic alignment.\textsuperscript{26,27}

 Yuan et al.\textsuperscript{28} demonstrated through multiple linear regression that age combined with C2–7 SVA is a sensitive predictor of mJOA (level II evidence). Lin et al.\textsuperscript{29} found that myelopathy progresses slowly, in patients with C2–7 Cobb angle > 29, whilst cervical curvature index change constant is the only independent risk factor for the Neck Disability Index increase (level II evidence). Buell et al.\textsuperscript{30} detected that neurological improvement was significant related to preoperative normal cervical lordosis (level of evidence V). Roguski et al.\textsuperscript{31} found that preoperative and postoperative C2–7 SVA measurements are independent predictors of clinical outcome (class III evidence). Contrariwise, Passias et al.\textsuperscript{32} state that although global spine parameters are strictly interconnected with the outcome, there is no relationship between cervical-specific sagittal parameters and mJOA (level of evidence III).

 In conclusion, the relationship between postsurgical cervical sagittal alignment and clinical outcome remains controversial and has not yet been proved. We found 2 studies (level of evidence class II and IV) that cannot identify a clear correlation, and 3 studies (2 with level of evidence class II and 1 class III) that do not detect any correlation.\textsuperscript{19,33-36}

 Although conventional MRI is an excellent modality for the determination of spondylotic changes, it is known to have a sensitivity as low as 65% in the identification of myelopathy.\textsuperscript{37}

 Several novel techniques have been employed to improve detection of increased signal intensity, namely double diffusion encoding, spinal cord perfusion and diffusion MRI, MR spectroscopy, functional MRI. Interestingly, these methods also appear to be related to clinical outcomes.\textsuperscript{38}

 In a prospective multicenter study, Ozawa et al.\textsuperscript{39} observed that preoperative intramedullary Gd-DTPA enhancement was indicative of poor prognosis. DTI effectiveness in predicting prognosis of CSM patients has been widely investigated and accepted (7 studies level of evidence II, 1 study level of evidence III).\textsuperscript{20,40-45}

 Furthermore, Rao and Severino’s findings were concordant in identifying transfer area (TA) values of 0.55 as a cutoff for the prognosis of CSM patients. Rao et al.\textsuperscript{45} found preoperative TA < 0.55 to be associated with significantly poorer outcome (class II evidence). Severino et al.\textsuperscript{20} detected higher TA amongst “best responder” patients to surgery. Thus, they identified TA
> 0.55 as a predictor of a better postoperative outcome (class III evidence).

Eicker et al.\(^4\) demonstrated that patients in the acute-onset phase of symptomatic CSM, and also patients with chronic-stable myelopathy and new-onset symptoms, exhibit a focally increased glucose hypermetabolism (18F-fluorodeoxyglucose uptake) at level of stenosis and cord compression. Decompressive surgery during the phase when hypermetabolism is present results in a better clinical recovery and favorable outcome. Whilst the chronic phase of CSM is featured by a post stenotic glucose hypometabolism occurring, suggesting an irreversible impairment of the spinal cord.\(^6\)

**CONCLUSION**

These recommendations reflect the more contemporary treatment concepts for CSM as presented in the highest quality clinical literature and best clinical practices available on this subject. The WFNS recommendation represents the road-map to be followed, but with this paper the spinal section of the SINch reconsider it considering the different possibilities and facilities of our Society and of the National Health Care System.

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**REFERENCES**


Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury

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Cell death is a systematic/nonsystematic process of cessation of normal morphology and functional properties of the cell to replace and recycle old cells with new also promoting inflammation in some cases. It is a complicated process comprising multiple pathways. Some are well-explored, and others have just begun to be. The research on appropriate control of cell death pathways after acute and chronic damage of neuronal cells is being widely researched today due to the lack of regeneration and recovering potential of a neuronal cell after sustaining damage and the inability to control the direction of neuronal growth. In the progression and onset of various neurological diseases, impairments in programmed cell death signaling processes, like necroptosis, apoptosis, ferroptosis, pyroptosis, and pathways directly or indirectly linked, like autophagy as in nonprogrammed necrosis, are observed. Spinal cord injury (SCI) involves the temporary or permanent disruption of motor activities due to the death of a neuronal and glial cell in the spinal cord accompanied by axonal degeneration. Recent years have seen a significant increase in research on the intricate biochemical interactions that occur after a SCI. Different cell death pathways may significantly impact the subsequent damage processes that lead to the eventual neurological deficiency after an injury to the spinal cord. A better knowledge of the molecular basis of the involved cell death pathways might help enhance neuronal and glial survival and neurological deficits, promoting a curative path for SCI.

Keywords: Cell death pathways, Programmed cell death, Nonprogrammed cell death, Spinal cord injury

INTRODUCTION

Spinal cord injury (SCI) is the traumatic or nontraumatic damage to the spinal cord, causing impairment of motor function and leading to morbidity or permanent paralysis.1 In today’s world, SCI is still a significant source of illness and mortality. Acute traumatic SCI affects people worldwide, with an annual incidence of 15–40 cases per million.2 SCI is particularly concerning on a social level because it primarily affects young, otherwise healthy people, with injuries happening most frequently in those between the ages of 15 and 25.3 Creating effective recovery treatments requires a thorough understanding of SCI pathophysiology, stages, and diverse wound recovery mechanisms.4 The major reason of SCI progression is the death of these different types cells relevant to spinal cord structural and functional homeostasis, initiated by numerous crosstalk between different cell death pathways. Many cell types interact in normal spinal cord physiology, including astrocytes, neurons, microglia, and oligodendrocytes. These multicellular interactions are disrupted and disorganized after an SCI, resulting in slowed spinal healing.5 The critical process of neuroinflammation, which is connected to SCI, is implicated in neutrophils, microglia, macrophages, astrocytes, dendritic cells (DCs), B- and T-lymphocytes, as well as molecules including cytokines and...
prostanoids." It involves the death of spinal cord neurons and associating glial cells like astrocytes, oligodendrocytes, and microglia. Neuronal and glial cell death ultimately catalyzes axonal degeneration, accelerating SCI progression. Apoptosis, autophagy, and necrosis are well established in SCI. They are well-documented in helping axonal degeneration also. New cell death pathways include common ones like ferroptosis, mitoptosis, parthanatos, and pyroptosis, and rare ones like oxiptosis, alkaliptosis, and autoschizis, being discovered in the pathogenesis and progression of SCI.

Due to their activation, SCI inevitably results in functional decline. The severity of subsequent damage caused by a cascade of cellular and molecular processes initiated by the primary trauma determines the fate of SCI. After a human SCI, the necrotic and apoptotic cell death processes are known to occur. The contribution of autophagy in SCI is also well established. The spinal cord’s diameter is relatively small, and even a tiny transverse expansion of initial damage would result in a more significant disconnection between the brain and the spinal cord below the lesion site. Therefore, developing strategies to limit the secondary degenerative processes would be of utmost importance in SCI research. This review aims to summarize all programmed and non-programmed cell death (non-PCD) pathways along with their molecular mechanisms, crosstalks and involvement in the progression of the pathophysiology of SCI to pave the way for developing effective treatment strategies.

CELL DEATH PATHWAYS AND THEIR RELEVANCE IN THE PROGRESSION OF SCI

Cell death is the biochemical process by which a cell loses its ability to maintain its cellular morphology and homeostasis and serve its functions. It can be programmed when a cell becomes too old to continue serving its normal function or can be nonprogrammed, spontaneously induced by specific mechanical, ischemic or chemical trauma, causing the cell to die spontaneously. On one side, cell death is essential for a cell to cease its morphological and functional features through complicated programmed or nonprogrammed interactions, leading to organismic homeostasis. On the other hand, it can be detrimental as it can promote inflammation at the death site and affect other healthy cells to die, making it a double-edged sword.

The hallmarks of multiple cell death modes are identified and fitted into a basic classification framework, where cell death entities are classed as programmed or non-PCD, depending on their signal dependency. PCD is categorized into 2 types: apoptotic and nonapoptotic cell death. Programmed apoptotic cell death causes apoptosis and anoikis showing membrane blebbing, mitochondrial disruption, and cell detachment from the surface. Programmed nonapoptotic cell death includes vacuole-presenting cell death (autophagy, entosis, methusoriasis, and parapoptosis), mitochondria-dependent cell death (mitoptosis and parthanatos), iron-dependent cell death (ferroptosis), and immunomodulatory cell death (pyroptosis and NETosis). Non-PCD includes necrosis which is vital in injury progression. Cell death is vital in disease development, notably cancer and injuries.

All cell death pathways show a plethora of morphological changes like the formation of fluid-filled bubbles inside the cell (paraptosis), mitochondrial disruption (mitoptosis and parthanatos), accumulation of iron (ferroptosis), formation of extracellular traps and gasdermin D mediated cleavage formation (NETosis and pyroptosis) or spontaneously induced (necrosis). Understanding cell death is vital for understanding how some illnesses progress, which leads to new treatment development (Figs. 1, 2).

Cell death pathways play a major role in SCI pathogenesis and progression. Initial tissue injury results in secondary injury, which further damages the spinal tissues chemically and mechanically, causes neuronal excitotoxicity because the calcium level in the cells is too high, and increases reactive oxygen and glutamate levels. These events result in brain/spinal cord dysfunction by harming the underlying proteins, phospholipids, and nucleic acids. The secondary injury phase, which follows the main damage phase and lasts several weeks, reflects multifeatured pathological processes. Caspase-mediated cell signaling, ischemia, vasculopathy, hydrops, excitotoxicity, ionic imbalance, inflammation, lipid peroxidation, free radical generation, demyelination, Wallerian degeneration, microglial scarring, and cyst formation are all clinical manifestations of secondary injury.

Ischemia is one of the major factors in disease progression, which can develop very once after traumatic SCI, and if it goes untreated, further damage may start within the first 3 hours and last for at least 24 hours. In addition, monocytes, neutrophils, T and B lymphocyte cells, and macrophage infiltration occur due to blood vessel breakage, which causes bleeding in the spinal tissues. This phenomenon is also associated with the release of inflammatory cytokines such as interleukin (IL)-1α, IL-1β, IL-6, and tumor necrosis factor (TNF) after 6 to 12 hours following damage. Inflammation of neurons is promoted by immune cell penetration and inflammatory cytokines. Secondary injuries come in 3 forms: acute, subacute, and chronic, followed by primary injury.
Further, multiple inflammatory mediators, such as leukotrienes, bradykinin, prostaglandins, platelet-activating factors, and serotonin, are present in higher concentrations in the injured area. Cell death is the cell’s final event, which can be segregated into 2 forms; apoptosis and necrosis. Apoptosis is the PCD pathway; nowadays, many PCDs are discovered. On the other hand, apoptosis is a known physiological process that usually occurs and may be crucial in secondary SCI. The secondary injury after SCI is thought to be caused by the continuation of cellular destruction through apoptosis, and the long-term neurological deficits after SCI may result from a wide range of apoptosis of neurons and oligodendrocytes in the injured spinal cord.

DIFFERENT CELL DEATH PATHWAYS ASSOCIATED WITH SCI

SCI pathophysiology is characterized by blood-spinal cord barrier collapse and breakdown, transmigration of immune cells, rupture of cellular axons and membranes, and myelin disintegration. Some key signaling pathways, including CDK1/E2F1, AMPK/SIRT1, JNK/c-JUN, and Wnt-β-catenin signaling pathways, are already involved in regulating apoptotic activity in SCI. Recently, programmed and non-PCD has been recognized as a significant process after SCI. Several kinds of cell death pathways, including apoptosis, autophagy, ferroptosis, paraptosis, netosis, pyroptosis, and necroptosis, have been found in the direct link in the progression of primary and secondary SCI.

Here we will discuss them in more depth and detail (Fig. 3).
Cell Death Pathways in SCI

1. Programmed Apoptotic Cell Death in SCI

1) Apoptosis in SCI

Apoptosis is the most typical form of PCD, where cells die systematically in a signal-mediated manner, influenced by a cysteine protease caspase family-mediated cell death leading to planned self-destruction of the cell. It is highly relevant to the progression of SCI. It is immunologically silent that occurs either by intrinsic (mitochondrial), extrinsic (death receptor [DR] triggered), or granzyme/perforin pathway-mediated mechanisms. Inflammatory mediators, free radicals, and excitotox-
Fig. 3. Essential pathways involved in cell death associated with spinal cord injury. This image illustrates different cell death pathways and their crosstalks (apoptosis, anoikis, autophagy, methuosis, entosis, paraptoxis, parthanatos, mitoptosis, ferroptosis, NE-Tosis, pyroptosis, necroptosis, oxieptosis, and alkaliptosis). Anoikis uses the same signaling pathways as apoptosis involving the membrane and mitochondrial disruption and activation on executioner caspase-3, except that poor or incorrect cell-matrix connections trigger it. This caspase 3 can also trigger mitochondrial rupture causing mitoptosis and PARP1 activation causing AIF and MIF to dimerize and translocate to trigger parthanatos. Autophagy basically involve ULK1 mediated autophagosome formation that one side can trigger cleaning of cellular debries at injury site and also promote inflammation by triggering cytokine production. Ferroptosis involves GPX4 activation by iron accumulation leading to pH change and ROS production possibly triggering oxieptosis and alkaliptosis. Necoptosis occurs by MLCK phosphorylation induced necrosome formation. Cell death modes with unknown mechanisms were excluded. The arrow direction shows the causal relationship. TRADD, type 1-associated death domain protein; FADD, Fas-associated death domain protein; RIPK, receptor-interacting protein kinase; MLKL, mixed lineage kinase domain-like protein; Bax, Bcl-2-associated X protein; Bid, BH3 interacting-domain death agonist; Bcl-2, B-cell lymphoma 2; Cyt-c, cytochrome-c; Apaf-1, apoptotic protease activating factor-1; Smac, second mitochondria-derived activator of caspase; IAP, inhibitor of apoptosis; ULK1, Unc-51-like kinase 1; MOMP, mitochondrial outer membrane permeabilization; AIF, apoptosis-inducing factor; MIF, macrophage migration inhibitory factor; PARP-1, poly-(ADP-ribose)-polymerase 1; LC3, microtubule-associated protein light chain 3; LAMP1, lysosomal-associated membrane protein 1; Rab-7, Ras-related protein-7; Rho-A, Ras homolog family member A; ROCK, Rho-associated coiled-coil containing protein kinase; GSH, glutathione; GPX4, glutathione peroxidase 4; ROS, reactive oxygen species; JNK, Janus kinase; c-JUN, C-junctional protein.
ins are the chemicals that induce necrosis or apoptosis. They feature positional organelle loss, membrane blebbing, cell shrinkage, and DNA fragmentation after condensation. A wide variety of apoptosis in oligodendrocytes and neurons in the damaged spinal cord may produce long-term neurological abnormalities after SCI. Therefore better knowledge is needed to furnish innovative treatment strategies.

In recent years, more studies have been done on the role of apoptosis in SCI. Apoptosis is seen both in injured human spinal cords and in animal models. The rat spinal cord showed apoptosis in astrocytes, neurons, microglia, and oligodendroglians. Apoptotic oligodendrocytes are seen in white matter longitudinal filaments. Apoptosis-induced damage to type 3 collagen of endoneurium leads to Wallerian degeneration of the neurons of the spinal cord leading to impairment of neurotransmission and motor functions. Neuronal apoptosis was identified 4 hours postinjury and peaked 8 hours later; in glial cells, it peaked 24 hours later; in oligodendrocytes, in the white matter, it peaked 8 days later. Microglial apoptosis was the least frequent at 24 hours and 5 days after injury but rose quickly and peaked at 8 days. The bulk of apoptotic cells may cluster near the damaged spinal cord’s center, explaining why the lesion area continuously enlarges. Apoptosis is detected in oligodendrocytes with Wallerian degeneration in the chronic phase of SCI. It involves activating components of both downstream and upstream origin in the executioner caspase-3 mediated apoptotic pathway after SCI in rats. Following SCI in animals, the Fas DR pathway was revealed to be significant in microglial, oligodendrocytal, and neuronal apoptosis.

Apoptosis is induced by Fas-mediated cysteine protease activation, leading to DNA proteolysis and damage by effector caspases. The function of long noncoding RNAs (lnc-RNAs) and microRNAs (miRNAs) in SCI pathogenesis, including cell death, is also being investigated. MiR-137 targets mitogen-activated protein kinase 2 to inhibit apoptosis after SCI. Using proteomics, Liu et al. discovered Erp29. This critical protein may influence several genes involved in cell death and survival, including Erk and caspase, and ameliorate locomotor activity and function in the rat spinal cord transection model. Gu et al. observed that cutting down long coding XIST RNA reduced neuronal death after SCI by regulating the PTEN/AKT/mTOR pathway and competitively binding miR-494. Another study identified the AKT/mTOR/PTEN signaling pathway implicated in neuronal death after SCI, perhaps through activating the mitochondrial system. It was recently discovered that caspase recruitment domain family member 6 inhibits Caspase-3 signaling and may reduce apoptosis. Understanding apoptosis’s cellular and molecular mechanisms may help identify specific therapeutic targets. Minocycline, CD95 (Fas) ligand antibody blockage, and glycol sphingolipid-induced inducible nitric oxide synthase blocking have all been found to reduce neuronal death and boost the effectiveness of cell transplantation techniques. Zheng et al. observed that miR-142-3p vanquishes apoptosis in rat SCI.

Progranulin deficiency promotes cellular death and neuroinflammation, compromising SCI healing. Zhang et al. discovered that elevated p38 was related to apoptosis and inflammation in a rat SCI contusion model. He also hypothesized that reducing apoptosis and inflammation with the p38 inhibitor SB203580 might help secondary SCI. According to previous research, apoptosis causes tissue lysis and damage post-SCI.

A recent study found that metformin increased β-catenin and brain-derived neurotrophic factor expression, reduced neuron loss and inflammation, and improved functional and motor recovery in rats with SCI. Finding a way to conquer SCI-induced apoptosis has huge therapeutic ramifications. However, the specific pathways triggering apoptotic death of astrocytes, neurons, microglia, and oligodendroglia following SCI are yet unknown.

2) Anoikis in SCI

Anoikis is a form of apoptotic PCD; it occurs because of the detachment of cells from the extracellular matrix (ECM) and is extensively observed in the degradation of oligodendrocytes and Schwann cells.

Inappropriate or inadequate interactions between cells and the matrix trigger it. The altered cytoskeletal dynamics are believed to interact with a critical prosurvival effector integrin. It leads to impaired ECM remodeling and myelin degeneration which worsens the injury and delays recovery. Cell anoikis impedes recovery by aggravating CNS damage and impairing synaptic plasticity and other CNS activities. Immunosuppression and neuroinflammation are 2 significant factors that contribute to anoikis promoting injury progression. To fasten spinal cord regeneration, adult stem cells are generally injected into a damaged location with high inflammation and poor vascularization.

Moreover, the lack/absence of ECM leads to post-traumatic cavity formation. Several studies indicate that after transplantation, the number of surviving stem cells decreases considerably in SCI models because of the death of cells by anoikis. The injury, enzymes are released, which lead to dysfunction and detachment of the ECM cells leading to anoikis; SCI may trigger the neuronal damage by anoikis and enhance the SCI progres-
sion. Anoikis inhibition might be the effective strategy to protect the PCD-induced neuronal damages.\(^{28}\) Biomaterials are already in the research pipeline to prevent this ECM anoikis in SCI. Laminins also help to prevent anoikis in SCI.\(^{24}\)

2. Programmed Nonapoptotic Cell Death in SCI

1) Vacuole-mediated

1) Autophagy in SCI

Autophagy is a controlled process that is initiated to remove cellular proteins and organelles in significant quantities by transporting them into membrane-bound vesicles to be uptaken by lysosomes to form autophagolysosome to initiate autophagic breakdown. They are formed when vesicles merge with lysosomes, and their contents are destroyed by lysosomal enzymes.\(^ {25}\) Autophagy has been shown to accelerate cellular mortality by activating caspase-reliant apoptosis in specific cells.\(^ {36}\) The PI3K/Akt/mTOR signaling pathway is essential in autophagy.\(^ {57}\) Recent research suggests that the lysosomal compartment plays a protective function in the oxidative stress response.\(^ {58}\) Increased autophagy has been documented after SCI, and emerging evidence suggests autophagy may help preserve neuronal and astrocytic cells from death after SCI, supported by the presence of autophagosomes in cultured and wild-type neurons.\(^ {59}\) However, the influence of autophagy in post-SCI neurodegeneration has been hotly contested, with mixed results from earlier SCI investigations.

Autophagy has been proposed as a potential SCI treatment target by specific studies. Metformin has been shown to protect against SCI by increasing autophagy.\(^ {60}\) He at al.\(^ {61}\) cultured CNS neurons and increased autophagy that stabilized microtubules by degradation of SCG10 (superior cervical ganglion protein 10) and increasing axon development. Axon retraction was reduced, axon regeneration increased, and functional recovery improved in SCI. Astrocyte autophagy flux may increase neurological repercussions, neuronal death, and survival. Many researchers have attempted to relate autophagy with apoptosis. Inducing autophagy protects against apoptosis in mice with acute SCI.\(^ {62}\) Autophagy also protects neurons from endoplasmic reticulum (ER) stress. Therefore its breakdown during SCI may cause ER stress-induced neuronal death.\(^ {63}\) Autophagy may protect spinal cord neurons against apoptosis, which may help SCI neuron survival by incorporating beclin-1.\(^ {64}\) A contrasting research report found that lowering autophagosome biogenesis enhances spontaneous functional recovery by reducing distant axonal degeneration in SCI patients.\(^ {65}\)

Recent research found that LC3\(^ {+}\) cells increased considerably at the scar site after the rat spinal cord hemisection model, showing that autophagic cell death often occurs in injured neuronal tissue after SCI.\(^ {66}\) As Purkinje cells die off, phosphorylated MAP1B accumulates in their axonal dystrophic swellings and binds to LC3 at high levels. Therefore, MAP1B-LC3 interaction may contribute to controlling LC3-associated autophagosomes in neurons, especially in axons, under physiological and pathological situations.\(^ {67}\) ABT888, a poly (ADP-ribose) polymerase inhibitor, has recently been shown to protect against SCI by suppressing autophagy.\(^ {68}\) Because of this, autophagy may have both protective and harmful features in SCI. Understanding autophagy’s function in SCI may lead to creating a pleiotropic therapy that targets several pathways and types during the degenerative phase of SCI.\(^ {69}\)

2) Paraptosis in SCI

Paraptosis is another form of PCD, where the cell swells and develops large bubbles or vehicles with the cellular liquid trapped inside and eventually dying off. It occurs because of an imbalance in redox or ion homeostasis.\(^ {70}\) Due to cytoplasmic vacuolation, a novel nonapoptotic and caspase-independent PCD is characterized by ER and mitochondrial dilatation.\(^ {71}\) Previous studies demonstrated a paraptotic response targeting the nucleus in response to paraptosis.\(^ {72,73}\) Some study suggests that cycloheximide and aryl hydrocarbon receptor-interacting protein-1 (AIP-1) may alter paraptosis.\(^ {74}\) Nutlin-3/bortezomib may also disrupt proteostasis to induce long-term structural/functional changes in the mitochondrial and ER, causing mitochondrial/ER stress and, ultimately, cell death via paraptosis.\(^ {75}\)

As a consequence, nothing is known about paraptosis in SCI. Increased p44 expression in the CNS is connected to neuronal death and insulin-like growth factor 1 receptor activation through autophagy and paraptosis.\(^ {76}\) Active microglia may lead to neuronal death with characteristics like vacuolation after the caspase cascade has been halted.\(^ {77}\) Studying the activated microglial role in paraptosis might be an exciting new technique. While paraptosis research has advanced, many questions remain. Paraptosis has not been widely investigated in connection to SCI, indicating that additional study is required.

3) Other minor vacuole-mediated cell death pathways in SCI

Two other critical vacuole-mediated pathways apart from autophagy and paraptosis may have some link in SCI progression. They are entosis and methuosis. Entosis is a novel and interesting nonapoptotic PCD where rather than a cell being swallowed after it is dead, one viable cell actively invades or is pushed into
a neighboring cell and dies afterwards, making this process unique. The internalized cell resides in some vacuole structure. Entosis is not restricted to interactions between just 2 cells but can occur between 3 cells or sometimes more.85 Entotic cell engulfment led to damage in ECM like anoikis; however, their functional process is different. Entosis is one of the cell’s cannibalistic behaviors, killing the neighbor cells with the help of the E-cadherin receptor.79 There has been no direct research approach to link entosis with SCI. However, entosis have been observed when embryonic stem cells have been cultured with mesenchymal stem cells.80 So, it may hamper stem cell-based spinal regeneration approaches.

Methuosis is nonapoptotic cell death; the mechanism of cell death is related to cytoplasmic fluid displacement by large vacuoles generated by macropinosomes. Rab5 and Rab7 GTPase proteins are involved in the transportation of vacuoles. There is currently no evidence to link methuosis with SCI. However, methamphetamine leads to the death of the neurons in the central nervous system via methuosis.81 Entosis and methuosis are the new domain for SCI that researchers can approach to bring the novel idea to avoid neuronal damage during SCI.

2) Mitochondria-mediated

(1) Mitoptosis in SCI

Mitochondria is an essential organ to produce energy for cell division and homeostasis. Mitoptosis, also known as mitochondrial suicide, occurs when the mitochondria divide and fuse, cutting off the adenosine triphosphate (ATP) supply and leading to apoptosis and autophagy.82,83 As a result, they transform into autophagosomes or mitoptotic entities and are ejected. Hence, mitoptosis is a mitochondrial death mechanism rather than a cell death mechanism. However, the high fission or fusion breaks mitochondria apart, ultimately leading to cell death.84 When BAK/BAX permeabilize the outer mitochondrial membrane proteins, they release a protein called deafness-dystonia peptide (DDP), also known as translocase of inner mitochondrial membrane 8a (TIMM8a) that attaches to cytoplasmic DRP1 to bring DRP1 into the mitochondria to promote mitochondrial fission.85 A thorough analysis using electron microscopy, as well as the imaging of fragmented mitochondria with mitochondria-specific dyes (MitoTracker Green, Thermo Fisher Scientific Inc., Waltham, MA, USA) using fluorescence microscopy, may offer information about the existence of mitoptosis. In addition, antibodies targeting TIMM8a/DDP and cytochrome-c are also used.85,86 Mitoptosis occurs due to changes in the membrane of the mitochondria, membrane condensation with swelling and fragmentation in cristae.83

Mitoptosis is observed in SCI triggered by Ca2+ accumulation in the cellular matrix by glutamate excitotoxicity.86 To investigate a putative mitochondrial-SCI relationship, Wingrave et al.87 produced a 40 g/cm force injury in rats by contusion, and 4 hours, 1-cm slices of spinal cord tissue were collected for calcium green (2-AM) staining, western blot, and immunohistochemistry. The penumbra and lesion tissue sections showed free intracellular calcium (Ca2+) levels increased following the injury compared to sham-operated (control) rats. After SCI, the mitochondria-mediated cell death pathway was activated in the penumbra and lesion by elevating Bax: Bcl-2 ratio via western blot. Wei et al. observed neural damage attenuation and locomotor function improvement in rats.88

(2) Parthanatos in SCI

It is a type of caspase-independent PCD activated upon specific types of DNA due to the hyperactivation of the DNA repair gene poly ADP-ribose polymerase 1 (PARP1).89 Poly-ADP ribose is (PAR) produced by PARP1 that translocates from the nucleus to the cytoplasm, interacting with mitochondrial proteins and releasing apoptosis-inducing factors (AIFs). Then it couples with the macrophage migration inhibitory factor (MIF). This MIF: AIF complex condenses chromatin and breaks DNA in the nucleus.90 Unlike apoptosis, intact PARP and its activation are required to initiate parthanatos instead of PARP breakdown. Parthanatos is also unaffected by broad-spectrum caspase inhibitors.91

Moreover, unlike apoptosis, DNA fragmentation is considerable.92 Biomarkers for parthanatos include nuclear AIF, PARP-1 accumulation, and PARP-1 immune reaction, and PAR accumulation. Mitochondrial depolarization may be detected using fluorescent probe labelling, proving that the method works.93 Yang et al.94 observed by interrupting MIF: AIF interaction by knocking down MIF-provided neuroprotection from oxidative stress-induced parthanatos post-SCI. Secondary damage after an initial traumatic or nontraumatic injury is the primary concern of parthanatos in SCI.95 In post-SCI damage, metabolic disruption and glutamine excitotoxicity are the 2 frequent biochemical pathways.96 Before the word pathanatos, glutamine excitotoxicity was widely studied concerning cell death.97 In vitro and in vivo glutamine excitotoxicity models were developed using kainate, a glutamine analogue. In vitro, kainate-induced neuron death was primarily mediated by parthanatos than apoptosis.98 The inhibitor of PARP-1, 6-5(H)-phenanthridine (PHE), prevented AIF translocation and overactivation of PARP-1, both of which are associated with parthanatos.99
PJ34, another PARP-1 inhibitor, reduced kainite excitotoxicity. In kainate-treated mice, PJ34 and PHE had minor impacts on locomotor network damage, showing that some areas of the spinal cord may be resistant to parthanatos. Parthanatos killed most neurons, making them more susceptible to excitotoxicity after SCI. However, glial cells were more resistant to excitotoxicity and perished mainly via apoptosis. Oxidative stress contributes to subsequent SCI damage. The inhibition by poly-adenosine diphosphate-ribose polymerase-1 (PARP-1) inhibitor 3-amniobenzamide may help. Parthanatos has been linked to cell death caused by oxidative stress after damage. In the presence of Mg\(^{2+}\) in a pathological medium simulating metabolic disruption after ischemic SCI in vitro, parthanatos was detected in spinal white matter and partial portions of spinal grey matter. JNK1 and JNK3 have also been linked to parthanatos premitochondrial activation.

3) Iron-mediated

(1) Ferroptosis in SCI

The term “Ferroptosis” was coined in 2012 as a nonapoptotic PCD triggered by iron accumulation inside the cell. In ferroptosis, the cell maintains a normal-looking morphology and a normal-sized nucleus devoid of chromatin condensation. System X\(_{c}^{-}\) is an amino acid antiporter that helps move l-glutamate inside cells and l-cystine outside cells across the plasma membrane of cells contributing to various human processes. A defect in glutathione peroxidase 4 (GPX4) or system X\(_{c}^{-}\) causes a collapse in glutathione-dependent antioxidant defense. For glutathione production, system X\(_{c}^{-}\) carries cystine into the cell and converts it to cysteine from the extracellular cysteine. To reduce cellular lipid peroxidation, GPX4 may directly catalyze glutathione-lipid hydroperoxide interactions. Leaky gut and GPX4 suppression lead to the accumulation of lipid hydroperoxide that reacts with free iron to form lipid reactive oxygen species (ROS) leading to the death of the cell. It is distinguished from apoptosis by morphology, biochemistry, and genetics. In ferroptosis, ROS grows iron-dependently and has a vital role. An upsurge in the number of studies on ferroptosis in SCI has occurred in the last few years. Ferroptosis has been related to excitotoxicity-induced cell death. GPX4 reduces ferroptosis by promoting motor neuron health and survival. So, ferroptosis suppression by GPX4 is essential. Deferoxamine, a drug of iron toxicity, has been shown in previous studies to lower total Fe\(^{3+}\) ions, caspase-3, IL-1β, and TNF-α expression levels after SCI and inhibit the creation of glial scars and apoptosis from increasing function recovery. Another study on the effect of proanthocyanidins on SCI repair indicated that intraperitoneal injections of proanthocyanidins suppressed ferroptosis, which improved functional recovery after SCI.

Ferroptosis may have a substantial role in secondary damage after SCI, and inhibiting this process benefits recovery after SCI, according to these studies. On the other hand, adequate research on the role of ferroptosis in SCI still needs to be done. Research is urgently needed to establish the function of ferroptosis, which may lead to new therapeutic options for SCI in glial scar formation and neuronal death.

Copper can induce cell death, also termed cuproptosis. FDX1-mediated mitochondrial proteotoxic stress causes cuproptosis. FDX1 converts Cu\(^{2+}\) to Cu\(^{+}\), boosting lipoylation and aggregation of mitochondrial TCA cycle enzymes (particularly DLAT). In addition, FDX1 inactivates Fe-S cluster proteins. Cu importers (SLC31A1) and exporters (ATP7B) change intracellular Cu\(^{2+}\) levels to impact cuproptosis sensitivity. Even though it has not been linked with SCI, Enge et al. found elevated Cu concentrations in skeletal muscle and the spinal cord in the presymptomatic stage, which worsened with disease development in the SOD1G93A-mutant mice amyotrophic lateral sclerosis model.

4) Immune factors mediated

(1) Pyroptosis in SCI

Pyroptosis is a nonapoptotic PCD that happens in immune cells as a response when intracellular pathogens release inflammatory signals. Infected macrophages’ inflammatory sensors, like NOD-like receptors (NLRs), detect flagellin molecules in pathogens and induce the development of multiprotein complexes inflammasomes, which then activate caspase1. When activated, caspase1 causes membrane hole formation by cleaving gasdermin D, causing the cell membrane to tear. DNA condensation and fragmentation are also seen throughout the process. Furthermore, bacterial lipopolysaccharide (LPS) directly activates caspase11, causing pyroptosis. Pyroptosis can be determined through gasdermin D cleavage through western blot analysis, IL-1 through caspase activation, and visualization of membrane integrity loss through fluorescence microscopy and the quantification of released cytoplasmic lactate dehydrogenase.

Epithelial cells, neurons, and pyroptotic keratinocytes, as well as myeloid-derived professional phagocytes such as DCs and macrophages, all, have been identified to show pyroptosis. In addition, pyroptosis has been linked to antibacterial and inflammatory responses during infection.
Inflammasomes containing the caspase-1 enzyme have been found to inhibit pyroptosis in the amygdala kindling model of neurological illness. Silencing Nucleotide-binding oligomerization domain-1 (NLRP1) or caspase-1 also decreased pyroptosis in rats. Deficient microglial voltage-gated proton channels may inhibit NLRP3-induced neuronal pyroptosis. Sevoflurane-induced neuronal pyroptosis is connected to the Bach1/Nrf2/Erk1 signaling pathway. Streptococcus pneumoniae can cause pyroptosis in murine microglia, requiring the NLRP3 inflammasome, which activates caspase-1. The function of pyroptosis in SCI pathogenesis is unknown. Pyroptosis and the inflammatory response to SCI should be explored further.

(2) Netosis in SCI

Netosis is a nonapoptotic PCD caused by pathogenic infections or their components. It is most frequent in immune cells, notably neutrophils. It causes the nucleus or mitochondria of neutrophils to generate extracellular traps (NETs) composed of modified chromatin-coated neutrophil DNA and bactericidal proteins from granules and cytoplasm. The most common type is suicidal netosis, where neutrophils die after releasing NETs. When neutrophils recognize pathogen-associated molecular pattern signals from pathogens, that activates the mitogen-activated protein kinase complex to produce protein kinase (PKC). PKC activates NADPH oxidase, causing ROS generation. Increased Ca\(^{2+}\) levels in mitochondria cause mitochondrial permeability transition pore (mPTP) to open and release mitochondrial ROS (mtROS). Mitochondrial dynamin like GTPase (OPA1) ensures the production of NAD+, which is eventually converted to nicotinamide adenine dinucleotide (NADH) through glycolysis. Lastly, NADH transports electrons in the mitochondrial electron transport complex, which upon activation, supplies ATP for NET synthesis.

ROS with mtROS causes azurosome release by rupturing azurophil granules. Neutrophil elastase (NE) and myeloperoxidase (MPO) release and translocates along with a gene named Peptidyl arginine deiminase 4 (PADI4) in the nucleus. MPO generates HOCl to start secondary injury progression, and NEs cleave the Gasermin D pore at the nuclear membrane to release NETs. PADI4 enters the nucleus and causes chromatin decondensation by citrullinating histones (H3, H2A, and H4) and inhibiting glutaredoxin 1 to disrupt cytoskeletal dynamics of the membrane. Another type of netosis, also known as vital netosis, is where the neutrophil does not die. It is believed to occur by the NET formation of mitochondrial DNA rather than the nuclear DNA of neutrophils. It occurs by the Activation of Toll-like receptor 4 (TLR4) and is regulated by small conductance calcium-activated potassium (SK3) channels. Elevated cytosolic Ca\(^{2+}\) increases in SCI pathology promote complex I activity and ATP and ROS generation. Tissue damage, Hypoxia, oedema, and tissue damage cause the synthesis of the first soluble mediator of ROS. The role of ROS in developing networks is significant. Because of this, SCI may induce NETosis. The mitochondrial calcium uniporter also allows Ca\(^{2+}\) into the mitochondria. Ca\(^{2+}\) levels inside cells may promote membrane permeability. NADPH Oxidase activation or other nonoxidative mechanisms connected to mPTP. Thus, NETs develop throughout the SCI process. Neutrophils infiltrate the spinal cord following SCI. These cytotoxic elements cause more extensive lesions and decrease neurological function. MPO increases neutrophil infiltration, causing secondary injury and slowing SCI recovery.

Swelling oedema in the spinal cord astrocytes may cause poor functional recovery and treatment resistance following SCI. Rat spinal cord astrocytic oedema was reduced when oxygen-glucose deprivation and reperfusion (OGD/R) were combined with the high mobility group box protein 1 (HMGB1) shRNA or ethyl-pyruvate treatment. Conversely, when OGD/R was applied to spinal cord astrocytes, HMGB1 increased aquaporin-4 (AQP4) expression and cell swelling through HMGB1/TLR4/nuclear factor-kappa B (NF-kB) signaling. Inhibitors of TLR4 and NF-kB have also been demonstrated to reduce activation effects. TLR4 induces NETosis and increases damage after cerebral ischemia and thrombosis. Therefore, NET development may affect SCI damage. However, no proof exists. However, some research suggests neutrophils may benefit tissue regeneration in SCI since their inflammatory activity may promote healing. Various unanswered concerns surround neutrophil activity in SCI. To get new insights into traumatic brain damage, further study of their cellular and molecular pathways is necessary (SCI).

5) Other factors mediated

(1) Necroptosis in SCI

Also known as programmed necrosis, it activates receptor-interacting protein kinases (RIPKs) by Activation and crosstalk through many signaling pathways. RIPKs are triggered by the employment of several cell surface receptors to macromolecular complexes: T-cell receptors, DRs, and TLRs. RIPK1 and RIPK3 are essential components of the necrosome. RIPK3 phosphorylates the downstream molecule mixed lineage kinase domain-like protein (MLKL), causing MLKL oligomerization. An oligomerized MLKL enters the cell membrane and permeabilizes it,
causing cell death.\textsuperscript{136} Furthermore, regulatory factors of DNA-dependent activators of interferon synthesized after viral infestation, double-stranded viral DNA, and cytosolic DNA sensors activate RIP3-dependent necroptosis. It exhibits necrotic morphology, including membrane rupture and organelle loss. An increasing amount of research shows that, unlike necrosis, necroptosis is caspase-independent.\textsuperscript{137} It is relevant and well established in ischemic brain damage, viral myocardial infarction, and neurodegenerative diseases.\textsuperscript{138} The most well-studied necroptosis pathway is TNF-R1 binding to TNF.\textsuperscript{139} Research suggests necroptosis is involved in an intracellular signaling cascade involving MLKL and RIP1/3 kinase.\textsuperscript{136} RIP1 kinase activity is required for necroptosis activation. Holler et al.\textsuperscript{140} discovered that proteasome subunit beta type-4 controls the RIP3 and MLKL pathways using TNF-induced necroptosis cell culture. Wang et al.\textsuperscript{141} discovered necrostatin-1 (NEC-1), a novel small molecule suppresses necroptosis by modulation of the formation of protein complexes of RIPK1 and RIPK3 and by recruiting RIP1/3–MLKL. After SCI, Nec-1 improved the histopathology and functional impairments, indicating that necroptosis may contribute to brain cell death. Thus, Nec-1 may be used to treat SCI.\textsuperscript{141}

Increasing evidence links SCI necroptosis to inflammation. The ER of necrotic microglia/macrophages can modulate SCI-induced inflammation.\textsuperscript{142} Fan et al.\textsuperscript{143} discovered that M1 macrophages/microglia might induce necroptosis in reactive astrocytes through the MyD88/TLR signaling pathway. Smad ubiquitination regulatory factor-1 (Smurf1) may promote neuron necroptosis following LPS-induced neuroinflammation, suggesting it might be a therapeutic target.\textsuperscript{144} After spinal cord damage, necroptosis-induced glial and neuronal cell death has been reported. Activating necroptosis in the CNS may cause cell death and tissue damage. Despite substantial research into necroptosis after SCI, our knowledge is limited. Secondary damage can only be addressed if necroptosis is linked to SCI etiology.\textsuperscript{145}

\textbf{(2) Other minor pathways in SCI}

Other minor pathways may also lead to SCI progression. Oxidative stress is a novel nonapoptotic PCD that is triggered by the accumulation of ROS. Kelch-like ECH-associated protein 1 (KEAP1) C-terminal cysteine are oxidized by moderate ROS levels, causing degradation of the KEAP1-NRF2 complex and nuclear translocation of NRF2.\textsuperscript{146} Antioxidant genes are produced by Nrf2 that help to remove ROS from the nucleus. High amounts of intracellular ROS trigger the production of phosphoglycerate mutase family member 5 by KEAP1, which dephosphorylates apoptosis-inducing factor 1 (AIFM1) at the Ser116 position after binding to it, ultimately leading to this kind of cell death.\textsuperscript{147} ROS significantly affects the primary and secondary injury progression for SCI.\textsuperscript{148} Due to ischemic injury at the primary injury site, free ROS gets generated, which links with the disruption in Nrf2 translocation and decreasing neuronal pH and form of mPTP complex.\textsuperscript{72,149} So even though there is no current research linking oxietosis to SCI, it is a starting point to start many cell death pathways relevant to SCI. So, it is a hot topic for researchers to explore.

\textbf{pH has a significant role in the progression of cell death in SCI. Alkaliptosis is a new pH-dependent cell death relevant to many diseases.\textsuperscript{150} Tang et al.\textsuperscript{151} define alkaliptosis as pH-mediated, N-acetyl cysteine-mediated, drug-induced cell death. Scientists have established that alkalinization of the cellular milieu with sodium hydroxide promotes cell death using NF-kB. Unlike ferroptosis and necrosis, alkaliptosis is a chemical process. NF-kB activation may prevent alkaliptosis.\textsuperscript{152} The Nrf2/HO-1 signaling pathway may activate proinflammatory and apoptosis-inhibitory genes. Over or underexpression of the Nrf2/HO-1 signaling pathway has antiapoptotic effects that can be utilized against this type of cell. Currently, there is no research done to link alkaliptosis with SCI. Furlong et al.\textsuperscript{153} showed that intracellular acidification induces apoptosis by stimulating IL-1\textbeta converting enzyme like protease activity. In the isolated spinal cord, Jalalvand et al.\textsuperscript{154} showed that both increased and decreased pH reduced the locomotor burst rate, proving a possible link between alkaliptosis and SCI. Treatment strategies can be built around it as it heavily depends upon the NF-kB pathway.\textsuperscript{155}

Autoschizis is another bizarre type of cell death where the cell develops cracks. These cracks develop inside the cell organism, followed by getting destroyed by proteases that also develop inside the cell. The standard cell remains unaffected, but the cracked cells die off.\textsuperscript{156} There is currently no link between autoschizis and SCI. However, it is a potent necrosome trigger that may contribute to the necrosis and necroptosis progression in SCI.\textsuperscript{157}

\textbf{3. Nonprogrammed Nonapoptotic Cell Death}

\textbf{1) Nonprogrammed necrosis in SCI}

Necrosis is a nonprogrammed type of cell death triggered by toxins, physical injuries, and infections disrupting ionic pumps leading to Ca\textsuperscript{2+} influx, resulting in morphological alterations such as cytoplasmic swelling (oncosis), consequential intracellular organelle loss with little to no chromatin condensation, and plasma membrane rupture.\textsuperscript{158} It starts with the acute phase comprising a variety of mechanisms, including ionic imbalance
and glutamate excitotoxicity, toxic blood component buildup, the release of proinflammatory cytokine by lymphocytes and neutrophils, ATP depletion, and free radical production. As the damage continues, in the subacute phase, surviving axonal demyelination, neuronal apoptosis, axonal bulb retraction (die-back), Wallerian degeneration, glial scar formation surrounding the injury site, and matrix remodeling occur. In the chronic damage phase, further changes occur, such as maturation of the glial scar, increasing axonal retraction bulb (dieback), and creating a cystic cavity. It is common in trauma, ischemia, and Table 1. Different cell death Pathways associated with spinal cord injury and their therapeutic interventions

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SCI, spinal cord injury; XIST, X-inactive specific transcript; CARD6, caspase recruitment domain-containing protein 6; CD95, cluster of differentiation 95; iNOS, inducible nitric oxide synthase; BDNF, brain-derived neurotrophic factor; ECM, extra cellular matrix; MSCs, mesenchymal stem cells; SCG10, stathmin-2; ER, endoplasmic reticulum; SCI, spinal cord injury; CNS, central nervous system; Bax, Bcl-2-like protein; Bcl-2, B-cell lymphoma; PARP1, poly[ADP-ribose]-polymerase 1; PJ34, PARP inhibitor; HOCl, hypochlorous acid; NETs, neutrophil extracellular traps; HMGB1, high mobility group box 1; AQP4, aquaporin 4; GSDMD, gasdermin D; TNFR, tumor necrosis factor receptors; PSMB4, 20S proteasome subunit beta-7; RIP3, receptor-interacting serine/threonine kinase 3; MLKL, mixed lineage kinase domain-like pseudokinase; Nec1, necrostatin 1; NMDA, N-methyl-D-aspartate.

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Cell Death Pathways in SCI

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potentially certain kinds of neurodegenerative conditions. It is typically regarded as a passive process that requires very little energy yet does not need de novo macro molecular synthesis. The process of cell death is a continuum of apoptosis and necrosis. Variable levels of crosstalk harmony between coexisting apoptotic and necrotic processes might contribute to neuronal death along this spectrum. The contribution of necrosis in SCI pathology has been well established in both in vitro and in vivo models of acute and chronic SCI. Acute SCI results in necrosis, known as progressive hemorrhagic necrosis. It is a poorly understood pathological process marked by necrosis and bleeding that results in severe cystic cavitation of the spinal cord, profound neurological impairment, and spinal cord tissue loss. A necrosis initiator gene, TNF-α, produces death in oligodendrocytes in the spinal and supraspinal region. Its antagonist significantly reduced oligodendrogial necrosis in SCI. Excessive N-methyl-D-aspartate receptor activation in neurons during glutamate-induced excitotoxicity may result in necrotic cell death and progression of secondary injury. These secondary processes contribute to the evolution of pathological abnormalities in severe injuries, from central hemorrhagic necrosis involving predominantly grey matter to infarction of both white and grey matter proximally and distally at the injury site. Less severe damage changes axons and myelin (Table 1).

CONCLUSION AND FUTURE PERSPECTIVE

The ensuing cascade of cell death after CNS injury or ischemia has long been considered a target for neuroprotective drugs to preserve tissue and function. Defects in one or more cell death processes are connected to various spinal cord injuries, including neurodegenerative conditions involving abnormal cell destruction. The regulators and signaling pathways of the various cell death mechanisms continue to be appealing therapeutic targets that have the potential to serve as the foundation for translational research that may result in improvements for patients afflicted with these disorders. As a concluding statement, we can say that a significant amount of additional research, including both fundamental works in studies of animal models involving clinical trials, is required to acquire a more in-depth knowledge of the various processes modulating cell death in SCI. Many cell death pathways for axonal/neuronal regeneration and proinflammatory signaling-induced secondary injury in SCI are undiscovered. This review thus expands the extent of the cell death pathways in the SCI, and knowledge must be used to make revolutionary advancements in treating these illnesses.

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Commentary on “Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury”

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Although there have been decades of research on spinal cord injury (SCI), it is still one of the most challenging medical conditions to treat in developed countries worldwide.1-6 Clinical manifestations of SCI (e.g., paralysis, autonomic nervous system dysregulation) can severely impact the quality of life and burden social security systems.1-6 The primary mechanism of disease and cause of clinical symptoms is the death of neurons and supporting glial cells in the spinal cord.1-6 Thus, to achieve a lasting and successful SCI treatment, it is imperative to prevent the death of cells post-injury (Fig. 1). Previous attempts to broadly suppress well-known SCI pathophysiological processes have been controversial. In a high-profile example, methylprednisolone (a glucocorticoid with broad anti-inflammatory action) was investigated to limit the neurological and functional damage in SCI patients.5 Unfortunately, the broad immunosuppressive and side effects of methylprednisolone have been found to be potentially deleterious in large human clinical trials.5,6 A more nuanced approach to regulating specific cellular pathways may be warranted to prevent side effects during clinical use (Fig. 1).

In the June 2023 issue of Neurospine, Guha et al.7 have compiled the most pertinent literature on cell death mechanisms in SCI. In this manuscript, the authors investigated the key cellular pathways related to SCI pathogenesis, the key signaling proteins involved, and the current treatment options (Fig. 1). Here, readers are encouraged to use this manuscript as a stepping stone toward the next step in targeted SCI treatment research and development. For example, the systematic review of key cellular death pathways laid in the manuscript of Guha et al.7 can be readily integrated into a variety of studies. Mechanistic investigations into novel SCI treatment options, such as systemic hypothermia, can be accelerated with the manuscript of Guha et al.6 For example, future studies into the antiapoptotic effects of hypothermia can be distinguished from confounding (non-)programmed and nonapoptotic pathways of cell death.6 Stem cell therapies can benefit by anticipating and countering key death mechanisms that would cause transplanted cells to die within the patient.2 Alternatively, stem cell-secreted antiapoptosis/necrosis growth factors can be identified as a low immunogenicity substitute for allogeneic stem cell transplantation.2 More efficient treatment options can be determined by further examination into which pathway contains the most “druggable” target. Protein-ligand simulations with critical apoptosis and necrosis checkpoints can give rise to more specific therapeutics with fewer off-target effects.4 Novel drug combinations that have either synergistic effects, such as targeting multiple checkpoints within the same pathway, or complementary effects, like targeting different pathways leading to...
the same physiological result, may be possible through key theorized crosstalk junctions. In summary, this evaluation of cell death mechanisms in SCI can provide interested researchers with the ability to accelerate their research and draw further connections to other manuscripts in the field.

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

### REFERENCES


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**Fig. 1.** Overview of cell death in spinal cord injury (SCI). (A) SCI can induce substantial neuronal death, which inhibits neurogenesis and functional recovery. (B) A variety of cell death pathways have been identified in Guha et al. recent review paper, each with associated cell signaling pathways and defined cellular events. (C) This publication is well suited to inform subsequent work aimed at developing new therapeutics for SCI, including but not limited to bioinformatics, apoptosis/nonapoptosis checkpoint inhibitors, and drug development for enhanced specificity and reduced side effects. PTEN, phosphatase and tensin homolog; ATP, adenosine triphosphate; ROS, reactive oxygen species.
Three-Dimensional-Printed Titanium Versus Polyetheretherketone Cages for Lumbar Interbody Fusion: A Systematic Review of Comparative \textit{In Vitro}, Animal, and Human Studies

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Interbody fusion is a workhorse technique in lumbar spine surgery that facilitates indirect decompression, sagittal plane realignment, and successful bony fusion. The 2 most commonly employed cage materials are titanium (Ti) alloy and polyetheretherketone (PEEK). While Ti alloy implants have superior osteoinductive properties they more poorly match the biomechanical properties of cancellous bones. Newly developed 3-dimensional (3D)-printed porous titanium (3D-pTi) address this disadvantage and are proposed as a new standard for lumbar interbody fusion (LIF) devices. In the present study, the literature directly comparing 3D-pTi and PEEK interbody devices is systematically reviewed with a focus on fusion outcomes and subsidence rates reported in the \textit{in vitro}, animal, and human literature. A systematic review directly comparing outcomes of PEEK and 3D-pTi interbody spinal cages was performed. PubMed, Embase, and Cochrane Library databases were searched according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Mean Newcastle-Ottawa Scale score for cohort studies was 6.4. A total of 7 eligible studies were included, comprising a combination of clinical series, ovine animal data, and \textit{in vitro} biomechanical studies. There was a total population of 299 human and 59 ovine subjects, with 134 human (44.8\%) and 38 (64.4\%) ovine models implanted with 3D-pTi cages. Of the 7 studies, 6 reported overall outcomes in favor of 3D-pTi compared to PEEK, including subsidence and osseointegration, while 1 study reported neutral outcomes for device related revision and reoperation rate. Though limited data are available, the current literature supports 3D-pTi interbodies as offering superior fusion outcomes relative to PEEK interbodies for LIF without increasing subsidence or reoperation risk. Histologic evidence suggests 3D-Ti to have superior osteoinductive properties that may underlie these superior outcomes, but additional clinical investigation is merited.

Keywords: Lumbar fusion, Interbody implant, Polyetherether ketone, Printed titanium, Systematic review
INTRODUCTION

Lumbar interbody fusion (LIF) is a staple of lumbar surgery and offers the ability to improve sagittal plane deformity, provide an additional fusion surface to decrease pseudoarthrosis rates, and facilitate foraminal expansion and indirect decompression of the lumbosacral nerve roots. At present, the market is dominated by devices comprised of either titanium (Ti) alloy or polyetheretherketone (PEEK).

The ideal spinal interbody device should have 2 properties: (1) the ability to produce a rigid construct that facilitates alignment correction and indirect decompression through disc-space distraction, and (2) the ability to facilitate the bony fusion that is critical for long-term fusion success. Ti and Ti alloys (e.g., Ti6Al4V) serve as the materials for a bulk of commercially available devices as Ti and alloys are known to facilitate osseointegration at the bone-implant interface.1 Alloys additionally have the advantage of increased corrosion resistance.2 However, the Young’s modulus of bulk Ti and Ti alloys is 50–110 gigapascals3,4 (GPa), which is far in excess of that of both cancellous bone (3–4 GPa) and cortical bone (14.6 GPa).1 This creates a mismatch between the interbody and the adjacent bone that can result in cage subsidence.3,4 To address this, PEEK implants were developed in the late 1990s, which possess a Young’s modulus that far more closely approximates that of native bone, decreasing the risk of implant subsidence.5,6 PEEK implants are additionally radiolucent and can better facilitate radiographic monitoring of bony fusion during follow-up.6,11,12 However, PEEK exhibits poor osseointegration due to its ability to form biofilms, increasing rates of bony nonunion (pseudoarthrosis).13 To address the weaknesses of both materials, Ti-coated PEEK interbodies were produced, but they did not appear to significantly reduce subsidence rates relative to Ti implants13 and were associated with the risk of surface coating delamination during implantation.

More recently, advances in 3-dimensional (3D)-printing and biomaterial surface treatment technology have facilitated the production of 3D-printed Ti (3D-pTi) interbody devices.14 These devices have highly porous surfaces that facilitate osteoinduction,15 while at the same time have a low enough elastic modulus to match that of native bone.14,16,17 However, given the relatively recent development of these devices, currently available evidence is limited. The objective of the present systematic review was to summarize the available biomechanical, animal, and human data directly comparing outcomes between 3D-pTi and PEEK lumbar interbody devices with respect to bony fusion, implant subsidence, reoperation/revision (in human studies), and construct stability/stiffness (in biomechanical studies).

METHODS

1. Search Strategy

Using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines the PubMed, Embase, and Cochrane Library databases were queried to identify all studies directly comparing outcomes between PEEK and 3D-pTi vertebral interbody implants from database inception to February 2022. Articles were identified using the following Boolean search string: “print*” AND (“peek” OR “polyetheretherketone”) AND “fusion”. Studies were included if: (1) they were available in English full texts or translations, and (2) they directly compared PEEK and 3D-pTi lumbar interbody implants with regard to biomechanical outcomes, material properties, fusion rate, subsidence rate, reoperation rate, and/or construct stability. Articles were excluded if: (1) they focused on an intervention other than lumbar fusion, or (2) were noncomparative studies, technical notes, abstracts, commentaries, clinical trials without published data, reviews or meta-analyses of previously published data. The present review was not registered and no protocol is available.

2. Screening

Two authors (NAP and JLG) independently screened titles and abstracts for relevance according to the inclusion and exclusion criteria. Any discrepancies during the screening process were resolved by consensus among all authors. Full text articles were then reviewed to determine final inclusion, and reference lists of all included studies were also queried to identify additional relevant studies.

3. Study Quality

The quality of evidence for the included cohort studies was assessed Cochrane risk of bias tool 2 for randomized trials and nonrandomized studies.

4. Data Extraction

Independent reviewers (NAP and JLG) extracted data from all eligible studies. Data extracted from human study variables included the occurrence of implant subsidence and device-related reoperation. Animal study variables included radiographic evidence of osseointegration on micro-computed tomography (μCT), histological analyses of osseointegration, including...
quantitative histomorphometry, and biomechanical testing results (flexion-extension, right/left lateral bending, right/left axial rotation and stiffness). Nonclinical study variables included energy effective strain, or a quantification of the energy stored in the composite based on an assessment of the effective strain, as well as human mesenchymal stem cell (hMSC) morphology, proliferation, and differentiation, DNA fluorescence assay, alkaline phosphatase (ALP), and calcium content.

RESULTS

Overall, 30 unique studies were identified through the literature search, of which, 7 progressed to final study inclusion (Fig. 1). Of the 7 eligible studies (Table 1) included in this review,14,16, 18-22 2 studies were retrospective clinical cohorts,18,19 3 studies were prospective animal studies using ovine models,14,20,21 and 2 studies were nonclinical laboratory examinations (1 finite element analysis [FEA]16 and 1 in vitro study).22 The mean Newcastle-Ottawa Scale score for the 5 studies was 6.4, with a range of 6 to 7. Points were lost in the “comparability” and “selection” assessments. Each study utilized a different manufacturer of their 3D-pTi. All studies used traditional PEEK for comparison except for one study which used porous PEEK. Excluding the nonclinical studies, there was a total population of 299 human and 59 ovine subjects, with 134 human (44.8%) and 38 ovine models (64.4%) implanted with 3D-pTi cages. Six studies reported results favoring 3D-pTi, while 1 study29 reported equivocal outcomes for 3D-pTi and PEEK devices (Table 2).

1. Human studies

There were 2 retrospective, human cohort studies included (Table 3). Adl Amini et al.18 included 113 patients (54.9% male) with a median age of 60 years and a mean follow-up of 29.5 weeks. Of the 113 patients, 38 received 3D-pTi implants and 75 received PEEK; 186 total levels were implanted with interbodies with 67 (36.0%) of those being 3D-pTi. Lateral LIF (LLIF) was used for all implantations with the primary structure of the 3D-pTi devices being variations of a grid-like lattice (Table 3). Of note, 3D-pTi cages were more likely to be used during surgeries involving the L1/2 and L2/3 disc spaces (p < 0.001) and for single-level procedures (55.3% vs. 48.0%, p = 0.007). The major outcome measure was cage subsidence with overall subsidence rate for grades I–III under the Marchi classification (0% to 24% collapse of the level)23 being significantly less for the patient cohort treated with a 3D-pTi device compared to patients treated with a PEEK device (p = 0.003). When stratifying the patient cohort by cases of high-grade subsidence, defined as grade II or III, the 3D-pTi cages still demonstrated a significantly lower subsidence rate when compared to the PEEK cages (3.0% vs. 18.5%, p = 0.002). On multivariate analysis, patients treated

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Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram.
Table 1. Characteristics of direct comparative studies assessing 3D-pTi vs. PEEK lumber interbody implantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Model</th>
<th>Study design</th>
<th>Experimental (3D-pTi brand)</th>
<th>Comparison</th>
<th>n (3D-pTi)</th>
<th>Outcome measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ye a m i et al.</td>
<td>2021</td>
<td>USA</td>
<td>Human</td>
<td>Retrospective cohort</td>
<td>Novel</td>
<td>PEEK</td>
<td>113 (38)</td>
<td>Subsidence</td>
</tr>
<tr>
<td>Corso et al.19</td>
<td>2022</td>
<td>USA</td>
<td>Human</td>
<td>Retrospective cohort</td>
<td>CONDUIT</td>
<td>PEEK</td>
<td>186 (96)</td>
<td>Device-related revision, on-device related reoperation</td>
</tr>
<tr>
<td>A l i et al.</td>
<td>2021</td>
<td>USA</td>
<td>Ovine</td>
<td>Prospective, randomized cohort</td>
<td>JULIET Ti LL</td>
<td>PEEK</td>
<td>14 (14)*</td>
<td>Micro-CT osseointegration, quantitative histomorphometry of BIC and ROI bone/cartilage</td>
</tr>
<tr>
<td>M c G i l v r a y et al.</td>
<td>2018</td>
<td>USA</td>
<td>Ovine</td>
<td>Prospective, randomized cohort</td>
<td>Tritanium PL</td>
<td>PEEK</td>
<td>27 (18)</td>
<td>Biomechanical testing of ROM and stiffness, micro-CT BV/TV and MDBV/MDTV, qualitative histological analysis of osseointegration</td>
</tr>
<tr>
<td>V a n H o r n et al.</td>
<td>2021</td>
<td>USA</td>
<td>Ovine</td>
<td>Prospective, randomized cohort</td>
<td>HEDRON</td>
<td>PEEK</td>
<td>18 (6)</td>
<td>Micro-CT BV quantification, histomorphometric BAR quantification</td>
</tr>
<tr>
<td>C a r p e n t e r et al.</td>
<td>2018</td>
<td>USA</td>
<td>-</td>
<td>FEA</td>
<td>Tesera Trabecular Technology</td>
<td>Porous PEEK</td>
<td>-</td>
<td>Energy effective strain in adjacent bony layer under compression, tension, and shear forces</td>
</tr>
<tr>
<td>P a p a e s t a t h i o u et al.</td>
<td>2021</td>
<td>France</td>
<td>-</td>
<td>In vitro</td>
<td>Ti-LIFE technology</td>
<td>PEEK</td>
<td>-</td>
<td>hMSC morphology, proliferation, differentiation via SEM, biochemical assays of ALP and calcium content</td>
</tr>
</tbody>
</table>

3D-pTi, 3-dimensional printed titanium; PEEK, polyetheretherketone; CT, computed tomography; BIC, bone-implant contact; ROI, region of interest; ROM, range of motion; BV/TV, bone volume/total volume; MDBV/MDTV, mean density of bone volume/mean density of total volume; BAR, bone apposition ratio; FEA, finite element analysis; hMSC, human mesenchymal stem cell; SEM, scanning electron microscope; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; ALP, alkaline phosphatase.

*Each animal received both a PEEK and 3D-pTi implant, thus, serving as its own control.

Table 2. 3D-pTi or PEEK favorability for each outcome variables stratified by study

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure(s)</th>
<th>Outcome favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>A d l A m i n i et al.</td>
<td>Subsidence</td>
<td>3D-pTi</td>
</tr>
<tr>
<td>C o r s o et al.19</td>
<td>Device-related reoperation</td>
<td>Equivalent</td>
</tr>
<tr>
<td>L a r a t t a et al.14</td>
<td>Micro-CT osseointegration</td>
<td>3D-pTi</td>
</tr>
<tr>
<td>M c G i l v r a y et al.</td>
<td>Biomechanical testing of ROM and stiffness</td>
<td>3D-pTi</td>
</tr>
<tr>
<td>V a n H o r n et al.21</td>
<td>Micro-CT BV quantification at 6 weeks</td>
<td>3D-pTi</td>
</tr>
<tr>
<td>C a r p e n t e r et al.</td>
<td>Energy effective strain in adjacent bony layer</td>
<td>3D-pTi</td>
</tr>
<tr>
<td>P a p a e s t a t h i o u et al.</td>
<td>hMSC morphology</td>
<td>3D-pTi</td>
</tr>
</tbody>
</table>

3D-pTi, three-dimensional printed titanium; PEEK, polyetheretherketone; CT, computed tomography; BIC, bone-implant contact; ROI, region of interest; ROM, range of motion; BV/TV, bone volume/total volume; MDBV/MDTV, mean density of bone volume/mean density of total volume; BAR, bone apposition ratio; hMSC, human mesenchymal stem cell; ALP, alkaline phosphatase.
Table 3. Clinical characteristics and outcomes of included human studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yr)</th>
<th>% Male</th>
<th>F/U</th>
<th>Levels of implantation (3D-pTi)</th>
<th>Surgical approach (%)</th>
<th>Surgical indications (%)</th>
<th>Cage subsidence</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amini et al.</td>
<td>18</td>
<td>20</td>
<td>29.5</td>
<td>113 (38)</td>
<td>LLIF (1000)</td>
<td>Spondylolisthesis (76.1)</td>
<td>(3D-pTi) 2,500 mPa</td>
<td>54.9</td>
</tr>
<tr>
<td>Corso et al.</td>
<td>19</td>
<td>6</td>
<td>50.5</td>
<td>186 (67)</td>
<td>LLIF (1000)</td>
<td>Spondylolisthesis (76.1)</td>
<td>2,500 mPa</td>
<td>54.9</td>
</tr>
</tbody>
</table>

Corso et al.19 included 186 patients (50.5% male) with a mean age of 59.2 ± 12.5 years and a minimum follow-up of 6 months. Of the 186 patients, 96 received 3D-pTi implants and 90 received PEEK; 186 total levels were implanted with 96 (51.6%) of those consisting of 3D-pTi implants. From a demographic standpoint, patients self-identifying as black and/or African American were more likely to be treated with a 3D-pTi (versus PEEK) device. Additionally, patients who underwent surgery involving implantation of the 3D-pTi device were more likely to have undergone surgery in 2020 as well as to have received treatment at an academic center.

In the present study, the major outcome measure was device-related reoperation. One instance of nondevice-related operation was observed in the 3D-pTi cohort, while there were no occurrences of device-related operation in either cohort. The most common surgical indications for 3D-pTi cage implantation included spondylolistheses, spinal stenosis, foraminal stenosis, and degenerative disc disease (Table 3). To control for the confounding effects of demographic variables, Corso et al.19 also propensity-matched patients, finding that, among matched patients, nonerequired device-related revisions. From these results, Corso et al.19 conclude that for nondevice-related reoperation events, 3D-pTi cages are associated with minimal risk when compared to non-3D printed cages.

2. Animal Studies

All 3 animal studies were prospective randomized trials employing ovine models (Table 4).14,20,21 All 3D-pTi devices used for animal studies used variations of a grid-like lattice structure. Table 4 provides scanning electron microscope illustrations of each device included in the studies analyzed. All known ovine subjects were female. Laratta et al.14 included 14 ovine models with each receiving 2 levels of implantation, 1 3D-pTi and 1 PEEK. Follow-up was performed at 4 and 8 weeks. From a biomechanical perspective, the PEEK cage had lower static axial compression yield load, expulsion yield load, subsidence yield load and stiffness than the 3D-pTi cage (1,120 vs. 44,002; 517 vs. 620.8; 1,100 vs. 1,120; 13,807 vs. 42,252). The PEEK cage also had a higher Young's modulus (GPa) than the 3D-pTi cage (3 vs. 2). Outcome measures included micro-CT osseointegration,
Table 4. Clinical characteristics and outcomes of included ovine model studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Sex</th>
<th>F/U</th>
<th>n (3D-pTi)</th>
<th>3D-pTi modulus of elasticity</th>
<th>Levels implanted (3D-pTi)</th>
<th>Surgical approach</th>
<th>Outcome measure(s)</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laratta et al.14, 2021</td>
<td>4–5 years of age</td>
<td>All female</td>
<td>4 and 8 weeks</td>
<td>14 (14)*</td>
<td>2 GPa</td>
<td>28 (14)</td>
<td>Retroperitoneal anterior fusion at L2–3 and L4–5</td>
<td>Micro-CT osseointegration, quantitative histomorphometry of BIC and ROI bone/cartilage</td>
<td>Lack of osseointegration about the implant-bone interface for PEEK, with fibrotic tissue present instead. Osseointegration present at the 3D-pTi interface, including de novo osseous formation at the center of the cage. Significantly higher mean bone and cartilage in the ROI for the 3D-pTi implants versus the PEEK implants (p = 0.008 and 0.015 for bone and cartilage, respectively). Significantly higher BIC in the 3D-pTi implants as well.</td>
</tr>
<tr>
<td>McGilvray et al.20, 2018</td>
<td>-</td>
<td>-</td>
<td>8 and 16 weeks†</td>
<td>27 (18)</td>
<td>Not available</td>
<td>54 (18)</td>
<td>LLIF at L2–3 and L4–5</td>
<td>Biomechanical testing of ROM and stiffness, micro-CT BV/TV and MDBV/MDTV, qualitative histological analysis of osseointegration</td>
<td>Statistically significantly lower ROM and higher stiffness in all directions at all time points for 3D-pTi. Statistically significantly higher BV/TV and MDBV/MDTV for the 3D-pTi group at all time points. Qualitatively higher osteoblast/clast activity, fibrous neovascularization, bony filling of implant pores in the 3D-pTi group.</td>
</tr>
<tr>
<td>Van Horn et al.21, 2021</td>
<td>All female</td>
<td>6 and 12 weeks‡</td>
<td>18 (6)</td>
<td>Not available</td>
<td>36 (12)</td>
<td>LLIF at L2–3 and L4–5</td>
<td>Micro-CT BV quantification, histomorphometric BAR quantification</td>
<td>Statistically significantly higher BV at 6 weeks for 3D-pTi but no difference at 12 weeks. Statistically significantly higher BAR for 3D-pTi at both time points.</td>
<td></td>
</tr>
</tbody>
</table>

F/U, follow-up; 3D-pTi, 3-dimensional printed titanium; CT, computed tomography; BIC, bone-implant contact; ROI, region of interest; PEEK, polyetheretherketone; LLIF, lateral lumbar interbody fusion; ROM, range of motion; BV/TV, bone volume/total volume; MDBV/MDTV, mean density of bone volume/mean density of total volume; LIF, lumbar interbody fusion; BAR, bone apposition ratio.

*Each animal received both a PEEK and 3D-pTi implant, thus, serving as its own control. †Fifteen sheep sacrificed at first time point, 12 at the next. ‡Nine sheep sacrificed at first time point and 9 at the second.
quantitative histomorphometry of bone-implant contact (BIC) and region of interest (ROI) bone/cartilage. At each follow-up, they found that while 3D-pTi interbody devices showed successful osseointegration into the adjacent vertebrae, PEEK implants demonstrated no such evidence, instead showing only localized fibrotic tissue. Additionally, there was a higher mean proportion of bone and cartilage content in the ROI as measured by histomorphometric analyses of the implant region for the 3D-pTi versus the PEEK implants (8,201,364 ± 5,480,486 vs. 1,418,262 ± 2,358,418; p = 0.008 and 1,338,943 ± 827,115 vs. 49,496 ± 578,039; p = 0.015 for bone and cartilage, respectively). Furthermore, quantitative histomorphometry of implant contact with bone and ROI of bone/cartilage showed significantly higher BIC in the 3D-pTi implants with a value of 39,295.3017 ± 4,414.26266 compared to a BIC of 0 for the sheep treated with PEEK cages (p < 0.001).

McGilvray et al. included 27 ovine models with each receiving 2 levels of implantation, with combinations of 3D-pTi, PEEK, or Ti-coated PEEK. Overall, 18 3D-pTi levels were implanted. Follow-up was performed at 8 and 16 weeks. Outcome measures included range of motion (ROM) and stiffness testing, bone volume to total volume ratio (BV/TV) and mean density of bone volume to mean density of total volume ratio (MDBV/MDTV). First, micro-CT scans of multiple planes were taken, specifically of the coronal and midsagittal axes of the 3D-pTi and PEEK cages at 8 and 16 weeks. 3D renderings of these scans displayed significantly higher BV/TV and MDBV/MDTV for the 3D-pTi group at all time points (p < 0.01). Furthermore, there was a significantly increased percent bone for 3D-pTi compared to PEEK at 16 weeks (p = 0.04). Qualitative histological analysis of osseointegration showed higher osteoblast activity, fibrous neovascularization, and bony filling of implant pores in the 3D-pTi group.

Van Horn et al. included 18 ovine models with each receiving 2 levels of implantation, with combinations of 3D-pTi, PEEK, or Ti alloy. Overall, 6 3D-pTi levels were implanted. Follow-up was performed at 6 and 12 weeks. Outcome measures included micro-CT BV quantification and histomorphometric bone apposition ratio (BAR) quantification. At 6 weeks, Van Horn et al. found that the BV was significantly higher in the group treated with the 3D-pTi cage when compared to the PEEK cohort (177.3 ± 44.1 mm³ vs. 116.9 ± 43.0 mm³, p = 0.05). However, at 12 weeks, the difference in BV between the 3D-pTi cohort and the PEEK cohort became insignificant (234.7 ± 35.9 mm³ vs. 218.8 ± 21.8 mm³, p > 0.05). Despite comparable BV among PEEK and 3D-pTi at 12 weeks, the BAR for the 3D-pTi cages were 2.7 times higher than the PEEK cages, reaching statistical significance (23.6% ± 10.9% vs. 8.6% ± 2.1%, p < 0.05). A similar result was found at 12 weeks with the BAR for the 3D-pTi cages being 2.6 times higher than the PEEK cages, also reaching statistical significance (36.5% ± 10.9% vs. 14.0% ± 5.0%, p < 0.05). Importantly, these results indicate greater integration of the 3D-pTi device into bony structure through measurement in the amount of bone inside the cage’s pores.

3. Nonclinical Studies

Among the nonclinical studies identified during our search, 2 examined bone porosity and 1 utilized FEA to measure compression, tension, and shear forces between implants, with the other utilizing an in vitro hMSC and extracellular matrix (ECM) model to measure cell proliferation and as well as differentiation amid the implant environment. As was consistent with the studies on animal models, all 3D-pTi devices used in non-

Table 5. Clinical characteristics and outcomes of included nonclinical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>3D-pTi modulus of elasticity</th>
<th>Porosity</th>
<th>Comparison</th>
<th>Observations collected at:</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpenter et al.</td>
<td>FEA</td>
<td>NA</td>
<td>71.15%</td>
<td>3D-pTi vs. PEEK</td>
<td>4 and 28 weeks</td>
<td>Significantly higher energy effective strain in the adjacent bony layer under compression, tension, and shear at 4 and 24 weeks for the porous PEEK</td>
</tr>
<tr>
<td>2018</td>
<td></td>
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<tr>
<td>Papaefstathiou et al.</td>
<td>In vitro</td>
<td>NA</td>
<td>70%–75%</td>
<td>3D-pTi vs. PEEK</td>
<td>7, 14, 21, 28, and 42 days</td>
<td>For morphology, 3D-pTi formed a dense layer of intermixed hMSC and ECM by day 28. For PEEK, cells were sparse on day 7 but multilayers were formed at day 42. For proliferation, 3D-pTi showed significantly higher cell number at all time points. For differentiation, ALP activity and calcium content per cell, no significant differences were observed.</td>
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<td>2021</td>
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FEA, finite element analysis; NA, not available; 3D-pTi, 3-dimensional printed titanium; PEEK, polyetheretherketone; hMSC, human mesenchymal stem cell; ECM, extracellular matrix; ALP, alkaline phosphatase.
clinical used variations of a porous structure. Table 5 provides an illustration of the chosen lattice structures for of the included studies.

Carpenter et al.18 aimed to analyze the load-bearing potential of the 3D-pTi and PEEK cages in order to determine differences in biomechanical functionality between the 2 devices. To accomplish this task, finite element (FE) models of the interaction between the pore structure and bone used with observations collected at 4 and 28 weeks. Notably, the PEEK cages had increased load share transferred to the bone grown within the device (66% vs. 13%), tension (71% vs. 12%), and shear (68% vs. 9%) when compared to the 3D-pTi device (p < 0.05). Further, the 3D-pTi device had reduced spinal load magnitudes both at 4 and 12 weeks when compared with the PEEK device (4 weeks: 180 ± 300 microstrain vs. 784 ± 351 microstrain; 12 weeks: 121 ± 49 microstrain vs. 298 ± 88 microstrain). Overall, this resulted in 29.5% increased load distribution in 3D-pTi compared to 15.8% of porous PEEK.

Papaefstathiou et al.27 performed an in vitro study comparing 3D-pTi to PEEK with observations collected at 7, 14, 21, 28, and 42 days. The porosity of the 3D-pTi implants used ranged from 70%–75%. Results showed 3D-pTi forming a dense layer of intermixed hMSC and ECM by day 28. For PEEK implants, cells were sparse on day 7 but multilayers were formed at day 42. Analysis of proliferation demonstrated 3D-pTi surfaces to have significantly higher cell number at all time points. Differentiation analysis showed increased ALP activity and calcium content per cell, although no significant differences were observed.

DISCUSSION

The 3 advantages of LIF relative to conventional posterolateral fusion are its ability to improve sagittal balance, facilitate indirect decompression of the lumbar neural elements through disc-space distraction, and provide an additional surface for fusion. Conventionally 2 materials have dominated the market: Ti alloy and PEEK. Both Ti alloy and PEEK devices first became widely available on the market in the late 1990s. Ti interbodies possess the advantage of being osteoinductive and are known to demonstrate high levels of osseointegration with native bone. However, these devices are radiopaque, which can limit radiographic assessment of fusion during follow-up.11 Additionally, Ti alloy has an elastic modulus that far exceeds that of cancellous bone. While this offers potentially greater mechanical stiffness at the time of implantation, it also increases the risk of implant subsidence.8 Though subsidence does not always necessitate operative revision, it is associated with loss of sagittal plane correction and neuroforaminal height loss, potentially counteracting 2 of the desired outcomes of interbody fusion. By comparison, PEEK has a much lower elastic modulus and an accordingly lower risk of implant subsidence. It is also radiolucent and can thereby better facilitate radiographic follow-up.9,12 However, PEEK is largely chemically inert and demonstrates poor osseointegration secondary to its proclivity to form biofilms.23 Ti-coated PEEK implants have been developed in an attempt to combine the advantages of both materials, but these hybrid devices do not appear to reduce subsidence risk relative to Ti implants23 and are associated with the risk of surface coating delamination during implantation.25

In this review, data from animal studies, human clinical series, and ex vivo experimental studies comparing PEEK and 3D-printed Ti interbody devices is presented. The data, while limited and primarily derived from animal and nonclinical studies, suggest that 3D-pTi devices are associated with decreased subsidence, increased osseointegration on micro-CT as well as qualitative histological analysis, increased BIC and ROI bone-to-cartilage ratio, increased ROM in all directions, increased stiffness, increased BV/TV, increased BAR, increased energy effective strain in the adjacent bony layer, increased implant cell proliferation, and favorable hMSC morphology as it relates to bony fusion. Taken together, 3D-pTi outperforms PEEK in 11 of the 14 outcomes. It is equivalent to PEEK in device-related reoperation, BV quantification at 12 weeks and cellular differentiation around the implant as measured by ALP and calcium content.

Advances in 3D printing technologies and materials science in the past 5–10 years have led to the availability of new 3D-printed Ti interbodies.26–29 3D-pTi devices are designed to imitate trabecular bone with highly porous surfaces, which both facilitates bony ingrowth30 and lowers the elastic modulus to the point that it more closely emulates that of cancellous bone.4,20,31–33 3D-pTi implants also have greater radiolucency relative to conventional Ti implants and so may allow for more accurate assessment of bony union.27 However, it must be noted that not all 3D-printed cages are the same, as cage properties vary significantly with the porosity of the printed Ti. Notably, while highly porous devices can allow for greater load sharing,30 porosities greater than 70% may become detrimental to the point that they can compromise structural integrity.18 Although high porosity may increase the load sharing capacity of 3D-pTi implants until it nearly approximates the load sharing properties exhibited by
In one study, re-

This same advantage should therefore 

Increased 

Plasma spraying can be used 

to create a bal-

FEA of PEEK implants, which have an elastic modulus compa-

table to cancellous bone, have shown lower von Mises stresses at the endplates of implanted interbody in FEA relative to con-

ventional Ti implants. This same advantage should therefore 

be possessed by modern 3D-pTi interbody devices. Indeed, this 

was shown clinically by Adl Amini et al. in their clinical series 
of 113 patients who underwent LLIF with 3D-pTi cages. Theo-

retically with modern 3D-printing technologies, the elastic mod-

ulus of the implant could be customized to the patient’s under-

lying bone density to allow for optimal implant-patient match-

ing. However, the cost-effectiveness of such a solution may be 

infeasible at present.

Additionally, with respect to clinical outcomes, Corso et al. reported no occurrence of 3D-pTi device-related revision sur-

geries within 6 months of the initial fusion procedure. For com-

parison, the randomized controlled trial conducted by Kersten et al. showed an additional procedure rate of 2.1% within 6 

months of PEEK interbody device implantation in transformami-

nal LIF (TLIF) procedures. Retreatment indications for correct-

ive decompression of implanted PEEK cages included an adja-

cent level complication or pseudarthrosis. Revision surgery is 

also recommend at higher rates when PEEK cages are used (3 

out of 24 patients, 12.5%) as compared to when 3D-pTi cages 

are used (revision was not recommended to any patient).18

Three-dimensional-printed Ti implants can also undergo surface treatment (e.g., adsorbed hydroxyapatite coating) to 

better facilitate bony ingrowth. Plasma spraying can be used to 

adjoin hydroxyapatite and Ti at the molecular level. This 

amalgam maintains the stiffness of the Ti while exploiting the 

osseointegrative properties of hydroxyapatite to create a bal-

anced implant not unlike 3D-pTi. While this is attractive in 

theory, studies have only demonstrated this coating’s effective-

ness in Ti pedicle screw stability and not yet in interbody spacer outcomes. Previous literature shows that reductions in 

stress due to the creation of a highly porous environment in-

creases the compressive shear strength. Kraft et al. created a 

novel 3D-pTi device, implanted in minimally invasive LLIF, with cage subsidence rates reported at 3.4% per implant, a 

rate lower than traditionally-used static PEEK cages (ranking 

from 10%–16.1%). There were specifically 2 cases of subsidence 

out of 59 interbodies implanted, both occurring within 4-level constructs and both resulting in asymptomatic outcomes not 

necessitating revision.

Histomorphological studies support the use of 3D-pTi implants 

over PEEK implants. 3D-pTi implants demonstrate robust osseo-

integration ingrowth as compared to PEEK implants, which show 

no demonstrable osseointegration in animal models. Noiset et al. demonstrated that PEEK lacks the ability to osseointegrate 
circumferentially around the cage and instead forms fibrous bony ingrowth. By contrast, 3D-pTi exhibits growth in a uniform manner 
due to the octahedral lattice configuration of the implant. The porous texture of the 3D-pTi cage appears integral to its ability 
to promote osteogenesis through. The porous structure pro-

motes de novo bone growth, remodeling, and capillary forma-
tion. In vitro work by Olivares et al. suggests that this may result from increased bone morphogenetic protein expression on 
microtextured Ti alloy. Stimulation and promotion of bone growth and remodeling most likely enhances the 3D-pTi im-

plant stability and fusion. The cellular properties found at the micro scale in 3D-pTi cages also contribute to the overall im-

proved osseointegration. Increased friction related from the 

porous surface of 3D-pTi cages has been reported to increase 

cell adhesion for bony ingrowth. Formation of F-actin fil-

ament highways in hMSCs caused improvements to cellular ad-

hesion compared to PEEK and 2D-Ti scaffolds. In addition, this mecanotransduction has been reported at the macroscopic 

level in ex vivo loading 3D spinal implants as well.

Increased bone-to-cage contact may also promote formation of an osteoblastic environment that promotes 3D-pTi cage-

mediated fusion. Van Horn et al. recorded an increased fusion-

related bone volume within the 3D-pTi device compared to 

PEEK. This increased bony surface apposition, understood as a 
surface area to volume ratio, was noted to increase steadily dur-

ing weeks 6 to 12 in subjects with 3D-pTi devices. Increased bony contact with the porous surface of the 3D printed device 

has been shown to generate reductions in ROM, furthering sta-

bilizing of the 3D-pTi device.

Notably, several other demographic and surgery-related fac-

tors have been associated with the functional and clinical out-

comes described in the studies included in this review. A study 

from Zavras et al. reviewing 144 patients who underwent an-

terior LIF (ALIF) found that older age, higher body mass index, 

patient frailty as quantified by the American Society of Anes-

thesiologists physical status classification grade, and a prior di-

https://doi.org/10.14245/ns.2346244.122
agnostic of osteoporosis were each factors associated with increased subsidence. Similar results were described by Phan et al. who found a positive association between obesity and increased rates of subsidence amongst patients who underwent ALIF. Regarding patient surgical characteristics, Peng et al. in a review of 32 patients undergoing ALIF, found that lower intraoperative pressure and complete removal of the intraoperative plate was associated with significantly reduced cage retropulsion. Building on these results, Yao et al., in a retrospective review of 93 TLIF patients, found that anterior cage positioning reduced subsidence. Several other studies have described similar outcomes in spinal fusion patient cohorts in regards to the geometry of device integration. Regarding the present review, only 2 of the included studies analyzed human cohorts. On multivariate analysis, Adl Amini et al. found only 2 other demographic or surgical factors that were a significant predictor of subsidence: diagnosis of degenerative disk disease and volumetric bone density. Corso et al. performed a propensity-matched study, eliminating the potential for confounding demographic variables to influence the final outcomes. However, as a result of cohort matching, they were unable to elucidate relationships between patient demographics, surgery-related factors and functional outcomes.

There are several limitations to the present study. Foremost is the relatively limited number of studies available providing direct comparison of 3D-pTi and PEEK interbody for LIF. Moreover, a majority of the studies included in the present review were animal or nonclinical studies, limiting the ability to reach broad conclusions about the advantage of 3D-pTi, though the preliminary evidence here appears to support its use over PEEK implants. Notably, none of the included studies included comparison between variations on the LLIF implants, namely ALIF devices, TLIF devices and posterior LIF devices, which may also have applications in clinical workflows. Deeper investigation into the generalizability of the highlighted results for these variations is warranted though previous reviews of literature have found that indications for the interbody fusion device used are contingent on anatomy rather than material used. As a result, we would not expect significantly different comparative outcomes for the device variations. Further, we were unable to compare demographic and surgery-related factors across studies although multivariate and cohort matching within studies identified independent relationships between device materials and functional outcomes. Additionally, each of the studies analyzed used different metrics for device characterization, such as young's modulus, and efficacy, such as subsidence rates and patient-driven outcomes, rendering comparison across studies, even in similar populations, difficult. Future studies may look to develop a standardized set of comparison tools for interbody devices.

Furthermore, additional analysis on the cost-effectiveness of these implants is merited. Crucial to development of a potential cost-effectiveness argument in favor of 3D-pTi, is the elimination of osteobiologics and their cost burden to a successful fusion surgery, owing to the superior osteointegrative character of 3D-pTi relative to standard interbodies. A most cost-effective solution may lie somewhere in between; Malone and colleagues utilized a 3D-pTi coated with a low cost β-tricalcium phosphate-hydroxyapatite ceramic graft in a retrospective series of 90 patients undergoing lateral lumbar fusion surgery and demonstrated successful fusion criteria in 99.3% of patients at 1-year follow-up without any instance of revision surgery or high-grade subsidence. Future studies investigating the cost-effectiveness of this implant must consider how it may obviate standard osteobiologics for achieving fusion. An additional limitation is the utilization of different 3D-pTi implants in each study. As demonstrated by prior biomechanical data, implant porosity significantly affects the elastic modulus and other biomechanical properties, along with the ability to facilitate osseo-integration. The exact impact on the clinical effectiveness of these devices is unclear. Further, none of the included study investigated the influence of unique lattice structures on-device efficacy. Future studies may look to analyze whether implant porosity and structure significantly impact device outcomes. Moreover, none of the included clinical studies reported greater than 1-year follow-up. As bony union can take more than a year, it is possible that fusion rates at later follow-up time points do not show a difference between 3D-pTi and PEEK implants, though the histopathological data support 3D-pTi as superior. Finally, the studies included in this review used devices made of 3D-pTi devices and commonly available PEEK materials. Since these studies have concluded, advancements in PEEK technology, such as addition of inorganic and organic phases, different minerals and modifications to structure and roughness, have occurred and future efforts should therefore compare 3D-pTi technology to these more modern, modified PEEK materials.

CONCLUSION

The present systematic review highlights the paucity of clinical data directly comparing outcomes between 3D-printed Ti implants and PEEK implants for LIF. The clinical and preclini-
cal data that is available supports the superiority of 3D-pTi in terms of fusion outcomes and osseointegration. The available clinical series additionally showed decreased rates of cage subsidence and no reports of reoperations or revision surgeries. Despite the promising preliminary data, additional human investigation, including cost analyses are merited.

NOTES

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3D-pTi vs PEEK: A Systematic Review

Patel NA, et al.


Commentary on “Three-Dimensional-Printed Titanium Versus Polyetheretherketone Cages for Lumbar Interbody Fusion: A Systematic Review of Comparative In Vitro, Animal, and Human Studies”

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Lumbar interbody fusion (LIF) surgery is a valuable approach to treating conditions such as degenerative disc disease, spinal instability, and various deformities. This surgical intervention employs multiple techniques, including anterior LIF (ALIF), posterior LIF (PLIF), transforaminal LIF (TLIF), oblique LIF, and lateral LIF, each tailored to address specific spinal issues.¹-³ Central to these techniques is the utilization of interbody devices, which are crafted from different materials designed to offer stability and encourage bone fusion. Among them, titanium (Ti) alloy and polyetheretherketone (PEEK) have been the dominant materials in the market since the late 1990s.⁴

Ti alloy and PEEK are the 2 dominant materials used in interbody devices.³ Ti alloys offer superior strength, biocompatibility, and osseointegration capabilities, making them ideal for promoting spinal fusion and ensuring long-term stability. On the other hand, PEEK offers radiolucency, a modulus of elasticity closer to that of human bone, and reduced stress shielding, which contributes to better patient outcomes and minimizes complications. However, there are drawbacks associated with each material as well. Ti alloys may lead to stress shielding effects. It has an elastic modulus far exceeding that of cancellous bone, which might increase the risk of implant subsidence. Moreover, it can pose challenges with imaging due to artifacts. On the other hand, although PEEK has excellent radiolucency, it is chemically inert. It demonstrates poor osseointegration due to its proclivity to form biofilms, potentially affecting the fusion process and long-term stability. These issues have led to ongoing research and the development of new materials and technologies.

Ti-coated PEEK implants represent a cutting-edge approach to combine the advantages of both Ti and PEEK materials, aiming to strike an optimal balance between their respective strengths.⁴ These hybrid implants seek to harness the biocompatibility and favorable mechanical properties of PEEK, along with the enhanced osseointegration potential of Ti. However, despite their innovative design, Ti-coated PEEK implants do not appear to sig-
significantly reduce subsidence risk compared to traditional Ti implants. Additionally, they carry the risk of surface coating delamination during the implantation process, which could compromise their effectiveness and lead to potential complications. Another promising area of research concentrates on developing composite materials that incorporate the benefits of multiple components. One such example is the investigation of a composite material composed of PEEK and hydroxyapatite, a naturally occurring mineral found in bone tissue. By combining these 2 materials, researchers hope to improve osseointegration—the direct structural and functional connection between living bone and the implant—while maintaining the desirable mechanical properties associated with PEEK, such as lower stiffness and better load distribution. This composite material could potentially offer better outcomes in spinal fusion surgery by enhancing implant-bone integration and reducing complications related to stress shielding and subsidence.

Recently, 3-dimensional-printed Ti (3D-pTi) interbody devices have gained attention for their porous structure. In this review, 2 retrospective human cohort studies with 299 human subjects showed that 3D-pTi devices demonstrated reduced subsidence rates and minimal device-related reoperation risk compared to PEEK devices. In 3 prospective animal model studies, 3D-pTi devices displayed better osseointegration, bone/cartilage content, and bone apposition ratios. Two nonclinical laboratory examination studies revealed that 3D-pTi devices had increased load distribution and better cell proliferation and differentiation than PEEK implants. Overall, the reviewed studies favored 3D-pTi over PEEK devices.

As described in the review, 3D-pTi interbody devices not only promote bone growth (osteoinduction) but also provide mechanical properties closely resembling native bone. This porous architecture is designed to facilitate osseointegration and reduce stress shielding, potentially enhancing long-term outcomes. Moreover, 3D-printing technology enables the customization of implant shapes and sizes to fit individual patients’ anatomies better. These devices are engineered to mimic trabecular bone with highly porous surfaces that encourage bony ingrowth and lower the elastic modulus to closely emulate cancellous bone. Furthermore, the 3D-pTi implants also exhibit greater radiolucency compared to conventional Ti implants. Thus, this could potentially enable a more accurate assessment of the bony union status. However, 3D-printed cages can differ significantly due to variations in the porosity of the printed Ti. While highly porous devices allow for greater load sharing, porosities above 70% may compromise structural integrity. High porosity increases the load-sharing capacity of 3D-pTi implants until it nearly approximates that of PEEK; however, below a critical threshold in the implant mass-to-volume ratio, intrapore struts become thinner and more vulnerable to degradation and buckling. This is due to the elastic modulus of 3D-pTi cages, which directly correlates with the degree of porosity. One study demonstrated that reducing the elastic modulus (E) using porous 3D modeling yielded a modulus similar to human bone.

From that point, another potential is that the 3D-pTi may also offer benefits in terms of reducing the risk of implant migration. The porous structure of these devices forms a rough surface, which promotes friction between the implant and adjacent endplates. This increased friction creates a more secure connection, potentially lowering the risk of migration. Implant migration is a concern in spinal fusion surgery, as it can lead to complications, such as nonunion, subsidence, or nerve impingement, which may require revision surgery. Therefore, reducing the risk of migration is essential for better patient outcomes.

Theoretically, modern 3D-printing technologies offer the potential to customize the elastic modulus of implants to match a patient’s underlying bone density, enabling optimal implant-patient compatibility. However, the cost-effectiveness of such a solution may currently be impractical. Additionally, potential challenges, including the high cost of 3D-printing technology and potential difficulties in maintaining manufacturing consistency, need to be addressed and overcome to fully realize the benefits of these promising 3D-pTi interbody devices.

3D-pTi interbody devices boast potential benefits beyond their osseointegration capabilities as they enhance radiographic properties. Radiolucency is a critical attribute for spinal implants, as it enables a more accurate assessment of fusion progress during follow-up appointments. Traditional Ti intrabodies, due to their high radiopacity, can hinder the radiographic evaluation of fusion by obscuring the visualization of the fusion mass. Devices with higher porosity levels generally exhibit greater radiolucency, making them even more advantageous for monitoring the fusion process and ensuring successful patient outcomes. However, it is essential to acknowledge that the degree of radiolucency may vary based on the specific design and porosity of the 3D-pTi implant.

The current study acknowledges a number of limitations that should be taken into consideration. First, there is a limited number of studies directly comparing 3D-pTi and PEEK interbody devices for LIF, with most being animal or nonclinical studies. This restricts the ability to draw broad conclusions, although preliminary evidence supports 3D-pTi use over PEEK implants.
The review does not compare variations like ALIF, TLIF, and PLIF devices, which may have clinical applications. Further investigation is needed, though previous reviews suggest device choice depends on anatomy rather than material. The studies used different metrics for device characterization and efficacy, making comparisons challenging. Therefore, future research should develop standardized comparison tools for this. Additionally, demographic and surgery-related factors were not compared across the studies. Different 3D-pTi implants were used in each study, with varying porosity and structure, which may impact clinical effectiveness. None of the included studies investigated the influence of unique lattice structures on device efficacy or had more than 1-year follow-up. Fusion rates at later time points might not show a difference between 3D-pTi and PEEK implants. The studies reviewed used 3D-pTi devices and commonly available PEEK materials, but advancements in PEEK technology have since occurred. Future efforts should compare 3D-pTi technology to these modern, modified PEEK materials. Finally, as previously described, the cost-effectiveness analysis and the potential impact of osteobiologics elimination on successful fusion surgery are also warranted.

In conclusion, 3D-printed Ti interbody devices represent a promising advancement in spinal fusion surgery. These implants offer several advantages over conventional Ti and PEEK devices, including improved osseointegration, reduced risk of implant subsidence, and better radiographic assessment of fusion. However, more research is needed to fully understand the long-term clinical outcomes and potential complications associated with these devices. Large, randomized controlled trials with extended follow-up periods are recommended to determine the true efficacy of 3D-pTi implants in spinal fusion surgery and to establish their role firmly in the treatment of degenerative spinal conditions.

- **Conflict of Interest:** The corresponding author, Jin-Sung Kim, is a consultant of Richard Wolf, GmbH, and Elliquence, LLC. The other authors have no conflicts of interest to declare.

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INTRODUCTION

In the last 20 years, sagittal alignment and balance of the spine have become one of the most important issues in the field of spine surgery. Adult spinal deformity (ASD) is caused by a number of factors that lead to structural changes in spinal alignment, followed by changes in balance mechanisms to achieve the most economical upright posture. The resulting disability and significant loss of quality of life require surgical treatment. However, if the intended sagittal alignment is insufficiently restored after surgery, patients often complain of persistent low back pain due to the so-called flatback syndrome. Recent studies emphasize that even in coronal plane deformities such as degenerative scoliosis, sagittal alignment are more important for health-related quality of life (HRQoL). The understanding of spinal sagittal alignment is necessary for the diagnosis and appropriate treatment of ASD.

We will discuss the currently used classification of ASD, the parameters of sagittal alignment, compensatory actions, and the relationship between sagittal alignment and clinical symptoms. Furthermore, we will also discuss the recently introduced Global Alignment and Proportion (GAP) scores and its clinical usage.

The Korean Spinal Deformity Society is publishing a series of review articles on spinal deformities to help spine surgeons better understand spinal deformities.

Keywords: Adult spinal deformity, Lumbar kyphosis, Spinal deformity
SCOLIOSIS RESEARCH SOCIETY-SCHWAB CLASSIFICATION

In 2007, Schwab et al.\(^6,7\) proposed a Clinical Impact Classification of ASD by applying the concept of sagittal alignment of the Lenke classification of pediatric scoliosis to ASD. This classification used radiologic parameters related to HRQoL and initially described 5 types of scoliosis based on the location of the apex of the scoliosis curve: type I, thoracic only; type II, upper thoracic major; type III, lower thoracic major; type IV, thoracolumbar major curve; type V, lumbar major curve.\(^7\) Schwab et al.\(^6,7\) used 3 radiological parameters, lumbar lordosis (LL) and intervertebral subluxation as sagittal modifiers, and sagittal vertical axis (SVA) as the global balance modifier. Based on other studies, the Scoliosis Research Society (SRS) revised the SRS-Schwab ASD classification in 2012 for a practical approach to radiologic classification of ASD.\(^9\) The classification utilizes spinal and pelvic parameters that have high interobserver and intraobserver reliability and are useful for classification.\(^9\) Patients are categorized by primary coronal deformity and SVA, pelvic tilt (PT), and pelvic incidence (PI)-LL mismatch are used as modifiers to determine sagittal deformity (Fig. 1).\(^9\)

These sagittal modifiers are not only related to pain and disability, but are also objective measures of spinopelvic deformity on the sagittal plane and can be used to guide surgical planning.

SPINOPELVIC PARAMETERS

The pelvis and hip joints serve as a balance regulator that controls the movement of the spine.\(^10,11\) The hip joints axis serves as a reference point for accessing the sagittal balance of the spine.\(^12,13\)

The parameters that indicate the shape and position of the sagittal curvature of the spine are called spinal parameters and the parameters that determine the shape and position of the pelvis are called pelvic parameters.\(^14,15\) While there are numerous spinal and pelvic parameters proposed by various authors,\(^14\) this paper will discuss the spinopelvic parameters listed as sagittal modifiers in the SRS-Schwab ASD classification, as well as other parameters that may be useful.

1. Normal Spinal Sagittal Profile

According to anatomical segmentation, the spine can be divided into cervical lordosis, thoracic kyphosis (TK), LL, and sacral kyphosis.

The TK is usually placed in the range of 20°–40°\(^16-18\) and is defined as hyper kyphosis if it exceeds 50°.\(^18\) The LL has a wider range, broadly considered with 20°–80° and narrowly 40°–60° as the normal range.\(^11,18-20\) The LL is usually 20° larger than the TK. The TK is closely correlated with the LL, and the larger the TK, the larger the LL. As age increases, the LL gradually decreases and the TK gradually increases.\(^19\) The average cervical lordosis is reported to be about 40°.\(^11\)

The segmental angles of the lumbar spine show that the L5 is approximately 20°, the L4 12°, the L3 9°, and the L2 5°. So, the lordotic angles of each segment account for approximately 40%, 30%, 20%, and 10% of the total LL, respectively.\(^21\) Two-thirds of LL is formed in the L4 to S1, making these 2 segments the most significant in LL.\(^21\) Therefore, when attempting to restore LL, emphasis should be placed on correction in these 2 segments.

2. Pelvic Parameters (Table 1) (Fig. 2)

To determine the sagittal alignment, it is important to understand and measure the parameters for pelvic orientation (version) and pelvic shape (morphology).\(^11\) The versions of the pelvis can be divided into anteversion, neutral, and retroversion with respect to the hip axis and can be determined by using positional parameters.\(^11,12,22\) The shape of the pelvis is determined by anatomical parameters (shape parameter, morphological parameter) that do not change significantly over the lifetime depending on the position of the pelvis.\(^11,14\) The most commonly used pelvic parameters are those described by Duval-Beaupère.
From the Spinopelvic Parameters to GAP Scores in ASD

Cho Y, et al.

1) Positional parameters of pelvis

The positional parameters are an indicator of the degree of rotation of the pelvis around the hip axis. Sacral slope (SS) is used as a positional parameter for the horizontal plane and PT is used for the vertical plane. In addition, overhang was described as an indicator of the degree of pelvic displacement with respect to the hip axis. The reference point for these parameters is the center of endplate of S1. Other pelvic parameters have been described by different authors, who described sacropelvic angle and sacropelvic translation, which are based on the hip axis and the posterior superior margin of sacrum. These are slight variations of the parameters described by Legaye et al. and Duval-Beaupère et al. Of these, the sacropelvic angle corresponds to PT and the sacropelvic translation corresponds to overhang.

(1) Pelvic tilt

PT refers to the spatial orientation of the pelvis, which denotes to how it is positioned anteriorly and posteriorly with respect to the transverse axis through the hip joints. PT is a dynamic pelvic parameter that changes with pelvic rotation and is normally not significantly affected by PI, so changes in PT are the important indicator of pelvic compensation in pathological conditions.

In the standing position, the average PT is tilted posteriorly by $13^\circ \pm 6^\circ$. As the PT increases due to pelvic compensation, the sacrum gradually becomes more horizontal and stands close to vertical. In this position, the acetabulum covers only the posterior aspect of the femoral head and further hip extension is limited. Mac-Thiong et al. stated that under normal circumstance, the upper limit of PT should ideally be no more than 50% of PI, and similarly, the ideal SS should be no less than 50% of PI. Theoretically, the maximum PT can occur until the endplate of sacrum is horizontal (SS = 0°) and further pelvic rotation is limited by hip extension reserve. Theoretically, the maximum value of PT is equal to PI (Fig. 3). In summary, pelvic posterior rotation, as a phenomenon of pelvic compensa-

Table 1. Spinopelvic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Theoretical values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic tilt</td>
<td>The angle between a line from the center of the femoral head to the midpoint of the sacral endplate and a vertical reference line drawn through the center of the femoral head</td>
<td>$10^\circ - 15^\circ$</td>
</tr>
<tr>
<td>Sacral slope</td>
<td>The angle between the sacral endplate and a horizontal line</td>
<td>$30^\circ - 50^\circ$</td>
</tr>
<tr>
<td>Pelvic incidence</td>
<td>The angle between the line from the center of the hip axis to the midpoint of the sacral endplate and a line perpendicular to the sacral endplate</td>
<td>$30^\circ - 80^\circ$</td>
</tr>
<tr>
<td>Sagittal vertical axis</td>
<td>The distance between the C7 plumb line (C7PL) and the posterior superior part of the S1</td>
<td>$&lt; 50$ mm</td>
</tr>
<tr>
<td>Spinal tilt</td>
<td>The angle formed by the horizontal line and the line connecting the center of the C7 vertebral body and midpoint of the sacral endplate</td>
<td>$90^\circ$</td>
</tr>
<tr>
<td>Spinosacral angle</td>
<td>The angle between the line from the center of the C7 vertebrae to the midpoint of the sacral endplate and the line of sacral endplate</td>
<td>$110^\circ - 150^\circ$</td>
</tr>
<tr>
<td>C7 translation ratio</td>
<td>The ratio parameter that divides the distance between the center of the sacral endplate and the C7PL by the distance between the center of the sacral endplate and the hip axis</td>
<td>$-0.9 \pm 1$</td>
</tr>
<tr>
<td>Spinopelvic angle</td>
<td>The angle formed by the line connecting the center of the C7 and the center of the sacral endplate and the line connecting the hip axis and the center of the sacral endplate</td>
<td>$130^\circ - 170^\circ$</td>
</tr>
<tr>
<td>T1 pelvic angle</td>
<td>The angle subtended by a line from the femoral heads to the center of the T1 vertebral body and a line from the femoral heads to the center of the superior sacral end plate</td>
<td>$&lt; 20^\circ$</td>
</tr>
</tbody>
</table>

Fig. 2. Spinopelvic parameters. C7PL, C7 plumb line; TK, thoracic kyphosis; LL, lumbar lordosis; SSA, spino sacral angle; SVA, sagittal vertical axis; SS, sacral slope; PT, pelvic tilt; PI, pelvic incidence.
From the Spinopelvic Parameters to GAP Scores in ASD

Cho Y, et al.

From the Spinopelvic Parameters to GAP Scores in ASD

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26,27

It is generally accepted that the ideal pelvic position is a PT < 20°, which is the goal of surgical treatment.28 The normal range of PT is broadly -5° to 30°. However, the normal range of PT varies depending on the individual’s PI. Unlike PI, PT increases with age as a compensatory response to a decrease in LL and an increase in TK.15

However, it is worth reconsidering whether PT simply refers to compensation for hip extension. PT practically refers to the pelvic posterior rotation angle, which combines the posterior rotation of the pelvis at the hip joint with the posterior rotation of the hip joint at knee flexion. Therefore, hip extension is the true pelvic compensation at the hip joint, and PT is the apparent pelvic compensation with compensatory knee flexion combined.

(2) Sacral slope

The SS is the important factor in determining the size and shape of lumbar curvature, and the shape and size of the lower lumbar vertebrae are directly affected by the size of the SS. By determining the shape and size of the lumbar spine, the SS determines the shape of the sagittal curvature of the entire spine.15,18

The relationship between SS and LL was first described by Stagnara et al.29 The greater the SS, the deeper the lumbar curvature (“dynamic back”) and conversely, the smaller the SS, the flatter the lumbar curvature (“static back”). The size of the lower lumbar curve is equal to the SS, indicating that the lower curve is important in determining the overall LL. Roussouly et al.30 described 4 types of LL in normal adults according to SS. SS is rarely affected by growth after the onset of walking. It has also been reported that PT increases with age but SS remains relatively unchanged.31

(3) Pelvic overhang

The horizontal distance between the center of the sacral end-plate and the hip axis is called pelvic overhang and represents the position of the sacrum with respect to the hip joint.23 When the pelvis is posteriorly rotated, pelvic overhang increases.23

(2) Anatomical parameters of pelvis

Anatomical parameters are indicators of the shape of the pelvis, which changes to some degree during growth, but does not change throughout life after the completion of growth, and does not change with the position of the pelvis. However, this anatomical parameter directly influences the positional parameters to determine the size and shape of the lumbar curvature, making it the fundamental factor in determining the overall shape of the spine. Anatomical parameters include PI and pelvic thickness.10,14

(1) Pelvic incidence

In 1992, Duval-Beaupére et al.22 and Legaye et al.10 described the ‘pelvic incidence’. This is similar to a vector for the load transmitted through the sacral endplate. PI represents the most important sagittal morphologic feature of the pelvis.8

In effect, PI is equal to the sum of the SS and the PT (PI = SS + PT). PI does not change with pelvic rotation around the hip joint. If the pelvis rotates posteriorly, PT increases and the SS decreases by the same amount. If the pelvis rotates anteriorly, PT decreases and SS increases.

PI is stabilized in adulthood and does not change with age, nor does it change with pelvic position.19 PI is a reliable measure of SS and LL.15,31 Recently, however, there have been reports that PI increases as a process of aging, even in adulthood.5 There is a significant chain of correlations between various pelvic and spinal parameters, of which PI plays the most pivotal role. Among these correlations, the correlations between PI and SS and between SS and LL is the highest.18 If PI is high, SS is large and if SS is large, LL and TK is large, which affects other spinopelvic parameters. Therefore, Legaye et al.10 stated that PI is the important factor that determines the shape of the spinal sagittal plane. However, the same PI does not always result in the same shape of the sagittal curvature because both the SS and the PT can be different.19 So, in the other’s opinions, PI-LL mismatch is acceptable in patients with high PI.

PT determines the position and orientation of the pelvis.
when standing. The larger the PI, the larger SS or the larger PT, or both increases. A pelvis with a small PI will have a short anteroposterior length and a long vertical pelvis, resembling the pelvis of a primate. In this case, the femoral head is located directly inferior to the sacral endplate. On the other hand, a pelvis with a large PI has a horizontal pelvis with a large anteroposterior diameter, a large SS, and the femoral head is located anterior to sacral endplate (Fig. 4).

A large PI allows for a large PT, but is limited by the extension range of the hip joint. On the other hand, a small PI allows for a small amount of posterior pelvic rotation, because of the large hip extension range, PT can occur theoretically until SS reaches zero degrees (PT = PI).

The PI also determines the relative position of the sacral endplate to the femoral head, which in turn determines the position of the spine in relation to the pelvis. Barrey et al. have shown that PI determines the ability to create pelvic retroversion and the patients with a larger PI have a larger range of control to PT and more room for compensatory adaptation. Those with a small PI usually have a small SS, so even a slight increase in PT can cause the SS to be close to 0, which has the advantage of moving the sagittal axis posteriorly, so it is thought that the pelvic compensatory ability is large. This means that SS can reach 0 degrees relatively easily with a small PI compared to a large PI. This is thought to be due to the limited range of hip extension.

3. Sagittal Alignment Parameters (Table 1; Figs. 5, 6)

Standing balance is achieved by the corrective or compensatory mechanisms of the pelvis in response to the various alterations that occur in the spinal column. The body’s gravitational lines regulate the body’s balance within a cone with a narrow point at the foot as the apex. When the body’s gravitational lines are within this cone, the body is in a balanced and economical posture, and when the body’s gravitational lines are outside of the cone, the body is out of balance. This is an uneconomical posture that requires a lot of compensation and energy. Dubousset named this the ‘cone of economy’.

The balance of the spine with respect to the pelvis is called spinal balance and is determined by the relationship between the C7 plumb line (C7PL). The balance of the pelvis with respect to the hip axis is called sacropelvic balance, and is determined by the relationship between the C7PL and the hip joint axis. The balance of the whole spine and pelvis with respect to the hip axis is called spinopelvic balance, and is determined by the relationship between the C7 PL and the hip axis, which is a sagittal balance that considers the shape of the spine and pelvic compensation together.

The methods of evaluating sagittal alignment are measuring the distance from a reference point (distance parameters), measuring the angle centered on a reference point (angular parameters), and measuring the ratio between the distances (distance parameters).

The distance parameter of sagittal alignment is typically represented by SVA and angular parameters include T1 pelvic an-
gle (TPA) and spinal tilt (ST). Sacropelvic balance is determined by PT or pelvic overhang (Fig. 2).

(1) Sagittal vertical axis

This distance is used as the important and representative parameters of spinal sagittal balance, and it is now standardized to use the SVA to determine spinal sagittal alignment and overall patient outcome.\textsuperscript{3,36} The SVA ranges normally within 5 cm. If the SVA exceeds ± 5 cm, it is considered a sagittal imbalance.\textsuperscript{37-39}

Just as the C7PL is the most commonly used reference line to measure sagittal balance, but it does not reflect the alignment of the cervical spine.\textsuperscript{40,41} It also does not reflect the role of the pelvis and lower extremities in sagittal alignment.\textsuperscript{41,42} Therefore, a global sagittal alignment using SVA alone fails to evaluate the compensatory actions of the pelvis and lower extremities.\textsuperscript{42} The PT, which is a parameter of compensation in the pelvis and knee joints, should be considered together.\textsuperscript{43,44} In addition, SVA is a parameter based on the posterior superior aspect of the sacrum rather than the hip axis, which is considered the important reference point for spinal balance, but SVA < 50 mm is recognized as one of the most important criteria for sagittal balance, which is equivalent to having the C7PL located posterior to the hip axis, and this threshold is consistent with a good HRQoL score.\textsuperscript{5,11}

In radiologic measurements, angular parameters and ratios are preferred over distance parameters because they are less sensitive to changes in radiologic magnification.\textsuperscript{45} Mac-Thiong et al.\textsuperscript{25} proposed 3 parameters to measure global spinal alignment: the angular parameters such as ST and spinosacral angle (SSA) and the ratio parameter (C7 translation ratio). These are parameters about the position of the C7 vertebra in relation to the pelvis or sacrum.

(2) Spinal tilt

ST is greater than 90°, which means that the center of the C7 located behind the center of the sacral endplate and less than 90 degrees means that center of the C7 is in front of the center of the sacral endplate.\textsuperscript{46}

(3) Spinosacral angle

Roussouly and Pinheiro-Franco\textsuperscript{18} showed that SSA is a quantitative measure of global kyphosis of the whole spine. In a well-balanced spine, SSA is proportional to SS and decreases with loss of LL. This relationship can be used as a guide to determine the need for kyphosis correction. There is a strong correlation between SSA and SS and LL.\textsuperscript{18,45} In normal individuals, SSA is predicted to average 135° ± 8° (110°–150°), ST is predicted to be 85°–100°, and ST is close to 90°.\textsuperscript{18}

ST can be considered a functional positioning parameter that indicates the global orientation of the spine with respect to the horizon, while SSA is considered a morphologic parameter that indicates the overall kyphosis of the spine. ST and SSA can be expressed as SSA = ST+SS.\textsuperscript{45} When sagittal imbalance occurs, ST can be maintained relatively stable by decreasing SS.\textsuperscript{18} In particular, normal SSA values can be used to determine the degree of overall kyphosis and the outcome of surgical treatment.\textsuperscript{47} On the other hand, ST is preferred over SSA because it is maintained in a narrow range (85°–100°) and is more closely related to the vertical line in normal adults.\textsuperscript{15}
(4) C7 translation ratio

This parameter is also an indicator using distance ratio, which can solve the problem of measurement error of distance parameter. It averages -0.9 ± 1.48. The distance anterior to the center of the sacral endplate is positive value.49 If the hip joint axis is located anterior to the center of the sacral endplate and the C7PL is located posterior to the center of the sacral endplate, the C7 translation ratio has negative value, and if the C7PL is in front of the hip joint axis and the center of the sacral endplate, it has a value greater than 1. It decreases in the case of compensatory balance and becomes greater than 1 in the case of decompensation.50

(5) Spinopelvic angle

Roussouly and Nnadi41 described spinopelvic angle for postural angle, which decreases with spinal kyphosis.

(6) T1 pelvic angle

SVA and PT can be altered by posterior pelvic rotation, knee flexion, or the use of bracing during standing.52 According to Lafage et al.,4 when measuring SVA alone, an increase in PT can mask spinal deformity, so PT must be considered in conjunction with SVA to identify patients with spinal deformity in the absence of abnormal SVA.

Protopsaltis et al.52 introduced a new parameter called TPA which is not affected by compensation of patient’s knee. In an individual, SVA and PT are interrelated and influence each other. This interaction is further modified by compensatory mechanisms to maintain sagittal balance, such as knee flexion and pelvic posterior rotation. However, since TPA is a parameter that considers ST and PT simultaneously, it is less affected by compensation.52 TPA was closely correlated with SVA, PI-LL, and PT, and HRQoL gradually worsened as TPA increased, and it was highly correlated with the Oswestry Disability Index (ODI).52 A TPA of 20° or more leads to an ODI of 40 or more, which is the criterion for severe disability, and it is recommended to aim for a TPA of 14° or less.52 Ryan et al.52 recommended that the surgical target for TPA be 10° to account for postoperative correction loss. TPA is the sum of T1 tilt and PT, so as the deformity increases, the TPA value also increases.53

According to Roussouly and Pinheiro-Franco,15,18 there are 3 things to access to quickly diagnose sagittal imbalance; (1) Pelvic angles: PI, PT, and SS, (2) type of LL, (3) positioning of C7PL (SSA, ST).

Barrey et al.44 stated that the following steps are necessary to analyze the spinal sagittal balance: (1) measurement of PI, (2) analysis of sagittal alignment by measuring SSA and C7PL/SFD ratio, (3) determination of compensatory mechanisms: LL, TK, presence of discopathy, and spondylolisthesis, (4) measurement of PT and knee flexion.

COMPENSATORY MOVEMENT

In the degenerative kyphotic changes in the spine, the sagittal alignment is maintained by hip extension, posterior rotation of pelvis, and creating lordosis in the adjacent segment of spine.55 Also, by flexing the knee joints, which relieves tension in the anterior hip joint, making it easier for the hips to extend.56 However, if the hips are not able to extend, the compensatory failure occurs. This can occur especially if there is a kyphotic deformity of the lower lumbar spine and the hip extendors are weakened at the same time, and Lee et al.57 described this phenomenon as ‘sagittal spinopelvic decompensation over the hip joint,’ which is contraindicated for surgical treatment of the lumbar spine. Not all compensatory mechanisms are observed in a single patient, but compensatory mechanisms will be present to varying degrees, depending on the flexibility of the spine, muscle condition, and degree of imbalance.44

Legaye et al.10 stated that pelvic posterior rotation is a sign of spinopelvic imbalance, but it does not always occur with spinopelvic imbalance.

The most basic concept of the compensatory mechanism is that it occurs by extending the neighboring segments of the kyphotic region.12 This can lead to hyperextension and posterior displacement of the neighboring segments, which can lead to adjacent segment disease. Focal hyperextension is effective in moving the above spine posteriorly, but it overloads the posterior structures of the segment, increasing the risk of spondylolisthesis, degenerative change of the facet joints, over-compensation of the spinous processes (Baetsrip's disease), and sometimes spondylolysis.12,55,58

A typical finding of sagittal imbalance in the elderly is a gradual anterior shift of the line of gravity due to increased TK and decreased LL. Once sagittal imbalance is out of range, compensation is required and several mechanisms are triggered to correct the imbalance.12 First, the posterior muscles of the spine will contract to try to keep the trunk upright, and over time, this can lead to muscle fatigue and pain. This process can also result in excessive pressure on the facet joints, which can also cause pain. Secondly, there is the posterior rotation of the pelvis around the femoral head. However, As the aging progresses, the hip joint undergoes degenerative changes and loses its range of motion. This eventually limits the ability to strengthen the PT.12
Also, even with normal hip range of motion, the pelvis cannot rotate posteriorly to infinity, and this posterior pelvic rotation is limited by a 10° hip extension allowance.\textsuperscript{23} Third, in more severe cases, it is compensated for by flexion of the knee joint, which is controlled by the quadriceps muscle.

The ability of the spine to compensate for these deformities is determined by the patient’s intrinsic pelvic morphology, defined by PI. Based on the equation SS+PT = PI, posterior rotation of the pelvis will decrease SS. The significance of this equation is that the ability to change PT or SS to compensate for a vertebral sagittal imbalance is determined by the size of the PI. A large PI has a greater ability to compensate for kyphotic deformity by increasing the posterior rotation of the pelvis and decreasing SS, whereas a small PI has less range to increase PT to restore sagittal alignment.\textsuperscript{32,33,54}

However, this is limited by the remaining hip extension range after pelvic posterior rotation has occurred. This is why, after maximal pelvic posterior rotation has occurred, the spinopelvic complex uses the next level of compensation, knee flexion.\textsuperscript{37} Therefore, in order to understand the global compensatory mechanism, it is important to understand the role of the knee joint as well as the hip joint.

**RELATIONSHIP OF SPINOPELVIC PARAMETERS TO CLINICAL SYMPTOMS**

Glassman et al.\textsuperscript{36} found that anterior shift of the SVA was the most reliable radiographic predictor of HRQoL in the review of 352 patients. The degree of disability correlated closely with the degree of kyphosis, especially in the lumbar spine compared to other parts of the spine. Therefore, in the surgical treatment of ASD, we strive to achieve a postoperative SVA < 50 mm, as this is the way to achieve a physiologic standing position and level gaze. The SVA of < 50 mm means that the C7 PL is eventually positioned posterior to the hip axis and this threshold corresponds to a favorable HRQoL score.\textsuperscript{28}

Schwab et al.\textsuperscript{28} showed that HRQoL is strongly correlated with this increase in PT and the ideal PT goal for surgery should be to achieve 20° or less. In ASD, if the increased PT is not recognized before the correcting surgery, the sagittal imbalance due to insufficient correction is likely to remain and lead to persistent symptoms.\textsuperscript{7} Therefore, the appropriate surgical goal is to return the PT to the normal range of 20° or less.\textsuperscript{28}

However, Lafage et al.\textsuperscript{8} analyzed spinopelvic parameters in 125 ASD patients to determine which parameters correlated best with HRQoL using ODI, SRS questionnaire, and 12-item Short Form health survey. TPA, which has been underutilized, had the highest correlation followed by SVA, and PT, which had the third highest correlation.\textsuperscript{53} TPA was strongly correlated with ODI (r = 0.52, p < 0.0001).\textsuperscript{31} In addition, it was found that as PT increases, HRQoL worsens, but the worst ODI is when SVA is large and PT is small, which may indicate compensatory failure.\textsuperscript{9}

Several studies have suggested thresholds for spinopelvic parameters that can cause pain and disability. It has been reported that PT > 22°, PI-LL > 11°, and SVA > 46 mm are associated with an ODI score of 40, which is a criterion for severe disability.\textsuperscript{7,28} Recent studies have suggested several other criteria such as Hamamatsu formula.\textsuperscript{59}

**GOALS FOR SURGICAL TREATMENT**

Schwab et al.\textsuperscript{28} suggest that to successfully restore harmonious spinopelvic alignment, 3 key parameters should be achieved: SVA < 50 mm, PT < 20°, and PI-LL < ± 9°. Using SSA as a reference, it is important that it do not exceed about 135° and PT is about 20°.\textsuperscript{53}

**THE GLOBAL ALIGNMENT AND PROPORTION SCORE**

The GAP score was first introduced by Schwab et al. in a published study. They recognized the need for a comprehensive and practical method to assess spinal alignment and balance in patients undergoing spinal deformity surgery, and developed the GAP score as a result.\textsuperscript{59-61}

The GAP score was based on the concept of global spinal alignment, which takes into account the interrelationships between different regions of the spine and the pelvis. The authors identified several key radiographic parameters including PT, PI, LL, TK, and SVA.\textsuperscript{51} The authors then combined these parameters into a single composite score, which they called the GAP score.\textsuperscript{60} The score ranges from 0 to 100, with higher scores indicating better spinal alignment. The authors validated the usefulness of the GAP score in a cohort of 69 patients who underwent spinal deformity surgery, and found that higher GAP scores were associated with better outcomes in terms of pain, disability, and HRQoL.\textsuperscript{59}

Since its introduction, the GAP score has become widely used in clinical practice to guide surgical decision making and postoperative management in patients with spinal deformity. Practical use of the GAP score in spinal deformity surgery involves
several steps. First, preoperative radiographs are obtained, and the various parameters used to calculate the GAP score are measured. Once these measurements have been obtained, the GAP score can be calculated using a formula that takes into account each of the individual parameters. The resulting score can then be used to guide surgical decision making, including the selection of surgical techniques and the extent of surgical correction. Postoperatively, the GAP score can be used to monitor patient outcomes and assess the effectiveness of surgical correction. For example, if a patient has a low GAP score preoperatively and a high score postoperatively, this indicates that the surgical correction was successful in improving spinal alignment. Although the usefulness of GAP score, several papers have argued that further prospective studies and revalidation of the GAP score are necessary, especially the validation between the GAP score and mechanical complication.

CONCLUSION

It is necessary to have a basic understanding of the ASD and the spinopelvic parameters. In addition, there are various compensatory actions that occur to maintain sagittal balance, which must be evaluated to determine correct sagittal alignment.

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From the Spinopelvic Parameters to GAP Scores in ASD

Cho Y, et al.


Biomechanical Comparison of Multilevel Stand-Alone Lumbar Lateral Interbody Fusion With Posterior Pedicle Screws: An In Vitro Study

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Objective: Lumbar lateral interbody fusion (LLIF) allows placement of large interbody cages while preserving ligamentous structures important for stability. Multiple clinical and biomechanical studies have demonstrated the feasibility of stand-alone LLIF in single-level fusion. We sought to compare the stability of 4-level stand-alone LLIF utilizing wide (26 mm) cages with bilateral pedicle screw and rod fixation.

Methods: Eight human cadaveric specimens of L1–5 were included. Specimens were attached to a universal testing machine (MTS 30/G). Flexion, extension, and lateral bending were attained by applying a 200 N load at a rate of 2 mm/sec. Axial rotation of ± 8° of the specimen was performed at 2°/sec. Three-dimensional specimen motion was recorded using an optical motion-tracking device. Specimens were tested in 4 conditions: (1) intact, (2) bilateral pedicle screws and rods, (3) 26-mm stand-alone LLIF, (4) 26-mm LLIF with bilateral pedicle screws and rods.

Results: Compared to the stand-alone LLIF, bilateral pedicle screws and rods had 47% less range of motion in flexion-extension (p < 0.001), 21% less in lateral bending (p < 0.05), and 20% less in axial rotation (p = 0.1). The addition of bilateral posterior instrumentation to the stand-alone LLIF resulted in decreases of all 3 planes of motion: 61% in flexion-extension (p < 0.001), 57% in lateral bending (p < 0.001), 22% in axial rotation (p = 0.002).

Conclusion: Despite the biomechanical advantages associated with the lateral approach and 26 mm wide cages, stand-alone LLIF for 4-level fusion is not equivalent to pedicle screws and rods.

Keywords: Stand-alone, Lateral interbody fusion, Multilevel, Extreme lateral interbody fusion, Lumbar lateral interbody fusion, Biomechanics

INTRODUCTION

Lateral lumbar interbody fusion (LLIF) is one minimally invasive operative technique used to create fusion in patients with degenerative lumbar spinal diseases.¹ Surgical advantages of LLIF as compared to anterior or posterior lumbar fusion include excellent visualization, preservation of ligamentous and bony structures contributing to spine stability, access for discectomy, and decreased mobilization of neurologic structures and vasculature.²-⁴ The lateral approach allows for implantation of interbody cages of large sizes, which facilitates restoration of disc height, correction of deformity, and dispersion of axial loads across the endplate.⁵-⁶ As a minimally invasive technique, LLIF has demonstrated less tissue trauma, low intraoperative blood loss, and faster recovery times compared to the open surgical approach. However, concerns remain regarding the stability of LLIF, particularly when multiple levels or large cages are utilized.
loss, and lower infection rates than open surgery. In addition, its efficacy has been shown in multiple clinical studies utilizing validated patient-reported outcome measures.

In practice, LLIF is usually combined with supplemental posterior fixation to enhance segmental stability, reduce subsidence, and thereby increase rates of instrumented fusion. Multiple level lateral interbody fusion combined with percutaneous pedicle screw fixation is a minimally invasive surgical strategy with high fusion rates and favorable radiographic and clinical results. The placement of supplemental posterior fixation represents an additional step of surgery and often repositioning of the patient, although single-position surgery has been attempted.

If stand-alone lateral interbody fusion can confer adequate biomechanical stability to promote fusion, this would be important knowledge because it could potentially obviate the need for posterior instrumentation. The literature suggests that a stand-alone lateral approach is sufficient in some situations. A recent systematic review of 22 studies by Manzur et al. found that stand-alone LLIF of various cage widths achieved pooled clinical fusion rate that was not statistically different from combined LLIF and posterior (circumferential) fusion. Biomechanically, single-level stand-alone LLIF has been reported to reduce the segmental range of motion (ROM) more than transforaminal lumbar interbody fusion (TLIF) or stand-alone anterior lumbar interbody fusion (ALIF).

Cage width may also have an important role in the feasibility of stand-alone lateral interbody fusion. In a cadaveric study of extra wide (26 mm) cages, Pimenta et al. found that increasing the width of the cages from 18 mm to 26 mm resulted in a more significant reduction of ROM. In addition, they reported that the stand-alone 26-mm LLIF was more rigid than TLIF with bilateral pedicle screws. Clinically, Lang et al. reported that 26-mm wide cages decreased subsidence compared to 22-mm and 18-mm wide cages.

Considering the previous works supporting stand-alone LLIF for single-level surgery and the favorable biomechanical profile of 26-mm cages, we sought to investigate a stand-alone LLIF approach to multilevel fusion. The biomechanical stability of multilevel stand-alone LLIF utilizing extra wide cages has not been characterized. This study compared the biomechanical stability of stand-alone LLIF using 26-mm cages for long multilevel fusion (L1–5, 4 levels) to posterior bilateral pedicle screws and rods. We chose bilateral pedicle screws and rods because this surgical strategy is widely accepted as providing adequate stability to promote spinal fusion. We hypothesized that the multilevel stand-alone LLIF will provide comparable stability as traditional pedicle screw fixation due to the use of extra wide cages.

**MATERIALS AND METHODS**

1. **Specimen Preparation**

Eight fresh-frozen human cadaveric specimens of L1–5 were included. Specimens were prepared by cleaning surrounding soft tissue and muscle and preserving the discs and spinal ligaments (supraspinous, interspinous, facet capsules, posterior longitudinal ligament, anterior longitudinal ligament). The mean specimen age was 66.5 ± 11.5 years. There were 7 male and 1 female specimen. The average body mass index was 31.1 ± 7.32 kg/m². All specimens were visually inspected to confirm no fracture, deformity, previous surgery, or severe spondylolisthesis.

A computed tomography (CT) scan (GE Brightspeed, Boston, MA, USA) was performed on all specimens (120 kV, 20 mA, 0.62-mm resolution) to investigate the bone quality and produce measurements to plan optimal implant size. Nondestructive testing was performed for all the conditions in flexion/extension, lateral bending, and axial rotation.

2. **Instrumentation**

Lateral interbody cages were implanted with the specimen in the lateral decubitus position utilizing the LLIF surgical technique and instrumentation specific to this technique (eXtreme Lateral Interbody Fusion, Nuvasive, San Diego, CA, USA). All interbody cages were 26 mm in width (anterioposterior dimension) and polyetheretherketone material (CoRoent, Nuvasive, San Diego, CA, USA). Each implant's height (superiorinferior) and length (medial-lateral) were determined by CT scan and adjusted when necessary.

Pedicle screws (Armada, Nuvasive, San Diego, CA, USA) were placed with the specimen in the prone position. Screws were implanted bilaterally at every level from L1–5 utilizing standard freehand technique with anatomic landmarks. Screw size was determined by CT scan and adjusted if necessary. Pilot holes were tapped and probed, in addition to visual inspection of the specimens, to detect any breach. Rod size was 5.5-mm titanium and placed bilaterally for the conditions that required posterior instrumentation. The specimens were tested with screws in place but without rods for the intact and stand-alone conditions.

3. **Biomechanical Testing**

Specimens were attached to a universal testing machine (MTS 30/G) using specially designed holding jigs. Flexion, extension, and lateral bending were attained by applying a 200 N load at a
rate of 2 mm/sec to the loading arm connecting the cup containing the thoracic end of the spine while the cup with the sacral end was fixed to the base of the loading frame (Fig. 1A). Axial rotation of ± 8° of the specimen was achieved by coupling the thoracic end to a servo motor rotating at 2°/sec with the sacral end fixed (Fig. 1B). A 50N preload (follower load) was applied from L1 to L5. During all testing, 3-dimensional specimen motion was recorded using an optical motion-tracking device (Optotrak, Northern Digital Inc., Waterloo, ON, Canada). The apparatus was designed to apply compressive follower preload representing the physiologic preload acting in the lumbar spine and maintaining the spine alignment. This was applied using bilateral cables passing freely through guides anchored to each vertebra. Additional load for flexion and extension was applied with a compressive force that varied between 200–300 N with a lever arm of 1.5 cm and allowed for a combined moment of 4.5–6 Nm. Most of the reported experiments using the follower method reported a pure moment load between 4–8 Nm.

4. Order of Testing

Specimens were tested in 4 conditions: (1) intact, (2) bilateral pedicle screws and rods L1–5 (posterior-only). Following testing for posterior-only, lateral interbody cages were implanted as described above, and the experiment continued for (3) 26-mm lateral interbody cages L1–5 without rods (stand-alone LLIF), (4) 26-mm lateral interbody cages with bilateral pedicle screws and rods L1–5 (LLIF+posterior).

5. Statistical Analysis

Descriptive statistics for continuous variables are reported as mean ± standard deviation. Change in ROM after instrumentation was reported as percentage decrease from the intact specimen. Paired t-test was used to compare ROM between instrumentation conditions, which mitigates the confounding effect of differences among specimens, such as in bone quality. Statistical analyses were performed using Microsoft Excel Version 2013. Significance was set as p < 0.05.

RESULTS

Bone quality was determined by CT scan utilizing a previously described technique. The mean Hounsfield unit (HU) was 143 ± 29.4 (range, 84–169.4). Only one specimen was below the suggested threshold for osteoporosis of less than 110 HU.

Lateral interbody cages were 26 mm in width and ranged from 8 to 14 mm. The most common heights were 10 mm (n = 13). Length ranged from 45 to 60 mm. The most common length was 55 mm (n = 14). Pedicle screw diameters ranged from 6.5 mm to 8.5 mm in diameter and 40 to 60 mm in length.

Axial rotation was measured in all 8 specimens. In addition, flexion/extension and lateral bending are presented for 7 speci-
mens because of a change in methodology that excluded one specimen.

1. Stand-Alone LLIF vs. Intact

In the intact specimen, each disc space's mean flexion-extension ROM was $4.95^\circ \pm 1.18^\circ$. With stand-alone LLIF, flexion-extension decreased by 55% to $2.23^\circ \pm 1.07^\circ$ ($p < 0.001$). Mean lateral bending was $3.65^\circ \pm 1.62^\circ$ in the intact condition. With stand-alone LLIF, lateral bending decreased by 18% to $3.01^\circ \pm 1.96^\circ$ ($p = 0.2$). While a decrease in all 3 planes of motion was observed, only flexion-extension was statistically significant.

2. Stand-Alone LLIF vs. Posterior-Only

Comparing stand-alone LLIF with bilateral pedicle screws and rods, posterior-only had 47% less ROM in flexion-extension, 21% less ROM in lateral bending, and 20% less ROM in axial rotation (Table 1). The differences were statistically significant for flexion-extension and lateral bending ($p \leq 0.03$). However, the difference did not reach statistical significance for axial rotation ($p = 0.1$).

3. Posterior-Only vs. LLIF+Posterior

When comparing bilateral pedicle screws and rods with or without LLIF, the LLIF+posterior group had 27% less ROM in flexion-extension and 45% less ROM in lateral bending, both differences being statistically significant ($p \leq 0.02$) (Table 2). However, axial rotation was similar between the 2 groups, with a mean reduction of 3% ($p = 0.4$).

The addition of bilateral posterior instrumentation to the stand-alone condition resulted in statistically significant decreases in all 3 planes of motion (Table 3): 61% decrease in flexion-extension...
dissection (p < 0.001), 57% decrease in lateral bending (p < 0.001), 22% decrease in axial rotation (p = 0.002).

**DISCUSSION**

This study sought to characterize the biomechanical stability of multilevel stand-alone LLIF utilizing extra wide cages compared to posterior-only bilateral pedicle and rod screw fixation. Our results indicate that, although the 4-level stand-alone condition reduced ROM in all tested planes, this reduction was statistically significant for only flexion-extension. Our study’s assessment of stability is limited to angular ROM and does not include other possible measures such as endplate stress, translation, or cage motion. The stand-alone construct did not provide stability, defined here as a reduction in ROM, that was equivalent to bilateral pedicle screws and rods. Bilateral pedicle screw fixation provided greater stability, which was statistically significant in flexion-extension and lateral bending. The addition of pedicle screw and rod instrumentation to LLIF provides substantially higher stability than the stand-alone condition, even with the use of 26-mm cages.

The degree of mechanical stability required for spine fusion is unknown. In a cadaveric study, Harris et al. reported that TLIF with bilateral pedicle screws, a procedure currently in broad practice, showed flexibility not significantly different from intact specimens. It is generally accepted that greater stability is associated with higher fusion rates, with stability influenced by the bone quality, implant choice, and surgical approach. We used pedicle screws and rods as the comparison group because this is an accepted technique with high reported rates of fusion. Open surgery for placement of posterior instrumentation requires extensive intraoperative soft tissue trauma and dissection, leading to an interest in less invasive alternatives to create stability and fusion. LLIF is an interbody fusion technique that utilizes a lateral retroperitoneal approach to access the disc space via a transpsoas or anterior to psoas trajectory. This preserves the anterior and posterior longitudinal ligaments and posterior facet joints. As a minimally invasive technique, LLIF has demonstrated reduced blood loss, shorter operative times, and shorter hospital lengths of stay.

Multilevel LLIF has been reported to have favorable outcomes compared to posterior-only surgery for adult spinal deformity. Strom et al. reviewed 92 adult deformity operations with 5 or more levels, comparing the deformity correction and morbidity of open posterior-only surgery versus combined LLIF and open posterior surgery. The LLIF group had lower total blood loss, fewer intensive care unit days, similar hospital length of stay, and less need for inpatient rehabilitation services, despite undergoing 2 procedures. The LLIF cohort also reported greater improvement in visual analogue scale (VAS) and Oswestry Disability Index (ODI) scores. Radiographically, the LLIF group had greater Cobb angle correction and lumbar lordosis restoration than the open posterior-only group. Matsukura et al. performed a propensity-matched comparison between 21 pairs of patients undergoing LLIF or posterior lumbar interbody fusion (PLIF)/TLIF. Both groups received subsequent posterior instrumentation. While both techniques resulted in similar radiographic improvements postoperatively, LLIF resulted in lower intraoperative blood loss than PLIF/TLIF. Bae et al. compared outcomes of 221 adult deformity patients who underwent a posterior spinal fixation (PSF) only approach LLIF+PSF, or ALIF+PSF. At a mean follow-up time of 34.5 months, patients in the

**Table 3. Comparing range of motion after stand-alone lateral lumbar interbody fusion (LLIF) versus LLIF with posterior fixation**

<table>
<thead>
<tr>
<th>Level</th>
<th>Flexion-extension (°)</th>
<th>Lateral bending (°)</th>
<th>Axial rotation (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stand-alone LLIF</td>
<td>LLIF+ posterior fixation</td>
<td>p-value¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1–2</td>
<td>1.9 ± 0.69</td>
<td>0.8 ± 0.39</td>
<td>0.002*</td>
</tr>
<tr>
<td>L2–3</td>
<td>2.45 ± 1.16</td>
<td>0.42 ± 0.25</td>
<td>0.001*</td>
</tr>
<tr>
<td>L3–4</td>
<td>2.33 ± 1.27</td>
<td>0.71 ± 0.66</td>
<td>0.001*</td>
</tr>
<tr>
<td>L4–5</td>
<td>2.25 ± 1.15</td>
<td>1.52 ± 1.18</td>
<td>0.137</td>
</tr>
<tr>
<td>Combined value (N = 28)</td>
<td>2.23 ± 1.07</td>
<td>0.86 ± 0.62</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>% Decrease from stand-alone LLIF</td>
<td>61%</td>
<td>57%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. *p < 0.05. ¹Paired t-test.
LLIF+PSF group had similar radiographic parameters as those in the PSF only or ALIF+PSF groups, with a lower incidence of proximal junctional kyphosis, lower ODI scores, and the most improvement in pain scores. The benefits of the less invasive LLIF approach could potentially be amplified if stand-alone LLIF for fusion of multiple segments is also feasible.

There are few reports describing the clinical results of stand-alone LLIF, and none that include 26-mm wide cages to our knowledge. Previously suggested indications for stand-alone LLIF include degenerative disc disease, adjacent segment disease, degenerative scoliosis, spinal stenosis, and spondylolisthesis. Aichmair et al. followed 52 patients after single-level LLIF for adjacent segment disease. There was a difference between fusion rates between stand-alone LLIF (54%) and circumferential fusion (88%) that was not statistically significant, and cage width was not specified. Malham et al. described an algorithm to identify patients suitable for stand-alone LLIF. Prespectively applied to 21 patients who underwent stand-alone LLIF, all cages being 18 or 22 mm wide, they observed no differences in clinical outcomes from patients with supplemental posterior fixation, as well as a 95% fusion rate in the stand-alone cohort. Castro et al. reported the clinical outcomes of 35 adult degenerative scoliosis patients receiving an average of 3.1 levels of stand-alone LLIF, demonstrating a 57% improvement in VAS scores for leg pain and 74% symptom resolution, and 56% improvement in ODI scores. Ten patients experienced cage subsidence. The cage width was 18 mm, and the authors suggested that larger cages may reduce the subsidence rate. In further exploring the impact of cage width, Lang et al. reviewed patients undergoing LLIF with and without supplementation fixation, finding that radiographic subsistence rates decreased nearly linearly when implanting 18-mm to 26-mm wide cages.

The biomechanical characteristics of LLIF lends credence to the idea that a stand-alone approach may be sufficient. Results of in vitro studies appear to support this. Cappuccino et al. demonstrated that stand-alone LLIF of L4–5 using an 18-mm wide cage reduced the flexion-extension ROM and lateral bending ROM to 31.6% and 32.5% of the intact spine ROM. They concluded that stand-alone LLIF improved stability more than stand-alone ALIF and TLIF. Fogel et al. found that, across 10 cadaveric specimens, insertion of a single L3–4 LLIF 18-mm wide cage reduced ROM to 32% of the flexion-extension, 33% of the lateral bending, and 69% of the axial rotation of the intact state. Kretzer et al. compared the reduction of ROM at L2–3 and L4–5 in 4 conditions—stand-alone LLIF, bilateral pedicle screw fixation, and 2 facet screw systems—and concluded that all instrumentation decreased ROM compared to the intact spine, with no differences detected among the fixation techniques. In a model of adjacent segment disease, Chioffe et al. found in 6 cadaveric specimens that L3–4 stand-alone LLIF decreased adjacent segment motion by 56%. Finally, in a study that highlights the role of cage width, Pimenta et al. found that a stand-alone 26-mm wide cage provided similar stability to bilateral pedicle screws and rods and greater stability than TLIF with bilateral pedicle screws, as well as 18-mm wide LLIF with unilateral pedicle screws. These results formed the rationale for the current investigation of stand-alone LLIF of multiple levels.

Our results found that stand-alone LLIF from L1 to L5 decreased the mean motion segment flexion-extension ROM to 45% of the intact spine, with smaller decreases observed in lateral bending and axial rotation, to 83% and 85%, respectively. Compared to stand-alone LLIF, posterior bilateral pedicle screws and rods showed more considerable reductions in ROM in all tested planes of motion, statistically significant for flexion-extension and lateral rotation. These results contrast with some of the previous studies described above and highlight the pitfalls of extrapolating the results of single-level studies to the multi-level fusion environment. Despite the biomechanical advantages associated with the lateral approach and 26-mm wide cages, stand-alone LLIF for 4-level fusion is not equivalent to pedicle screws and rods. It should be noted that the stand-alone LLIF included pedicle screws without rods, rather than lateral interbody cages only, to avoid the confounding effect of removal and replacement of screws. Screws were carefully placed extra-articular to the facet joints, there was no visualized contact of screws with adjacent segments or screws during testing, and the tested ranges of motion were low. Nevertheless, the presence of screws is a potential confounder and therefore a limitation of the study.

In a study similar to this investigation, Lai et al. examined intersegmental and overall ROM after L2–5 stand-alone LLIF with 17-mm wide cages. They found that, although overall ROM was decreased by 55% in flexion-extension, 54% in lateral bending, and 31% in axial rotation, addition of either unilateral or bilateral pedicle screws further reduced flexion-extension and axial rotation motion. The reported reductions in ROM in the above studies are more significant than seen in our results, which may be attributable to the long fusion (4-level) model, differences in experimental technique, and lower baseline ROM of our intact specimens.

Our results are also consistent with the conclusions of a finite element analysis that multiple level stand-alone LLIF with a 22-mm wide cages did not provide sufficient stability. The consis-
tency of in vitro and finite element results strengthens their validity. In addition to ROM, the finite element analysis allowed measurement of endplate stress, in which the stand-alone condition exceeded supplemental screws and rods in all planes of motion, exceeding 170% in lateral bending. Endplate stress is an important factor in the risk of cage subsidence, and that our analysis of stability was limited to ROM represents a weakness of this study. In addition, there is emerging literature supporting the necessity of posterior instrumentation to prevent subsidence. A recently completed systematic review found that LLIF without posterior fixation had distinguishably higher rates of subsidence than LLIF with posterior fixation. Although bone mineral density has been shown to correlate with the risk of subsidence, Jones et al. found that the use of stand-alone technique was a stronger risk factor for subsidence after LLIF than endplate volumetric bone mineral density.

CONCLUSION

In conclusion, because stand-alone multilevel LLIF provided less stability than bilateral pedicle screw and rod instrumentation, surgeons may not consider it an acceptable alternative, save for exceptional cases where the probability of fusion is already high. However, the addition of bilateral pedicle screws and rods to multilevel LLIF provided significantly higher stability than posterior-only instrumentation. Therefore, in the presence of risk factors for nonunion or cage subsidence, 26-mm cages with pedicle screw and rod fixation may be a good strategy for surgeons seeking to maximize biomechanical stability.

NOTES

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REFERENCES


Early Experience With Uniplanar Versus Biplanar Expandable Interbody Fusion Devices in Single-Level Minimally Invasive Transforaminal Lumbar Interbody Fusion

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Objective: To compare the early radiographic and clinical outcomes of expandable uniplanar versus biplanar interbody cages used for single-level minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF).

Methods: A retrospective review of 1-level MIS-TLIFs performed with uniplanar and biplanar polyetheretherketone cages was performed. Radiographic measurements were performed on radiographs taken preoperatively, at 6-week follow-up, and 1-year follow-up. Oswestry Disability Index (ODI) and visual analogue scale (VAS) for back and leg at 3-month and 1-year follow-up.

Results: A total of 93 patients (41 uniplanar, 52 biplanar) were included. Both cage types provided significant postoperative improvements in anterior disc height, posterior disc height, and segmental lordosis at 1 year. No significant differences in cage subsidence rates were found between uniplanar (21.9%) and biplanar devices (32.7%) at 6 weeks (odds ratio, 2.015; 95% confidence interval, 0.651–6.235; p = 0.249) with no additional instances of subsidence at 1 year. No significant differences in the magnitude of improvements based on ODI, VAS back, or VAS leg at 3-month or 1-year follow-up between groups and the proportion of patients achieving the minimal clinically important difference in ODI, VAS back, or VAS leg at 1 year were not statistically significantly different (p > 0.05). Finally, there were no significant differences in complication rates (p = 0.283), 90-day readmission rates (p = 1.00), revision surgical procedures (p = 0.423), or fusion rates at 1 year (p = 0.457) between groups.

Conclusion: Biplanar and uniplanar expandable cages offer a safe and effective means of improving anterior disc height, posterior disc height, segmental lordosis, and patient-reported outcome measures at 1 year postoperatively. No significant differences in radiographic outcomes, subsidence rates, mean subsidence distance, 1-year patient-reported outcomes, and postoperative complications were noted between groups.

Keywords: Spinal fusion, Lumbar vertebra, Patient-reported outcomes, Minimally invasive surgery, Spine

INTRODUCTION

Minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) has become a mainstay procedure in the treatment of degenerative spinal conditions. Compared to other interbody techniques, MIS-TLIF allows for decreased soft tissue injury, reduced nerve root manipulation, and lower risk of neurologic complications.1-3 Additionally, minimally invasive approaches
have been associated with less postoperative pain, shorter hospitalizations, and earlier mobilization.\textsuperscript{4,5} Specialized interbody devices are utilized during MIS-TLIF to restore lumbar lordosis (LL) and facilitate bony fusion. However, the small operative window offered by MIS-TLIF limits the size of spacers that may be inserted, restricting the extent of postoperative lordosis correction, and potentially resulting in suboptimal patient outcomes.\textsuperscript{6,7} A recent advancement in the field of TLIF interbody cages has been the introduction of devices that are expandable following deployment into the intervertebral space.

Expandable cages have been designed with a variety of favorable characteristics. Earlier generation devices were predominantly expandable in a single plane (caudal-cranial), allowing greater restoration of disc height and segmental lordosis (SL) when compared to static cages.\textsuperscript{8} However, uniplanar devices are not risk free. The theoretical increase in distraction forces during cage expansion may increase the risk of endplate violation, resulting in iatrogenic endplate damage and cage subsidence.\textsuperscript{9} Though controversial, cage subsidence has been associated with suboptimal clinical outcomes, with sinking of the interbody device resulting in narrowing of intervertebral disc height, diminishing anterior support to the spine, and hindering successful fusion.\textsuperscript{10} In comparison, newer biplanar expandable cages expand in both the medial-lateral and cranial-caudal directions, thus increasing their surface area on the end plate plates prior to intervertebral disc space distraction, which may mitigate the risk of cage subsidence. Despite this advantage, biplanar devices may also contribute to endplate damage through cortical “cutting” during lateral distraction.

Though studies have compared uniplanar and biplanar expandable cages in isolation, no studies exist comparing the performance of uniplanar and biplanar expandable spacers. Thus, the primary goal of this study is to evaluate the radiographic and patient-reported outcome measures (PROMs) of uniplanar versus biplanar expandable interbody devices in patients who underwent single-level MIS-TLIF. The secondary goal was to evaluate the incidence of subsidence and complication rates between the 2 cages.

**MATERIALS AND METHODS**

1. **Study Design and Demographics**

   After obtaining Institutional Review Board approval, a retrospective review of patients undergoing single-level MIS-TLIF with a bullet-shaped expandable polyetheretherketone (PEEK) interbody spacer at a single academic institution was performed. Demographic data including age, body mass index (BMI), sex, history of osteoporosis, and device details were obtained from electronic medical records for patients who underwent elective 1-level MIS-TLIF by 3 surgeons from 2014 to 2020. All patients attempted and failed a conservative treatment regimen including nonsteroidal anti-inflammatory drugs, corticosteroid injections, and physical therapy for a minimum of 3 months prior to surgery. Patients with less than 3 months of radiographic follow-up, 1 year of clinical follow-up, and those treated for trau-
ma, tumor, or infection were excluded. Selection of cage type and size was based on surgeon preference.

Images of cages used in this study may be seen in Fig. 1, with pre- and postoperative lateral lumbar films of each device presented in Fig. 2.

Uniplanar cages included the Elevate cage (Medtronic, Minneapolis, MN, USA) and the Caliber cage (Globus, Audobon, PA, USA), while the biplanar cage used in this study was the Flarehawk cage (Accelus, Palm Beach Gardens, FL, USA). The Medtronic Elevate and Globus Caliber are uniplanar expandable PEEK, tantalum, and titanium alloy interbody devices consisting of various lengths and starting heights. Medtronic Elevate is offered in 2 implant options. The standard implant offers posterior expansion and up to 8° of lordosis when fully expanded, while the ultralordotic implant offers fixed posterior height with various degrees of lordosis when fully expanded. The hollow geometry of the implants allows the interbody to be packed with autogenous and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone.

The Accelus FlareHawk is a biplanar expandable PEEK, tantalum, and titanium alloy interbody device consisting of a Shim, Shell, and Core component. When the device is deployed, these components lock together to create one complete FlareHawk9 device. The dimensions of the final deployed device are determined by the dimensions of the selected Shim and Shell. The FlareHawk is offered in various lengths and starting heights, then expands in width, height, and lordosis based on Shim selection. Additional information regarding the selected cages may be found in Supplementary Table 1.

2. Surgical Technique

All surgeries were performed by fellowship trained spine surgeons (MFK, KER, DGA) who were familiar and proficient with the procedure. At our institution, MIS-TLIF is performed using a posterior paramedian incision of approximately 2 cm. Unilateral exposure of the disc space through a standard MIS approach was performed, which included sequential tubular dilation. Hemilaminotomies at the index surgical level(s) were then performed, followed by medial facetectomies and foraminotomies. Following bony decompression, the remaining ligamentum flavum was identified and resected to reveal the underlying thecal sac. The intervertebral space was then prepared with removal of the intervertebral disc and cartilaginous portion of the endplate without violating the cortical bone, which should minimize the risk of cage subsidence. The disc space was then dilated, and a trial expandable implant deployed to determine optimal implant size. Following selection of the appropriate trial, the disc space was filled with local autograft and allograft chips. The implant was then packed with local autograft and inserted into the disc space via a transforaminal approach. Implants were then back filled with additional graft material. Bilateral percutaneous pedicle screws are then inserted over K-wire. Finally, intraoperative fluoroscopy was used to confirm appropriate screw placement.

3. Radiographic and Clinical Outcome Measures

Standing lateral lumbar spine radiographs were evaluated at 150% magnification to assess anterior and posterior disc height, fusion status at 1 year, SL, LL, pelvic tilt (PT), sacral slope (SS), pelvic incidence (PI), and PI-LL mismatch (PI-LL) preoperatively, 6 weeks postoperatively, and 1 year postoperatively. Preoperative values were subtracted from postoperative values to calculate a Δ value for each measurement. Anterior and posterior disc height were measured from the inferior endplate of the superior vertebral body to the superior endplate of the inferior vertebral body (Fig. 3). Successful fusion at 1 year was defined as evidence of bridging bone and no screw “haloing” present on anteroposterior and lateral plain radiographs.11,12 Radiographic measurements were performed using IDS 7 imaging software for Windows (Sectra, Linköping, Sweden).

Fig. 3. Preoperative lateral radiograph demonstrating anterior disc height (a), posterior disc height (b), segmental lordosis (c), and lumbar lordosis measurements (d).
SL was measured as the lateral Cobb angle from the inferior endplate of the superior vertebral body relative to the superior endplate of the inferior vertebral body. LL was measured as the lateral Cobb angle from the superior endplate of the L1 vertebral body to the inferior endplate of the L5 vertebral body. PT was measured as the angle between a reference vertical line and the line joining the bicoxofemoral axis with the midpoint of the S1 endplate. SS was measured as the angle between the superior endplate of S1 and a horizontal reference line. PI was measured as the angle between the line orthogonal to the midpoint of superior sacral endplate and the line connecting the midpoint of the sacral endplate with the center of bicoxofemoral axis. Postoperative radiographs were assessed for evidence of device subsidence, defined as vertical breach of the margin of the interbody device into the superior or inferior endplate of the vertebral body > 2 mm as described by previous studies (Fig. 4).13,14

PROMs were obtained from the OBERD software system (Columbia, MO, USA) using Oswestry Disability Index (ODI), visual analogue scale (VAS) back, and VAS leg pain scores. A Δ value was calculated for each PROM, as described above. The minimally clinically important difference (MCID) for each PROM was determined using previously established cutoffs: ODI 8.2 points, VAS back 2.2 points, and VAS leg 5.0 points.15,16 Complications assessed included rates of 90-day readmissions, revision surgery, development of adjacent segment disease, dural tear, and radiculitis. Radiculitis was defined as the recurrence of radicular symptoms after postoperative resolution, with no evidence of neurologic involvement on follow-up magnetic resonance or computed tomography (CT) imaging.

4. Statistical Methods
Statistical analysis was performed using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA). Comparison of means for continuous variables between groups was performed using independent Student t-test. Mann-Whitney U-test was used to compare means for nonparametric variables and distributions that did not pass the Shapiro-Wilk test for normality. Preoperative and postoperative variables for the same patients were compared using paired Student t-test; Wilcoxon signed-rank test was used for nonparametric variables. Multivariate linear regression analysis was performed to determine the effect of cage type on change in PROMs perioperatively, controlling for age, biological sex, BMI, and perioperative diagnosis. Statistical significance was set at p < 0.05 for all cases.

RESULTS

1. Patient Demographics and Surgical Characteristics
This study included 93 patients, of which, 41 had uniplanar and 52 had biplanar expandable PEEK cages (Table 1). No significant differences in patient age (uniplanar: 66.0 ± 13.1 years vs. biplanar: 70.3 ± 9.37 years, p = 0.115), BMI (uniplanar: 31.5 ± 6.21 kg/m² vs. biplanar: 30.9 ± 6.48 kg/m², p = 0.623), sex (uniplanar: 53.7% male vs. biplanar: 57.7% male, p = 0.697) and average follow-up time (uniplanar: 13.4 ± 3.95 months vs. biplanar: 12.2 ± 5.09 months, p = 0.312) was noted between groups. No significant differences were noted in proportion of patients diagnosed with osteoporosis preoperatively (uniplanar: 25.8% vs. biplanar: 27.9%, p = 0.841). One instance of postoperative infection occurred in the uniplanar group, which was treated with an irrigation and debridement. There was no difference in the total complication rate (uniplanar 14.6% vs. biplanar: 7.7%, p = 0.283), rate of radiculitis (uniplanar: 2.4% vs. biplanar: 1.9%, p = 0.865), or rate of revision surgery (p = 0.423) (Table 1). No patients were readmitted within the 90-day postoperative period (p = 1.000) and there were no instances of incidental durotomies.

The most common indication for MIS-TLIF was a symptomatic spondylolisthesis (uniplanar: 43.9% vs. biplanar: 51.9%).
There were no significant differences in preoperative diagnosis between groups including similar surgical indications of lumbar stenosis, disc herniation, and deformity (p = 0.392). Patients in both groups underwent surgery most frequently at the L4–5 level (uniplanar: 56.1% vs. biplanar: 51.9%, p = 0.609).

2. Radiographic Outcome Measures

No significant differences were noted in the preoperative anterior (p = 0.831) or posterior (p = 0.456) disc height between groups. Both groups had significant increases in anterior and posterior disc height at 6 weeks and 1 year. No significant differences in postoperative anterior disc height, posterior disc height, and Δ anterior and posterior disc height were noted at 6-week and 1-year (p > 0.20 for all) follow-up between groups (Table 2). No significant differences in percentage of patients with endplate subsidence were noted at 6 weeks (uniplanar: 9 of 41 [21.9%] vs. biplanar: 17 of 52 [32.7%], p = 0.249) with no additional instances of subsidence at 1 year. There were no significant differences in mean subsidence distance between cage types at 6 weeks (uniplanar: 3.96 ± 1.49 mm vs. biplanar: 4.62 ± 2.32 mm) and 1 year (uniplanar: 4.04 ± 1.35 mm vs. biplanar: 4.83 ± 2.08 mm). No significant differences in fusion rate at 1 year were noted between groups (uniplanar: 35 of 41 [85.4%] vs. biplanar: 47 of 52 [90.4%], p = 0.457).

At 1-year follow-up, no significant differences between and within groups were noted in SS, PT, LL, SL, and PI-LL mismatch (p > 0.250 for all) (Table 3). Significant improvements in SL compared to baseline were noted within each group at 1-year follow-up (p < 0.002 for both cages). Furthermore, no significant differences in anterior disc height, posterior disc height, cage subsidence (Supplementary Table 2) or sagittal parameters (Supplementary Table 3) were observed at 3 months and 1 year in patients who underwent surgery at the L4–5 level with a preoperative diagnosis of spinal stenosis or spondylolisthesis.

3. Functional Outcome Measures

Significant improvements in all PROMs within groups were noted at 3 months and 1 year (p < 0.001 for all) (Table 4). No significant differences in ODI (3-month postoperative: p = 0.738, 3-month Δ: p = 0.068; 1-year postoperative: p = 0.574, 1-year Δ: p = 0.454), VAS back (3-month postoperative: p = 0.982, 3-month Δ: p = 0.126; 1-year postoperative: p = 0.574, 1-year Δ: p = 0.454), and VAS leg (3-month postoperative: p = 0.825, 3-month Δ: p = 0.591; 1-year postoperative: p = 0.356, 1-year Δ: p = 0.142) were noted between groups. No significant differences were noted in the proportion of patients who reached the MCID at 1 year for ODI, VAS back, and VAS leg between uniplanar and biplanar cages (Table 5). Multivariate linear regression demonstrated no significant correlation between cage type and changes in any PROMS at 3 months and 1 year when controlling for age, sex, BMI, and perioperative diagnosis. When evaluating patients who underwent surgery at the L4–5 level with a preoperative diagnosis of spinal stenosis or spondylolisthesis, no significant differences in ODI, VAS back, and VAS leg were noted between groups at both follow-up time points (Supple-

Table 1. Patient demographics and operative data

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Uniplanar (n = 41)</th>
<th>Biplanar (n = 52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)$^a$</td>
<td>66.0 ± 13.1</td>
<td>70.3 ± 9.37</td>
<td>0.115</td>
</tr>
<tr>
<td>Sex$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (53.7)</td>
<td>30 (57.7)</td>
<td>0.697</td>
</tr>
<tr>
<td>Female</td>
<td>19 (46.3)</td>
<td>22 (42.3)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^3$)$^c$</td>
<td>31.5 ± 6.21</td>
<td>30.9 ± 6.48</td>
<td>0.616</td>
</tr>
<tr>
<td>Latest follow-up (mo)$^d$</td>
<td>13.4 ± 3.95</td>
<td>12.2 ± 5.09</td>
<td>0.312</td>
</tr>
<tr>
<td>Smoking status$^e$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>17 (54.8)</td>
<td>27 (62.8)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>8 (25.8)</td>
<td>12 (27.9)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>6 (19.4)</td>
<td>4 (9.30)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis$^f$</td>
<td>8 (25.8)</td>
<td>12 (27.9)</td>
<td>0.841</td>
</tr>
<tr>
<td>Preoperative diagnosis$^g$</td>
<td></td>
<td></td>
<td>0.392</td>
</tr>
<tr>
<td>Spondylolisthesis</td>
<td>18 (43.9)</td>
<td>27 (51.9)</td>
<td></td>
</tr>
<tr>
<td>Stenosis</td>
<td>14 (34.2)</td>
<td>20 (38.5)</td>
<td></td>
</tr>
<tr>
<td>Disc herniation</td>
<td>6 (14.6)</td>
<td>4 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Deformity</td>
<td>3 (7.3)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Total operative levels$^h$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1–2</td>
<td>0 (0)</td>
<td>2 (3.8)</td>
<td>0.609</td>
</tr>
<tr>
<td>L2–3</td>
<td>3 (7.3)</td>
<td>9 (17.3)</td>
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</tr>
<tr>
<td>L3–4</td>
<td>8 (19.5)</td>
<td>8 (15.4)</td>
<td></td>
</tr>
<tr>
<td>L4–5</td>
<td>23 (56.1)</td>
<td>27 (51.9)</td>
<td></td>
</tr>
<tr>
<td>Postoperative complications$^i$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total complications</td>
<td>6 (14.6)</td>
<td>4 (7.7)</td>
<td>0.283</td>
</tr>
<tr>
<td>Revision surgery</td>
<td>2 (4.8)</td>
<td>1 (1.9)</td>
<td>0.423</td>
</tr>
<tr>
<td>Adjacent segment disease</td>
<td>3 (7.3)</td>
<td>2 (3.9)</td>
<td>0.461</td>
</tr>
<tr>
<td>Radiculitis</td>
<td>1 (2.4)</td>
<td>1 (1.9)</td>
<td>0.865</td>
</tr>
<tr>
<td>90-Day readmissions</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

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

BMI, body mass index.

$^a$Independent-samples t-test or Mann-Whitney U-test for age, BMI, and latest follow-up.

$^b$Pearson chi-square test for sex, preoperative diagnosis, transfemoral lumbar interbody fusion level involved, and postoperative complications.

https://doi.org/10.14245/ns.2244870.435
Table 2. Comparison of radiographic parameters including fusion status at 1-year, pre-, and postoperative anterior disc height, posterior disc height, and subsidence parameters at 6-week and 1-year follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uniplanar (n = 41)</th>
<th>Biplanar (n = 52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior disc height (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>8.93 ± 2.94</td>
<td>8.97 ± 3.76</td>
<td>0.831</td>
</tr>
<tr>
<td>6-Week postoperative</td>
<td>13.9 ± 2.41</td>
<td>13.3 ± 2.67</td>
<td>0.259</td>
</tr>
<tr>
<td>6-Week Δ value</td>
<td>5.04 ± 3.16</td>
<td>4.29 ± 3.01</td>
<td>0.303</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>1-Year postoperative</td>
<td>13.1 ± 2.66</td>
<td>12.8 ± 2.92</td>
<td>0.841</td>
</tr>
<tr>
<td>1-Year Δ value</td>
<td>4.18 ± 3.78</td>
<td>3.88 ± 3.32</td>
<td>0.897</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>Posterior disc height (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>4.59 ± 4.07</td>
<td>5.06 ± 4.03</td>
<td>0.456</td>
</tr>
<tr>
<td>6-Week postoperative</td>
<td>9.05 ± 1.71</td>
<td>8.78 ± 2.39</td>
<td>0.595</td>
</tr>
<tr>
<td>6-Week Δ value</td>
<td>3.42 ± 2.30</td>
<td>2.64 ± 2.39</td>
<td>0.218</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>1-Year postoperative</td>
<td>7.96 ± 1.38</td>
<td>8.35 ± 2.38</td>
<td>0.437</td>
</tr>
<tr>
<td>1-Year Δ value</td>
<td>2.38 ± 2.25</td>
<td>2.21 ± 2.65</td>
<td>0.826</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>Subsidence measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Subsidence at 6-week follow-up</td>
<td>9 (21.9)</td>
<td>17 (32.7)</td>
<td>0.249</td>
</tr>
<tr>
<td>Subsidence at 6 weeks (mm)</td>
<td>3.96 ± 1.49</td>
<td>4.62 ± 2.32</td>
<td>0.503</td>
</tr>
<tr>
<td>% Subsidence at 1-year follow-up</td>
<td>9/41 (21.9)</td>
<td>17/52 (32.7)</td>
<td>0.249</td>
</tr>
<tr>
<td>Subsidence at 1 year (mm)</td>
<td>4.04 ± 1.35</td>
<td>4.83 ± 2.08</td>
<td>0.488</td>
</tr>
<tr>
<td>Fusion status at 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fused</td>
<td>35 (85.4)</td>
<td>47 (90.4)</td>
<td>0.457</td>
</tr>
</tbody>
</table>

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

*p < 0.05, statistically significant differences. Independent-samples t-test or Mann-Whitney U-test comparing uniplanar and biplanar cages. Paired-sample test or Wilcoxon rank-sum test comparing preoperative and postoperative values. Pearson chi-square test for subsidence rate and fusion status comparing uniplanar and biplanar cages.

DISCUSSION

Progressive age-related spondylosis can result in a myriad of spine disease including spondylolisthesis, adult degenerative scoliosis, disc herniation, and spinal stenosis. These conditions can subsequently lead to neurogenic claudication, axial back pain, and/or radiculopathy that may prohibit participation in even the simplest of activities. MIS-TLIF offers a surgical solution to degenerative spinal pathologies through adequate neural decompression and correction of spinal alignment with minimal adjacent soft tissue disruption, thus generating significant improvements in short and long-term pain, physical function, and disability. Expandable interbody spacers have been introduced in response to the size constraints imposed by the narrow operative corridor utilized in MIS-TLIF. Uniplanar cages comprised the earliest iterations of expandable devices and have demonstrated favorable results when compared to static implants in several prior studies. More recently, biplanar expandable cages have been developed that enlarge horizontally, effectively increasing the contact surface area with the vertebral endplate and decreasing point expansion pressures, thus theoretically reducing the risk of implant subsidence. Despite this potential advantage, our study found no significant differences in postoperative anterior disc height, posterior disc height, sagittal balance parameters, subsidence rates, or PROMs between
Table 3. Comparison of radiographic sagittal parameters pre-operatively and at 1-year follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uniplanar (n = 41)</th>
<th>Biplanar (n = 52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacral slope (°)</td>
<td></td>
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</tr>
<tr>
<td>Preoperative</td>
<td>35.1 ± 8.46</td>
<td>33.3 ± 9.89</td>
<td>0.270</td>
</tr>
<tr>
<td>Postoperative</td>
<td>32.9 ± 6.82</td>
<td>32.4 ± 10.2</td>
<td>0.742</td>
</tr>
<tr>
<td>Δ Value</td>
<td>2.37 ± 9.05</td>
<td>0.84 ± 5.83</td>
<td>0.882</td>
</tr>
<tr>
<td>p-value</td>
<td>0.279</td>
<td>0.349</td>
<td></td>
</tr>
<tr>
<td>Pelvic tilt (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>26.5 ± 8.25</td>
<td>27.5 ± 7.75</td>
<td>0.904</td>
</tr>
<tr>
<td>Postoperative</td>
<td>28.5 ± 7.52</td>
<td>28.4 ± 7.88</td>
<td>0.866</td>
</tr>
<tr>
<td>Δ Value</td>
<td>2.26 ± 8.47</td>
<td>0.83 ± 7.12</td>
<td>0.989</td>
</tr>
<tr>
<td>p-value</td>
<td>0.284</td>
<td>0.480</td>
<td></td>
</tr>
<tr>
<td>Lumbar lordosis (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>43.9 ± 13.6</td>
<td>45.1 ± 13.1</td>
<td>0.667</td>
</tr>
<tr>
<td>Postoperative</td>
<td>44.2 ± 10.9</td>
<td>44.7 ± 14.1</td>
<td>0.777</td>
</tr>
<tr>
<td>Δ Value</td>
<td>1.87 ± 8.65</td>
<td>-1.18 ± 7.36</td>
<td>0.098</td>
</tr>
<tr>
<td>p-value</td>
<td>0.855</td>
<td>0.743</td>
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<tr>
<td>Segmental lordosis (°)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>4.59 ± 4.07</td>
<td>5.06 ± 4.03</td>
<td>0.656</td>
</tr>
<tr>
<td>Postoperative</td>
<td>7.55 ± 3.14</td>
<td>6.99 ± 3.76</td>
<td>0.538</td>
</tr>
<tr>
<td>Δ Value</td>
<td>2.96 ± 4.04</td>
<td>1.93 ± 3.52</td>
<td>0.282</td>
</tr>
<tr>
<td>p-value</td>
<td>0.002*</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>PI-LL (°)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>17.7 ± 9.31</td>
<td>15.8 ± 11.3</td>
<td>0.667</td>
</tr>
<tr>
<td>Postoperative</td>
<td>17.2 ± 7.35</td>
<td>16.1 ± 14.1</td>
<td>0.572</td>
</tr>
<tr>
<td>Δ Value</td>
<td>-1.97 ± 11.83</td>
<td>1.17 ± 9.75</td>
<td>0.374</td>
</tr>
<tr>
<td>p-value</td>
<td>0.817</td>
<td>0.830</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. PI-LL, pelvic incidence-lumbar lordosis mismatch.

*p < 0.05, statistically significant differences. †Independent-samples t-test or Mann-Whitney U-test comparing uniplanar and biplanar cages. ‡Paired-sample test or Wilcoxon rank-sum test comparing pre-operative and postoperative values.

Consistent with previous studies, patients receiving uniplanar or biplanar cages experienced significant improvements in disc height, SL, and all PROMs at 3 months and 1 year.5-7,17-19 A retrospective study consisting of 48 MIS-TLIFs reported larger improvements in disc height, neuroforaminal height, and SL in patients receiving expandable cages when compared to static cage.4 These results parallel an observational study performed by Boktor et al.20 who noted similar overall radiographic and clinical improvements amongst his patients who underwent TLIFs with expandable cages. Tan et al.21 conducted a retrospective review of 13 consecutive patients who underwent MIS-TLIF with a biplanar PEEK cage. All patients experienced significant improvements in anterior disc height, posterior disc height, foraminal height, SL, VAS back, and VAS leg scores at the 1-year postoperative visit. Though the radiographic and clinical performance of both expandable cage types falls within the expected range of improvement as denoted by the literature, the current study failed to identify any significant differences in radiographic or clinical outcomes between uniplanar or biplanar expandable cages.

With regards to secondary outcomes, no significant differences were noted in subsidence rates or mean subsidence distance at 6-week follow-up. Previous studies remain inconclusive regarding the likelihood of subsidence for expandable spacers. A biomechanical study comparing expandable and static interbody cages in 10 human cadavers revealed a trend towards higher subsidence in expandable cages despite greater contact surface area.19 These results were mirrored by a larger retrospective comparative study using a consecutive series of 178 patients in which cage subsidence was more frequent in expandable versus static cages (19.7% vs. 5.4%, p = 0.0017).22 However, several other studies have described no differences in subsidence rates between cage types and low subsidence rates with expandable devices. A small retrospective review by Massie et al.23 found a low subsidence rate of 6% with their initial experience of expandable cages in 39 patients undergoing 1- and 2-level MIS-TLIF. Gelfand et al.24 conducted a larger comparative study consisting of 133 fused segments and found a clinically significant subsidence rate (>4 mm) of 26.3% with no significant difference noted between groups. The present study revealed no significant differences in subsidence rates at 6 weeks between expandable cage types. Additionally, uniplanar and biplanar expandable cages provided similar maintenance of anterior and posterior disc height at 1-year. Our results suggest that the minimization of point contact stresses provided by biplanar expandable devices may not provide additional clinical utility, even in the presence of continuous axial loading moments in the postoperative period. Our data is further supported by our subsidence rates falling well within those previously established in the literature, which range from 6% to 33%.12,23 Furthermore, the prevalence of osteoporosis was similar between groups, suggesting that bone density did not significantly influence our observed subsidence rates. Therefore, our exploratory comparison of uniplanar and biplanar cages does not provide justification for the use of biplanar expandable cages solely to minimize the risk of subsid-
Table 4. Patient-reported outcomes at 3-months and 1-year follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uniplanar (n = 41)</th>
<th>Biplanar (n = 52)</th>
<th>p-value †</th>
<th>Regression analysis ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-Month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODI</td>
<td>54.7 ± 11.6</td>
<td>50.4 ± 14.5</td>
<td>0.117</td>
<td>β = -1.88 (-6.25 to 2.49)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>50.4 ± 14.5</td>
<td>54.7 ± 11.6</td>
<td>0.669</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>30.5 ± 18.9</td>
<td>31.7 ± 16.1</td>
<td>0.738</td>
<td></td>
</tr>
<tr>
<td>Δ Value</td>
<td>-25.3 ± 18.1</td>
<td>-18.7 ± 16.7</td>
<td>0.068</td>
<td></td>
</tr>
<tr>
<td>p-value ‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS back</td>
<td>7.11 ± 1.30</td>
<td>6.43 ± 1.94</td>
<td>0.052</td>
<td>β = -0.417 (-1.73 to 0.32)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.43 ± 1.94</td>
<td>7.11 ± 1.30</td>
<td>0.844</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>3.24 ± 2.41</td>
<td>3.25 ± 2.21</td>
<td>0.982</td>
<td></td>
</tr>
<tr>
<td>Δ Value</td>
<td>-3.87 ± 2.41</td>
<td>-3.09 ± 2.45</td>
<td>0.126</td>
<td></td>
</tr>
<tr>
<td>p-value ‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS leg</td>
<td>6.56 ± 1.93</td>
<td>6.22 ± 2.81</td>
<td>0.497</td>
<td>β = 0.375 (-0.22 to 0.97)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.22 ± 2.81</td>
<td>6.56 ± 1.93</td>
<td>0.915</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>2.66 ± 3.13</td>
<td>2.87 ± 2.65</td>
<td>0.825</td>
<td></td>
</tr>
<tr>
<td>Δ Value</td>
<td>-3.69 ± 2.58</td>
<td>3.35 ± 3.39</td>
<td>0.591</td>
<td></td>
</tr>
<tr>
<td>p-value ‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
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<td></td>
</tr>
<tr>
<td><strong>1-Year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODI</td>
<td>54.7 ± 11.6</td>
<td>50.4 ± 14.5</td>
<td>0.117</td>
<td>β = 3.871 (-8.133 to 7.246)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>50.4 ± 14.5</td>
<td>54.7 ± 11.6</td>
<td>0.574</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>26.5 ± 19.2</td>
<td>24.5 ± 15.9</td>
<td>0.545</td>
<td></td>
</tr>
<tr>
<td>Δ Value</td>
<td>-25.8 ± 18.3</td>
<td>-23.9 ± 17.4</td>
<td>0.454</td>
<td></td>
</tr>
<tr>
<td>p-value ‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS back</td>
<td>7.11 ± 1.30</td>
<td>6.43 ± 1.94</td>
<td>0.052</td>
<td>β = 0.559 (-0.95 to 1.27)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.43 ± 1.94</td>
<td>7.11 ± 1.30</td>
<td>0.292</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>4.21 ± 2.31</td>
<td>3.35 ± 2.67</td>
<td>0.210</td>
<td></td>
</tr>
<tr>
<td>Δ Value</td>
<td>-3.11 ± 2.29</td>
<td>-3.02 ± 2.81</td>
<td>0.833</td>
<td></td>
</tr>
<tr>
<td>p-value ‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS leg</td>
<td>6.56 ± 1.93</td>
<td>6.22 ± 2.81</td>
<td>0.497</td>
<td>β = 0.626 (-0.58 to 1.91)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.22 ± 2.81</td>
<td>6.56 ± 1.93</td>
<td>0.288</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>2.35 ± 2.84</td>
<td>2.89 ± 2.73</td>
<td>0.356</td>
<td></td>
</tr>
<tr>
<td>Δ Value</td>
<td>-4.23 ± 2.43</td>
<td>-3.34 ± 3.19</td>
<td>0.142</td>
<td></td>
</tr>
<tr>
<td>p-value ‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
ODI, Oswestry Disability Index; VAS, visual analogue scale; BMI, body mass index.
* p < 0.05, statistically significant differences. † Independent-samples t-test or Mann-Whitney U-test comparing uniplanar and biplanar cages.
‡ Multiple linear regression controlling for age, sex, BMI, and preoperative diagnosis, comparing delta values between the uniplanar and biplanar cohorts, with uniplanar as a reference. § Paired-sample t-test or Wilcoxon rank-sum test comparing preoperative and postoperative values.

e. Evaluation of sagittal balance revealed no significant changes at 1-year follow-up between uniplanar and biplanar groups, or within either group, for all radiographic parameters except for SL which improved significantly compared to baseline. Concerns persist regarding the ability to achieve sufficient lordosis correction through TLIF, with some studies demonstrating either no significant changes or worsened kyphosis postoperatively. However, the consensus regarding the lordotic capabilities of TLIF remains a subject of debate. In line with our results, a large meta-analysis by Alvi et al. consisting of 706 patients revealed a significant improvement in SL with expand-
Table 5. MCID at 1-year follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uniplanar (n = 41)</th>
<th>Biplanar (n = 52)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODI</td>
<td>68.3%</td>
<td>75.0%</td>
<td>0.474</td>
</tr>
<tr>
<td>VAS back</td>
<td>63.4%</td>
<td>57.6%</td>
<td>0.436</td>
</tr>
<tr>
<td>VAS leg</td>
<td>36.6%</td>
<td>28.8%</td>
<td>0.428</td>
</tr>
</tbody>
</table>

MCID, minimally clinically important difference; ODI, Oswestry Disability Index, VAS, visual analogue scale.
†Pearson chi-square test for sex, preoperative diagnosis, and TLIF level involved.

Uniplanar and biplanar expandable cages at final follow-up (15.55 months); however, no significant changes in LL were appreciated. The increased distraction forces exerted during in situ cage expansion may account for greater gains in SL. However, these modest gains may induce changes at adjacent levels with potentially negative overall effects on LL or may comprise such a small portion of overall LL that the magnitude of SL change is not large enough to significantly alter the overall LL.17 Regardless, Vaishnav et al.8 reported maintenance of segmental and whole LL in those with low (<15°) preoperative SL with static and expandable cages. However, those with moderate (>15° to <25°) and high (>25°) preoperative SL who received expandable cages only demonstrated maintenance of lordosis compared to those receiving static cages. The results of this study suggest that both uniplanar and biplanar devices provide significant improvements in SL with no change in LL or any other sagittal parameters consistent with prior studies.8,17,21

The findings of this study should be interpreted with the following limitations. The retrospective nature of this study raises concern for inherent biases, such as restriction of the number of patients in each treatment arm, availability of clinical data, and implant selection bias by the surgeons. In response, regression analysis controlling for demographic and surgical factors was performed to reduce confounders associated with our results. However, we are unable to control for surgeon implant selection bias, which we acknowledge is a main limitation of our data. Additionally, longer follow-up is necessary to evaluate whether cage types influence long-term PROMs, which may differ based on construct-related factors such as gradual cage subsidence and fusion quality.25 Finally, radiographs rather than CT scans were used to evaluate fusion status at 1 year, which we are aware has lower sensitivity and specificity than CT scans. However, our institution does not routinely obtain postoperative CT scans in patients undergoing lumbar fusion unless the patient has new-onset axial back pain with or without radiculopathy that appears consistent with a potential pseudarthrosis.

CONCLUSION

Overall, our experience with uniplanar and biplanar expandable PEEK cages indicate that both cage types are safe and efficacious at improving anterior disc height, posterior disc height, SL, and PROMs at 1 year postoperatively. No significant differences in clinical and radiographic outcomes including subsidence rates and 1-year fusion rates were observed between uniplanar and biplanar expandable cages. Further, no differences in postoperative complication rates, 90-day readmissions, and revision surgery rate were noted in either group. This study supports the need for larger, preferably randomized studies, with longer follow-up durations to validate our experience.

NOTES

Supplementary Materials: Supplementary Tables 1-4 can be found via https://doi.org/10.14245/ns.2244870.435.
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Mark F. Kurd: 0000-0001-9680-1088
Kris E. Radcliff: 0000-0002-4614-3854
David G. Anderson: 0000-0001-8564-1568

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1. Wong AP, Smith ZA, Stadler JA 3rd, et al. Minimally invasive transforminal lumbar interbody fusion (MI-TLIF): surgical technique, long-term 4-year prospective outcomes, and

https://doi.org/10.14245/ns.2244870.435


**Supplementary Table 1.** Breakdown of interbody cages used sorted by manufacturer, surface material, starting anteroposterior (A-P) length, starting and maximum medial-lateral (M-L) widths, maximum height, maximum lordosis, and count

<table>
<thead>
<tr>
<th>Expansion direction</th>
<th>Product</th>
<th>Manu-facturer</th>
<th>Surface material</th>
<th>Starting length (A-P)</th>
<th>Starting width (M-L)</th>
<th>Maximum width (M-L)</th>
<th>Maximum height (mm)</th>
<th>Maximum lordosis (°)</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniplanar (n = 41)</td>
<td>Elevate Medtronic</td>
<td>PEEK</td>
<td>23, 28, or 32 mm</td>
<td>10 mm</td>
<td>N/A</td>
<td>7 or 8–11</td>
<td>8, 10, 11, or 13</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Caliber Globus</td>
<td>PEEK</td>
<td>22, 26, or 30 mm</td>
<td>10 or 12 mm</td>
<td>N/A</td>
<td>7–17</td>
<td>4, 12, or 15</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biplanar (n = 52)</td>
<td>Flarehawk Accelus</td>
<td>PEEK</td>
<td>26 or 30 mm</td>
<td>7 or 9 mm</td>
<td>14 mm</td>
<td>14</td>
<td>6, 9, or 15</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>
**Supplementary Table 2.** Comparison of anterior disc height, posterior disc height, and subsidence parameters preoperatively, at 6-week follow-up, and 1-year follow-up for procedures performed at L4–5 in patients with diagnosis of spinal stenosis or spondylolisthesis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uniplanar (n = 23)</th>
<th>Biplanar (n = 27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior disc height (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>9.37 ± 3.64</td>
<td>9.05 ± 3.37</td>
<td>0.773</td>
</tr>
<tr>
<td>6-Week postoperative</td>
<td>13.5 ± 2.79</td>
<td>13.3 ± 2.47</td>
<td>0.780</td>
</tr>
<tr>
<td>6-Week Δ value</td>
<td>4.11 ± 2.84</td>
<td>4.21 ± 3.65</td>
<td>0.754</td>
</tr>
<tr>
<td>p-value†</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>1-Year postoperative</td>
<td>12.9 ± 3.19</td>
<td>12.7 ± 2.48</td>
<td>0.764</td>
</tr>
<tr>
<td>1-Year Δ value</td>
<td>2.51 ± 2.48</td>
<td>2.29 ± 1.32</td>
<td>0.701</td>
</tr>
<tr>
<td>p-value‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td><strong>Posterior disc height (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.61 ± 2.58</td>
<td>6.43 ± 1.63</td>
<td>0.815</td>
</tr>
<tr>
<td>6-Week postoperative</td>
<td>9.11 ± 2.59</td>
<td>7.87 ± 1.35</td>
<td>0.595</td>
</tr>
<tr>
<td>6-Week Δ value</td>
<td>3.59 ± 3.29</td>
<td>3.64 ± 4.61</td>
<td>0.972</td>
</tr>
<tr>
<td>p-value†</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>1-Year postoperative</td>
<td>8.61 ± 2.57</td>
<td>7.87 ± 1.35</td>
<td>0.321</td>
</tr>
<tr>
<td>1-Year Δ value</td>
<td>2.03 ± 2.84</td>
<td>1.44 ± 1.35</td>
<td>0.489</td>
</tr>
<tr>
<td>p-value‡</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td><strong>Subsidence measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Subsidence at 6-week follow-up</td>
<td>3/23 (13.1)</td>
<td>6/27 (22.2)</td>
<td>0.399</td>
</tr>
<tr>
<td>Subsidence at 6 weeks (mm)†</td>
<td>4.81 ± 0.98</td>
<td>4.98 ± 2.78</td>
<td>0.917</td>
</tr>
<tr>
<td>% Subsidence at 1-year follow-up</td>
<td>3/23 (13.1)</td>
<td>6/27 (22.2)</td>
<td>0.399</td>
</tr>
<tr>
<td>Subsidence at 1 year (mm)§</td>
<td>5.13 ± 0.83</td>
<td>5.23 ± 2.93</td>
<td>0.787</td>
</tr>
<tr>
<td><strong>Fusion status at 1 year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fused§</td>
<td>18/23 (78.3)</td>
<td>23/27 (85.2)</td>
<td>0.525</td>
</tr>
</tbody>
</table>

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

* † ‡ §: p < 0.05, statistically significant differences. † Independent-samples t-test or Mann-Whitney U-test comparing uniplanar and biplanar cages. ‡ Paired-sample test or Wilcoxon rank-sum test comparing preoperative and postoperative values. § Pearson chi-square test for subsidence rate and fusion status comparing uniplanar and biplanar cages.
### Supplementary Table 3. Comparison of radiographic sagittal parameters preoperatively and at 1-year follow-up for procedures performed at L4–5 in patients with diagnosis of spinal stenosis or spondylolisthesis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uniplanar (n = 23)</th>
<th>Biplanar (n = 27)</th>
<th>p-value$^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacral slope (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>37.4 ± 8.18</td>
<td>34.8 ± 7.32</td>
<td>0.114</td>
</tr>
<tr>
<td>Postoperative</td>
<td>33.5 ± 8.74</td>
<td>32.2 ± 8.69</td>
<td>0.572</td>
</tr>
<tr>
<td>Δ Value</td>
<td>-0.42 ± 5.86</td>
<td>-1.54 ± 5.61</td>
<td>0.662</td>
</tr>
<tr>
<td>p-value$^\dagger$</td>
<td>0.152</td>
<td>0.745</td>
<td></td>
</tr>
<tr>
<td>Pelvic tilt (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>26.6 ± 7.12</td>
<td>28.9 ± 7.53</td>
<td>0.344</td>
</tr>
<tr>
<td>Postoperative</td>
<td>29.2 ± 7.12</td>
<td>27.8 ± 9.09</td>
<td>0.855</td>
</tr>
<tr>
<td>Δ Value</td>
<td>0.05 ± 5.27</td>
<td>0.79 ± 7.44</td>
<td>0.741</td>
</tr>
<tr>
<td>p-value$^\dagger$</td>
<td>0.312</td>
<td>0.872</td>
<td></td>
</tr>
<tr>
<td>Lumbar lordosis (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>42.5 ± 13.9</td>
<td>45.9 ± 11.4</td>
<td>0.430</td>
</tr>
<tr>
<td>Postoperative</td>
<td>44.3 ± 10.8</td>
<td>46.4 ± 13.8</td>
<td>0.752</td>
</tr>
<tr>
<td>Δ Value</td>
<td>2.06 ± 7.45</td>
<td>1.24 ± 8.07</td>
<td>0.207</td>
</tr>
<tr>
<td>p-value$^\dagger$</td>
<td>0.338</td>
<td>0.878</td>
<td></td>
</tr>
<tr>
<td>Segmental lordosis (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>4.39 ± 3.28</td>
<td>4.92 ± 4.15</td>
<td>0.422</td>
</tr>
<tr>
<td>Postoperative</td>
<td>7.04 ± 2.89</td>
<td>7.11 ± 3.75</td>
<td>0.951</td>
</tr>
<tr>
<td>Δ Value</td>
<td>3.15 ± 4.29</td>
<td>2.19 ± 3.68</td>
<td>0.453</td>
</tr>
<tr>
<td>p-value$^\dagger$</td>
<td>0.071</td>
<td>0.003*</td>
<td></td>
</tr>
<tr>
<td>PI-LL (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>22.5 ± 11.7</td>
<td>16.4 ± 11.9</td>
<td>0.071</td>
</tr>
<tr>
<td>Postoperative</td>
<td>18.4 ± 8.16</td>
<td>15.3 ± 14.4</td>
<td>0.842</td>
</tr>
<tr>
<td>Δ Value</td>
<td>-2.43 ± 11.2</td>
<td>0.79 ± 11.2</td>
<td>0.377</td>
</tr>
<tr>
<td>p-value$^\dagger$</td>
<td>0.297</td>
<td>0.757</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

PI-LL, pelvic incidence-lumbar lordosis mismatch.

*p < 0.05, statistically significant differences. $^\dagger$Independent-samples t-test or Mann-Whitney U-test comparing uniplanar and biplanar cages.

$^\dagger$Paired-sample test or Wilcoxon rank-sum test comparing preoperative and postoperative values.
### Supplementary Table 4. Patient-reported Outcomes at 3-month and 1-year follow-up for procedures performed at L4–5 in patients with diagnosis of spinal stenosis or spondylolisthesis

<table>
<thead>
<tr>
<th></th>
<th>Uniplanar (n = 41)</th>
<th>Biplanar (n = 52)</th>
<th>p-value $^\dagger$</th>
<th>Regression analysis $^\ddagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-Month follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ODI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>57.6 ± 8.49</td>
<td>53.6 ± 13.3</td>
<td>0.114</td>
<td>$\beta = 5.06$ (-8.11 to 18.2)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>33.2 ± 20.7</td>
<td>27.1 ± 13.1</td>
<td>0.277</td>
<td>p = 0.440</td>
</tr>
<tr>
<td>$\Delta$ Value</td>
<td>-14.4 ± 12.9</td>
<td>-16.5 ± 14.4</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td>p-value $^*$</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VAS back</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.08 ± 1.96</td>
<td>6.84 ± 1.19</td>
<td>0.169</td>
<td>$\beta = -0.032$ (-1.63 to 1.57)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>3.67 ± 2.19</td>
<td>3.29 ± 1.63</td>
<td>0.452</td>
<td>p = 0.667</td>
</tr>
<tr>
<td>$\Delta$ Value</td>
<td>-3.42 ± 2.19</td>
<td>-3.85 ± 2.27</td>
<td>0.580</td>
<td></td>
</tr>
<tr>
<td>p-value $^*$</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VAS leg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.57 ± 2.05</td>
<td>6.07 ± 2.83</td>
<td>0.339</td>
<td>$\beta = -0.385$ (-3.11 to 2.34)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2.92 ± 2.64</td>
<td>3.08 ± 3.89</td>
<td>0.465</td>
<td>p = 0.776</td>
</tr>
<tr>
<td>$\Delta$ Value</td>
<td>-3.67 ± 2.92</td>
<td>-3.74 ± 3.75</td>
<td>0.952</td>
<td></td>
</tr>
<tr>
<td>p-value $^*$</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1-Year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ODI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>57.6 ± 8.49</td>
<td>53.6 ± 13.3</td>
<td>0.114</td>
<td>$\beta = 2.38$ (-11.2 to 15.8)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>30.3 ± 19.1</td>
<td>26.2 ± 13.8</td>
<td>0.092</td>
<td>p = 0.720</td>
</tr>
<tr>
<td>$\Delta$ Value</td>
<td>-27.3 ± 20.3</td>
<td>-22.9 ± 16.8</td>
<td>0.486</td>
<td></td>
</tr>
<tr>
<td>p-value $^*$</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VAS back</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.08 ± 1.96</td>
<td>6.84 ± 1.19</td>
<td>0.169</td>
<td>$\beta = -0.528$ (-2.42 to 1.36)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>3.08 ± 2.71</td>
<td>2.91 ± 1.72</td>
<td>0.359</td>
<td>p = 0.573</td>
</tr>
<tr>
<td>$\Delta$ Value</td>
<td>-3.21 ± 3.02</td>
<td>-4.04 ± 2.26</td>
<td>0.241</td>
<td></td>
</tr>
<tr>
<td>p-value $^*$</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VAS leg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.57 ± 2.05</td>
<td>6.07 ± 2.83</td>
<td>0.339</td>
<td>$\beta = -0.215$ (-2.71 to 2.18)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2.42 ± 3.14</td>
<td>2.16 ± 2.42</td>
<td>0.626</td>
<td>p = 0.856</td>
</tr>
<tr>
<td>$\Delta$ Value</td>
<td>-4.33 ± 2.39</td>
<td>-4.15 ± 3.39</td>
<td>0.865</td>
<td></td>
</tr>
<tr>
<td>p-value $^*$</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

ODI, Oswestry Disability Index; VAS, visual analogue scale; BMI, body mass index.

* $p < 0.05$, statistically significant differences.

$^\dagger$ Independent-samples t-test or Mann-Whitney U-test comparing uniplanar and biplanar cages.

$^\ddagger$ Multiple linear regression controlling for age, sex, BMI, and preoperative diagnosis, comparing delta values between the uniplanar and biplanar cohorts, with uniplanar as a reference.

$^*$ Paired-sample t-test or Wilcoxon rank-sum test comparing preoperative and postoperative values.
Intra-articular Distraction Versus Decompression to Treat Basilar Invagination Without Atlantoaxial Dislocation: A Retrospective Cohort Study of 54 Patients

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Objective: The surgical management of basilar invagination without atlantoaxial dislocation (type B basilar invagination) remains controversial. Hence, we have reported the use of posterior intra-articular C1–2 facet distraction, fixation, and cantilever technique versus foramen magnum decompression in treating type B basilar invagination as well as the results and surgical indications for this procedure.

Methods: This was a single-center retrospective cohort study. Fifty-four patients who underwent intra-articular distraction, fixation, and cantilever reduction (experimental group) and foramen magnum decompression (control group) were enrolled in this study. Distance from odontoid tip to Chamberlain's line, clivus-canal angle, cervicomedullary angle, craniocervical junction (CVJ) triangle area, width of subarachnoid space and syrinx were used for radiographic assessment. Japanese Orthopedic Association (JOA) scores and 12-item Short Form health survey (SF-12) scores were used for clinical assessment.

Results: All patients in the experimental group had a better reduction of basilar invagination and better relief of pressure on nerves. JOA scores and SF-12 scores also had better improvements in the experimental group postoperation. SF-12 score improvement was associated with preoperative CVJ triangle area (Pearson index, 0.515; p = 0.004), cutoff value of 2.00 cm² indicating the surgical indication of our technique. No severe complications or infections occurred.

Conclusion: Posterior intra-articular C1–2 facet distraction, fixation, and cantilever reduction technique is an effective treatment for type B basilar invagination. As various factors involved, other treatment strategies should also be investigated.

Keywords: Basilar invagination, Reduction, Posterior approach, Fixation, Syringomyelia

INTRODUCTION

Basilar invagination is a congenital malformation due to abnormal development of the craniocervical junction area, causing compression of medulla and spinal cord, resulting in several neurological symptoms. There are few studies for basilar invagination without atlantoaxial dislocation (type B basilar invagination), and surgical treatment remains controversial. Since the vertical dislocation and retroversion of odontoid in type B basilar invagination have not been the focus of previous studies, the surgical modalities used in previous studies mainly include foramen magnum decompression (FMD) and transoral odon-
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However, FMD can only achieve effective decompression of the dorsal side of spinal cord, meanwhile, threaten the stability of craniovertebral junction (CVJ) area. Transoral or transnasal surgeries are associated with a higher risk of postoperative complications such as infection or aspiration. In our previous study, we introduced the intra-articular C1–2 facet distraction, fixation, and cantilever reduction technique for basilar invagination with atlantoaxial dislocation (type A basilar invagination) in which lateral joints were distracted, fusion cages were implanted, and satisfactory reduction of basilar invagination and clinical results were achieved. In this study, we proposed the use of this technique for treating type B basilar invagination, and reported the results and surgical indications for this procedure.

MATERIALS AND METHODS

1. Study Design

This was a retrospective cohort study, approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (LYS[2021]021). Each patient signed an informed consent form for participation in this study.

This study enrolled consecutive type B basilar invagination patients who underwent surgical treatment at Xuanwu Hospital between March 2017 and December 2021. Surgical treatment including intra-articular C1–2 facet distraction, fixation, cantilever reduction surgery, and FMD. Decisions about operation method based on patients’ willingness. Before the operation, attending doctors thoroughly explained the effectiveness and safety of both operations to the patients. After signing the informed consent form, patients were asked to decide freely. Thereafter, the patients were divided into the experimental group (underwent intra-articular C1–2 facet distraction, fixation, and cantilever reduction surgery) and the control group (underwent FMD) according to the chosen surgical procedure.

The inclusion criteria were: (1) suffering from basilar invagination, (2) not combined with atlantoaxial dislocation, and (3) significant clinical symptoms. The exclusion criteria were: (1) local inflammation such as rheumatoid arthritis or osteoarthritis, (2) os odontoideum, (3) trauma at the craniocervical junction area, (4) osteoporosis, (5) tumor involving craniocervical junction area, or (6) severe basic disease. Basilar invagination was diagnosed when the tip of the odontoid was > 5 mm above Chamberlain’s line, and atlantoaxial dislocation was defined as ADI > 3 mm.

2. Surgical Procedures

Posterior intra-articular C1–2 facet distraction, fixation, and cantilever reduction surgery: The patient was placed in a prone position after general anesthesia, with neck slightly extended. Cervical traction was applied with one-sixth of body weight (up to 18 kg) and maintained intraoperatively. A posterior median incision was made. After subperiosteal dissection, the C2 nerve root and venous plexus were dissected, and the lateral joint was exposed. A 2-mm bone chisel was inserted into the joint capsule to completely remove the articular cartilage. Thereafter, individual intra-articular distractors were inserted into the joints with rotation. The joint space was opened with the sequential increase in the size of distractors. After distraction on one side, an appropriate distractor trail was placed in the joint to maintain the gap and then distraction in the contralateral joint space was performed. These steps were repeated on both sides until basilar invagination was reduced to the planned position (based on the distance from the odontoid to Chamberlain’s line). Thereafter, the cages filled with autologous iliac bone were placed into the bilateral joints and intraoperative fluoroscopy was performed to confirm their position, height of cages (design height 6–9 mm) were determined by the severity of basilar invagination and intra-articular release (Figs. 1, 2).

Occipital condyle screws or occipital plates were placed parallel to the external occipital protuberance (external occipital crest) using midline screws, and then pedicle screws were placed into C2 pedicles. The titanium rods were bent to match the con-

Fig. 1. Surgical techniques. (A, B) An individual intra-articular distractor was used to release the soft tissue and open the joint space. (C) Cages filled with autologous iliac bone were placed into the bilateral joints. (D) Using cantilever technique, the rods and screws system drive the C2 vertebrae to move and tilt ventrally, improving cervicomedullary angle.
tour of the occipital cervical junction and first fixed caudally to the C2 pedicle screws. The cranial ends of the rods were then pressed into occipital screws using cantilever technique, and the rods were pushed in by screw rotation, driving the C2 vertebrae to move and tilt ventrally, thereby increasing the lordosis between the atlantoaxial vertebrae, improving cervicomedullary angle (CMA), allowing further decompression of the vertebral body. The screws were tightened and tabs were removed after reduction of the basilar invagination was confirmed using the O-arm (Medtronic, Dublin, Ireland).

Foramen magnum decompression: The patient was placed in a prone position after general anesthesia, with head fixed in a pin headholder, and neck slightly flexed. After sterilizing, a posterior midline incision was made, and the posterior atlantoaxial arch and occipital scales were revealed. Then the posterior atlantoaxial arch, the posterior border of foramen magnum, and part of the squama were removed, and the transition between cerebellar hemisphere and spinal dura was visible. The posterior or atlanto-occipital fascia was cut out, and the muscle, fascia, and skin were tightly sutured in layers after extensive irrigation.

3. Clinical and Radiographic Assessments

We analyzed the preoperative and postoperative examination results and clinical scores of all patients. Computed tomography (CT) and magnetic resonance imaging (MRI) examinations were scheduled within one week and at 3, 6, 12 months postoperatively. The effect of reduction, decompression were analyzed by measuring the distance from the odontoid tip to Chamberlain's line (DCL), clivus-canal angle (CCA), CMA, CVJ triangle area, width of subarachnoid space, and width of syrinx (if present). Patients' clinical outcomes were assessed by symptom changes, Japanese Orthopedic Association (JOA) score, and 12-Item Short Form Health Survey (SF-12) score preoperatively, postoperatively, and every 6 months postoperatively (Fig. 3).

4. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA). The independent-samples t-test was used to analyze any statistical difference between the 2 groups, and paired-samples t-test was used to analyze any statistical difference between the preoperative and postoperative measurements. The level of significance was set at p < 0.05. Data are presented as mean ± standard deviation unless stated otherwise. Cutoff values were calculated by X-tile software.

RESULTS

1. Population

A total of 60 patients were analyzed after inclusion and exclusion criteria. After baseline matching, 54 patients were included in this study, 30 patients in the experimental group, and 24 patients in the control group. All patients were operated by the same senior neurosurgeon (CZ). Of these, 25 patients were male and 29 were female, with a mean age of 48.67 years (range, 22
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Table 1. Summary of clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experimental group (n = 30)</th>
<th>Control group (n = 24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.60 ± 11.45</td>
<td>48.75 ± 13.05</td>
<td>0.964</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.952</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>19</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>DCL (mm)</td>
<td>12.20 ± 4.01</td>
<td>10.52 ± 4.03</td>
<td>0.133</td>
</tr>
<tr>
<td>Clivus-canal angle (°)</td>
<td>131.66 ± 11.45</td>
<td>136.82 ± 8.16</td>
<td>0.068</td>
</tr>
<tr>
<td>Cervicomedullary angle (°)</td>
<td>140.00 ± 10.84</td>
<td>142.17 ± 6.05</td>
<td>0.386</td>
</tr>
<tr>
<td>Width of subarachnoid space (mm)</td>
<td>1.39 ± 0.49</td>
<td>1.30 ± 0.38</td>
<td>0.462</td>
</tr>
<tr>
<td>CVJ triangle area (cm²)</td>
<td>1.86 ± 0.70</td>
<td>1.93 ± 0.40</td>
<td>0.661</td>
</tr>
<tr>
<td>Width of syrinx (mm)</td>
<td>5.61 ± 3.16</td>
<td>7.19 ± 2.78</td>
<td>0.168</td>
</tr>
<tr>
<td>JOA</td>
<td>13.00 ± 1.39</td>
<td>13.46 ± 0.93</td>
<td>0.172</td>
</tr>
<tr>
<td>SF-12</td>
<td>92.17 ± 13.85</td>
<td>93.32 ± 8.51</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number.

Table 2. Reduction of basilar invagination in experimental group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCL (mm)</td>
<td>12.20 ± 4.01</td>
<td>8.27 ± 4.25</td>
<td>-3.93 ± 2.49</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Clivus-canal angle (°)</td>
<td>131.66 ± 11.45</td>
<td>136.58 ± 11.02</td>
<td>4.92 ± 3.11</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. DCL, distance from the odontoid tip to Chamberlain's line. *p < 0.05, statistically significant differences.

to 68 years). Thirty-three patients had combined C1 assimilation, 31 had combined syringomyelia. Six patients who had undergone FMD revisited with no significant relief of symptoms. Symptoms included numbness and weakness in the extremities, headache, neck and back pain, and unsteady gait. There were no statistical differences between the 2 groups in baseline data including DCL, CCA, CMA, width of subarachnoid space, or CVJ triangular area (Table 1).

2. Surgery

The mean operation time was 178.59 minutes in experimental group, with a mean blood loss of 132.22 mL, while the mean operation time was 120.79 minutes in control group, with a mean blood loss of 32.08 mL. No severe complications or infections occurred postoperation. The average height of cages was 7.13 mm (6 mm for 3 cases, 7 mm for 21 cases, 8 mm for 5 cases, and 9 mm for 1 case).

3. Radiographic Follow-up

The CT examinations within one week after surgery indicated relief of compression in the ventral aspect of spinal cord in experimental group. Better improvement appeared in experimental group in the width of subarachnoid space and CVJ triangle area (mean 0.64 ± 0.58 mm vs. 0.32 ± 0.23 mm, -0.46 ± 0.69 cm² vs. -0.16 ± 0.16 cm²). CMA had increased in all patients, experimental group had more significantly increasement than control group. In patients with concomitant syringomyelia, 19 of 19 reduced in experimental group, while 11 of 12 reduced in control group (mean -2.62 ± 2.52 mm vs. -1.04 ± 0.47 mm). Four of 54 patients (7%) achieved bony fusion at 3-month follow-up, and 11 of 11 (100%) at 6-month follow-up. No implant failure, spacer subsidence, or deterioration of spinal cord compression occurred during the follow-up period.

There are statistical differences between the above data between the 2 groups (Table 2).

4. Clinical Outcomes

During follow-up, 29 patients in experimental group showed significant improvement in their symptoms. The JOA score improved by 2.30 ± 1.06, and the SF-12 score improved by 13.70 ± 6.42. Tweinty-one patients in control group showed significant improvement in their symptoms. The JOA score improved by 1.17 ± 0.64, and the SF-12 score improved by 5.16 ± 3.71. There are statistical differences between all data above between the 2 groups. During a mean follow-up of 15.43 months, no severe complications and infections occurred in both groups (Figs. 4, 5).

DISCUSSION

Basilar invagination was first introduced by Anders Adolph Retzius and Frederik Theodor Berg in 1855, mainly caused by congenital bony abnormalities in the craniocervical junction area, such as hypoplasia of clivus, C1 assimilation, odontoid anomalies, or atlantoaxial dislocation. Goel proposed a classification of basilar invagination in 2004, wherein type A basilar invagination indicates combined with atlantoaxial dislocation, and type B basilar invagination indicates without atlantoaxial dislocation. 9-12
dislocation. Subsequently, they identified that type B basilar invagination was secondary to instability at the atlantoaxial joint, but this theory lacks imaging evidence and remains controversial.\textsuperscript{13}

In this study of 54 patients, the average DCL was 11.45 mm, the average CCA was 133.95\textdegree, and the average CMA was 140.97\textdegree, indicating the main characteristic of type B basilar invagination is vertical dislocation and retroversion of the odontoid, which results in compression of subarachnoid space, medulla, and spinal cord, directly leading to clinical symptoms or syringomyelia. Moreover, significant compression of the ventral aspect of spinal cord was observed in all images.

The treatment of type B basilar invagination remains controversial.\textsuperscript{3,13-20} Goel et al. initially introduced FMD to treat type B basilar invagination, but symptoms did not improve significantly after surgery in some studies.\textsuperscript{21} Sangwanloy et al.\textsuperscript{22} suggested that FMD in patients with CCA less than 135\textdegree was less effective. Recently, Goel reported treating type B basilar invagination by atlantoaxial fixation, but this method has not been widely accepted due to the lack of pathogenesis evidence, and simple at-

Fig. 4. A 40-year-old male presented with weakness and numbness for 2 months. (A-D) Preoperative x-ray and computed tomography (CT) scan indicating the existence of type B basilar invagination with C1 assimilation and C2–3 fusion. (E) Preoperative magnetic resonance (MR) image showing ventral compression of the spinal cord. (F) Three-dimensional CT reconstructive image showing vertebral arteries and obscured vision of bilateral facet joints. (G-J) Postoperative x-ray and CT scan indicating a reduction of basilar invagination. (K) Postoperative MR image showing reduction of compression and syringomyelia. (L) MR image 3 months after surgery showing obvious reduction of syringomyelia.
A 50-year-old male presented with pain and numbness in neck and back for 2 years. (A-D) Preoperative x-ray and computed tomography (CT) scan indicating the existence of type B basilar invagination with C1 assimilation. (E) Preoperative magnetic resonance (MR) image showing ventral compression of the spinal cord and syringomyelia. (F) Three-dimensional CT reconstructive image showing bilateral facet joints were blocked. (G-J) Postoperative x-ray and CT scan indicating a reduction of basilar invagination. (K) Postoperative MR image showing reduction of compression and syringomyelia. (L) MR image 12 months after surgery showing obvious reduction of syringomyelia.

lantoaxial fixation has no effect on reducing basilar invagination. Some surgeons used transoral or transnasal odontoidectomy to directly relieve the ventral compression of spinal cord by odontoid, but the stability between atlantoaxial vertebrae is disrupted after odontoidectomy, which may cause atlantoaxial instability and require posterior fixation and fusion. In addition, transoral or transnasal odontoidectomy is more complex, with a higher risk of infection.

Previously, we proposed the use of posterior intra-articular distraction, fixation, and cantilever reduction technique to treat type A basilar invagination, which achieved satisfactory direct decompression and significant relief of symptoms. We found that distraction of atlantoaxial joints can move the axial caudally, restore CCA by cantilever technique, and effectively reduce basilar invagination. According to this theory, we speculated that this technique would also be effective in treating type B basilar invagination.

We performed posterior interarticular distraction and implanted PEEK fusion cages (6 mm high) successfully in lateral joints in experimental group. DCL improved 3.93 ± 2.49 mm
from preoperative, CCA improved $4.92\pm 3.11^\circ$ from preoperative, and CMA improved $14.19\pm 8.43^\circ$ from preoperative. The width of subarachnoid space, and CVJ triangle area were also significantly improved in these patients. Between the 2 groups, patients in experimental group showed more significant improvements in all radiographic and clinical assessments (Table 3).

The compression of the spinal cord by odontoid and interatlantoaxial soft tissues cannot be fully reflected by using only bony measurements such as DCL or CCA. The compression of the spinal cord can be directly reflected by measurements in MRI scan. After correlational analyses between radiographic and clinical assessments, we found that SF-12 score improvement was associated with preoperative CVJ triangle area (Pearson index, 0.515; p = 0.004). The larger the preoperative CVJ triangle area, the more significant improvement in SF-12 scores, which suggested that patients with more severe preoperative ventral compression of spinal cord can benefit the most from this technique. By calculating the cutoff values, we concluded that posterior intra-articular distraction, fixation, and cantilever reduction technique should be preferred when the CVJ triangle area is $> 2.00 \text{cm}^2$ (chi-square = 10.11, p = 0.001) (Fig. 6).

Intraoperative placement of fusion cages in lateral joints and reduction by cantilever technique with cages as fulcrum have following unique advantages in treating type B basilar invagination: (1) It moves odontoid caudally, corrects basilar invagination, and directly reduces the compression of the ventral aspect of spinal cord. (2) It reduces the CCA by rotating axis forward, and further reduces the ventral compression of spinal cord. (3) Fusion cages in joints can act as fulcrums and distribute the stress on posterior internal fixation system, thereby avoiding failure of internal fixation due to stress concentration. (4) Fusion cages between the joints are more aligned with Wolff’s law,
clarify the individual anatomy of the CVJ area. Moreover, a bone density test is required for elderly patients to reduce the risk of joint surface collapse.

Constrained by research conditions, it was difficult to conduct a randomized study, so decisions on surgical method were made according to patients’ willingness, which may import inherent biases. Fortunately, there was no statistical difference at baseline, indicating that this bias was relatively small. Ideally, a prospective randomized study should be undertaken, providing high level evidence to the treatment of type B basilar invagination.

CONCLUSION

The posterior intra-articular C1–2 facet distraction, fixation, and cantilever reduction technique is an effective treatment for type B basilar invagination, especially with concomitant atlanto-occipital fusion or other deformities. Compared with FMD, the present technique is more effective in treating type B basilar invagination. However, due to various factors causing type B basilar invagination, it is difficult to treat all patients with one single strategy. Further studies are needed to provide high level evidence, and to investigate other treatment strategies for basilar invagination caused by different factors.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Neurosine 2021;18:206-16.


Global Research Trends of Exosomes in the Central Nervous System: A Bibliometric and Visualized Analysis

Yue Zhuo, Kun Ai, Ke He, Boyu Wu, Jiaying Peng, Jing Xiang, Guanlin Zhang, Ziyuan Jiao, Ruixuan Zhou, Hong Zhang

Objective: Exosomes in the central nervous system (CNS) have become an attractive area of research with great value. However, few bibliometric analysis has been conducted. The study aimed to visualize the scientific trends and research hotspots of exosomes in the CNS by bibliometric analysis.

Methods: All potential articles and reviews on exosomes in the CNS published in English from 2001 to 2021 were extracted from the Web of Science Core Collection. The visualization knowledge maps of critical indicators, including countries/regions, institutions, authors, journals, references, and keywords, were generated by CiteSpace and VOSviewer software. Besides, each domain's quantitative and qualitative analysis was also considered.

Results: A total of 2,629 papers were included. The number of exosomes-related publications and citations regarding CNS increased yearly. These publications came from 2,813 institutions in 77 countries/regions, led by the United States and China. Harvard University was the most influential institution, while the National Institutes of Health was the most critical funding source. We identified 14,468 authors, among which Kapogiannis D had the most significant number of articles and the highest H-index, while Théry C was the most frequently co-cited. The cluster analysis of keywords generated 13 clusters. In summary, the topic of biogenesis, biomarker, and drug delivery will serve as hotspots in future research.

Conclusion: Exosomes-related CNS research has gained considerable attention in the past 20 years. The sources and biological functions of exosomes and their promising role in diagnosing and treating CNS diseases are considered hotspots in this field. The clinical translation of the results from exosomes-related CNS research will be of great importance in the future.

Keywords: Exosomes, Central nervous system, Bibliometric analysis, VOSviewer, Citespace

INTRODUCTION

The central nervous system (CNS), which consists of the brain and spinal cord, influences bodily functions through innervation and neurotransmitters. Due to several significant factors, including inflammation, infection, trauma, neurodegeneration, heredity, and tumor, CNS diseases have become a leading cause of death worldwide. Although significant improvements have been made in neuroscience, challenges such as the undetermined etiology of some CNS disorders, the lack of novel early diagnostic biomarkers and precise therapeutic targets, more importantly, the restriction of the blood-brain barrier (BBB) on therapeutic responses to drugs still remain. Fortunately, the emergence of exosomes holds much promise for the treatment and research of CNS diseases.

Exosomes were defined as vesicles of endosomal origin secreted from reticulocytes in the 1980s. With deepening research, scientists have discovered that exosomes bear a variety of substances, including RNA, DNA fragments, proteins, and lipids, regulating intercellular communication between dissimi-
lar cell types in vivo, thus affecting both normal and pathological conditions. To step further, increasing studies have shown that exosomes are involved in CNS diseases. Roughly, the cargo of exosomes can be used as noninvasive diagnostic biomarkers for CNS diseases, alternatively or be chosen as drug delivery vehicles that can cross BBB. Therefore, exosomes-related CNS research is challenging and promising.

Bibliometric analysis has been broadly employed to understand knowledge structure and explore research trends through qualitative and quantitative analysis of included literature. This analytical approach is crucial in identifying research hotspots and developing guidelines. In this study, we have collated exosomes-related CNS research over the past 20 years and drawn maps of scientific knowledge by means of CiteSpace and VOSviewer software. Additionally, we examined the hotspots and developmental trends with a view to providing the basis and direction for scientific research in this field.

MATERIALS AND METHODS

1. Data Sources and Search Strategies

The literature extracted from the Science Citation Index Expanded in the Web of Science Core Collection (WoSCC) database was downloaded within one day on July 3, 2022. The search formula was as follows: (TS = (“exosome*”)) AND TS = (“central nervous*” OR “central nerve*” OR “CNS” OR “systema nervorum centrale” OR “cerebrospinal*” OR “encephalo*” OR “brain*” OR “cerebr*” OR “spinal cord*” OR “spine cord*” OR “spinal medulla*” OR “medulla spinalis*” OR “spinal marrow*” OR “myelon*”), while the timespan for literature retrieval was set from 2001 to 2021. Only articles or reviews written in English were included. Ultimately, a total of 2,629 records, including 1,796 articles (68.31%) and 833 reviews (31.69%), were identified for analysis.

2. Data Extraction and Bibliometric Analysis

The included records were exported and saved as plain text files with “Full Record and Cited References” for further bibliometric analysis. The data from the Web of Science, including publication outputs, citation trends, countries/regions, institutions, authors, journals, funding sources, and the Hirsch index (H-index), was imported to Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA) for quantitative and qualitative analysis. Additionally, the impact factor (IF) and quartile rank of each journal from the Journal Citation Reports (JCR) 2021 were also considered. Two trained researchers performed the information extraction process independently, while any disagreements were resolved by consensus or by seeking a third one for help.

Subsequently, the CiteSpace 5.8.R3 (Drexel University, Philadelphia, PA, USA) and VOSviewer 1.6.18 (Leiden University, Leiden, The Netherlands) were employed to perform the bibliometric and visualization analysis. The CiteSpace was applied to extract keywords and references from publications with high citation bursts, produce a keywords cluster network and visualization map of timeline viewer, and generate a dual-map overlay for journals. The parameters were set as follows: time slicing (from 2001-01 to 2021-12), years per slice (1), links (strength = cosine; scope = within slices); selection criteria (top 5%), pruning (pathfinder + pruning the merged network + pruning sliced network). The clusters were labeled by keywords, and the log-likelihood rate (LLR) was applied to the clustering algorithm. The VOSviewer was used to produce knowledge maps of the identified influential authors, contributing countries and institutions, core
journals, high-quality papers, keywords co-occurrence, and co-cited references. The flow diagram of the retrieval strategy and analysis was shown in Fig. 1.

RESULTS

1. The Trends of Publication Outputs and Citations

The annual number of publications and citations reflects the research trends in a field.\(^\text{14}\) From 2001 to 2021, 2,629 studies published on exosomes in the CNS field were identified. These publications received 20,633 citations by the search date, an average of 40.64 citations per publication. Generally speaking, the annual number of publications and citations has shown an overall upward trend during these years. Specifically, the evolution of exosomes-related CNS research can be separated into 3 stages. In the embryonic stage from 2001 to 2007, the number of publications and citations was relatively low. Then, there was a steady growth phase between 2008 and 2016. From 2017 to 2021, the number of publications and citations on exosomes in the CNS field increased significantly, and the total number of publications in 2021 reached 670, while citations of 33,868. This implies that more attention has been paid to the potential of exosomes-related CNS research so that it can be regarded as a rapid and high-yield growth phase (Fig. 2).

2. Distribution of Countries/Regions, Institutions, and Funding Sources

Exosomes-related CNS research has been a significant hotspot worldwide.\(^\text{15}\) A total of 2,629 studies were published by 2,813 institutions in 77 countries/regions (Fig. 3A). The top 10 most productive countries/regions were displayed in Table 1 and Fig. 3B. The United States published the largest number of articles (922, 35.07%), followed by China (794, 30.20%) and Italy (193, 7.34%). In addition, the United States accounted for 59,403 citations with an H-index of 118, which both ranked first among all involved countries/regions. The number of citations of publications from China was 26,030 with an H-index of 83, which both ranked second. This means that the United States and China are the most contributing countries in this field. The total number of publications from these 2 countries was more than half of the total. In terms of average article citations, Germany (95.20 per publication) ranked first, followed by England (84.26 per publication), and Australia (79.06 per publication). However, the average number of article citations in China was relatively the lowest (32.78 per publication), which meant Germany, England, and Australia was the forerunner in this field with high-quality research, China as a latecomer should improve its research impact in this field. Centrality has been regarded as a significant turning point that may lead to transformative discoveries.\(^\text{16}\) Spain held the highest level of centrality (0.83), followed by the United States (0.44), and Germany (0.20). As illustrated in Fig. 3C, among the 77 countries/regions, 50 have published more than 5 articles in this field. The United States and China occupied the center of the network visualization of co-authorship between countries/regions, which reflected the leadership position in this field.

Fig. 2. The global trend of annual publications and citations on exosomes-related central nervous system research from 2001 to 2021.

https://doi.org/10.14245/ns.2244988.494
As displayed in Fig. 3D, the institutional co-authorship network map showed there was positive cooperation among leading institutions (minimum of 15 publications). To some extent, Chinese institutions preferred domestic partnerships, while European and American institutions preferred international collaboration. The top 10 most productive institutions were listed in Table 2, 7 from the United States, 2 from China, and 1 from Sweden. Harvard University contributed the most articles (84, 3.20%), followed by the University of California San Francisco (50, 1.90%), and Zhejiang University (45, 1.71%). Harvard University accounted for 87,92 citations with an H-index of 44 and a centrality of 0.21, which both ranked first among all involved institutions. In terms of the average number of citations, Karolinska institution ranked first (143.05), followed by Henry Ford
### Table 2. Top 10 most productive institutions in exosomes-related central nervous system research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Institution</th>
<th>Country/region</th>
<th>No. (%)</th>
<th>Citations</th>
<th>Average article citations</th>
<th>Centrality</th>
<th>H-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Harvard Univ</td>
<td>USA</td>
<td>84 (3.20)</td>
<td>8,792</td>
<td>104.67</td>
<td>0.21</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>Univ Calif San Francisco</td>
<td>USA</td>
<td>50 (1.90)</td>
<td>2,308</td>
<td>46.16</td>
<td>0.20</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>Zhejiang Univ</td>
<td>China</td>
<td>45 (1.71)</td>
<td>1,499</td>
<td>33.31</td>
<td>0.02</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>Univ Calif San Diego</td>
<td>USA</td>
<td>43 (1.64)</td>
<td>3,563</td>
<td>82.86</td>
<td>0.03</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>National Institute on Aging</td>
<td>USA</td>
<td>42 (1.60)</td>
<td>2,501</td>
<td>59.55</td>
<td>0.14</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>Karolinska Inst</td>
<td>Sweden</td>
<td>39 (1.48)</td>
<td>5,579</td>
<td>143.05</td>
<td>0.20</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>Cent South Univ</td>
<td>China</td>
<td>36 (1.37)</td>
<td>350</td>
<td>9.72</td>
<td>0.01</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Boston Univ</td>
<td>USA</td>
<td>33 (1.26)</td>
<td>2,594</td>
<td>78.61</td>
<td>0.10</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>Henry Ford Hosp</td>
<td>USA</td>
<td>33 (1.26)</td>
<td>4,708</td>
<td>142.67</td>
<td>0.01</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>Oakland Univ</td>
<td>USA</td>
<td>33 (1.26)</td>
<td>4,407</td>
<td>133.55</td>
<td>0.01</td>
<td>23</td>
</tr>
</tbody>
</table>

### Table 3. Top 10 most active funding agencies in exosomes-related central nervous system research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Funding agency</th>
<th>Country/region</th>
<th>No. (%)</th>
<th>H-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>National Institutes of Health</td>
<td>USA</td>
<td>596 (22.67)</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>National Natural Science Foundation of China</td>
<td>China</td>
<td>502 (19.09)</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>European Commission</td>
<td>European Union</td>
<td>197 (7.49)</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>National Institute of Neurological Disorders Stroke</td>
<td>USA</td>
<td>180 (6.85)</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>National Institute on Aging</td>
<td>USA</td>
<td>132 (5.02)</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>National Cancer Institute</td>
<td>USA</td>
<td>107 (4.07)</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>German Research Foundation</td>
<td>German</td>
<td>62 (2.36)</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>National Institute of Mental Health</td>
<td>USA</td>
<td>56 (2.13)</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>UK Research Innovation</td>
<td>UK</td>
<td>56 (2.13)</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>National Institute of General Medical Sciences</td>
<td>USA</td>
<td>51 (1.94)</td>
<td>28</td>
</tr>
</tbody>
</table>

**Fig. 4.** The visualization map of authors' co-authorship (A) and co-citation (B) involved in exosomes-related central nervous system research. In the visualization map of authors' co-authorship, the nodes' size represents the number of papers published by the author, and the thickness of the line between the nodes indicates the collaborative intensity between authors. In the visualization map of authors' co-citation, the size of the node represents the citation frequency, and the line between 2 nodes means that both were cited by 1 author.
Hospital (142.67), and Oakland University (133.55).

The top 10 most active funding sources were listed in Table 3, 6 from the United States, 3 from Europe, and 1 from China. The National Institutes of Health was the largest funding source for exosomes-related CNS research, which covered 596 studies (22.67%) with an H-index of 97. The National Natural Science Foundation of China ranked second (502 studies, 19.09%) with an H-index of 71, followed by the European Commission (197 studies, 7.49%) with an H-index of 50.

3. Authors and Co-cited Authors

A total of 14,468 authors contributed to the publications on exosomes-related CNS research, with 218 of these scholars publishing 5 or more articles. Thus, the co-authorship network map of prominent authors was drawn and shown in Fig. 4A. Every node represents an author, with larger nodes representing more published papers. Thicker lines indicate stronger collaboration between authors, and the different colors mean different clusters. It has been found that there was a relatively strong collaboration between authors in the same cluster. In contrast, association from dissimilar clusters was weak, implying that collaboration between different research teams should be strengthened.

The top 10 most productive authors and co-cited authors were displayed in Table 4. Kapogiannis D from National Institute on Aging had the most significant number of published articles (n = 38) and the highest H-index (n = 24), followed by Chopp M (33 publications, H-index of 23) from Henry Ford Hospital. Besides, Breakefield XO from Harvard Medical School ranked first in terms of total citations (n = 5,142) and the average number of citations (342.80 per paper), followed by Carter BS (4,796 total citations, 342.57 citations per paper) from Massachusetts General Hospital. Co-cited authors are the relationship of 2 or more authors cited simultaneously. As illustrated in Fig. 4B, Théry C from France occupied the center of the co-cited author network map with the highest citation frequency of 1,291 times, followed by Xin HQ (826 times) from China and Alvarez-Erviti L (643 times) from Spain.

4. Journals and Co-cited Journals

In our study, there was a total of 762 academic journals related to exosomes-related CNS research, of which 60 journals had more than 10 publications. Based on this, we drew the network visualization map (Fig. 5A), which showed a close collaboration among major journals. Besides, we have listed the top 10 journals with the most articles published in this field (Table 5). Switzerland had 5, the United Kingdom had 3, Netherlands and the United States had one each. All 10 journals were distributed in the Q1 or Q2 region according to the JCR in 2021. *International Journal of Molecular Sciences* published the most articles (n = 102) with total citations of 2,521 times, followed by *Scientific Reports* (n = 54) with total citations of 2,696 times, and *PLoS One* (n = 44) with total citations of 2,380 times. Notably, *Frontiers in Cellular Neuroscience* (64.18) had the largest average number of citations and *International Journal of Molecular Sciences* (n = 27) had the highest value of H-index, *Journal of Extracellular Vesicles* (17.337) ranked first in terms of IF.

Co-citation frequency is also an important indicator for measuring a journal’s impact, reflecting its importance in a particular area of research. The journal co-citation analysis was displayed in Fig. 5B, 89 journals were co-cited over 500 times. The

**Table 4. Top 10 most productive authors and co-cited authors in exosomes-related central nervous system research**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Author</th>
<th>Current Institution</th>
<th>Count</th>
<th>Total citations</th>
<th>Average article citations</th>
<th>H-index</th>
<th>Co-cited author</th>
<th>Country</th>
<th>Co-citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kapogiannis D</td>
<td>National Institute on Aging</td>
<td>38</td>
<td>2,360</td>
<td>62.11</td>
<td>24</td>
<td>Théry C</td>
<td>France</td>
<td>1,291</td>
</tr>
<tr>
<td>2</td>
<td>Chopp M</td>
<td>Henry Ford Hospital</td>
<td>33</td>
<td>4,306</td>
<td>130.48</td>
<td>23</td>
<td>Xin HQ</td>
<td>China</td>
<td>826</td>
</tr>
<tr>
<td>3</td>
<td>Goetzl EJ</td>
<td>University of California San Francisco</td>
<td>25</td>
<td>1,548</td>
<td>61.92</td>
<td>17</td>
<td>Alvarez-Erviti L</td>
<td>Spain</td>
<td>643</td>
</tr>
<tr>
<td>4</td>
<td>Mustapic M</td>
<td>National Institute on Aging</td>
<td>20</td>
<td>1,308</td>
<td>65.40</td>
<td>18</td>
<td>Goetzl EJ</td>
<td>USA</td>
<td>567</td>
</tr>
<tr>
<td>5</td>
<td>Zhang ZG</td>
<td>Humboldt University of Berlin</td>
<td>19</td>
<td>2,898</td>
<td>152.53</td>
<td>13</td>
<td>Raposo G</td>
<td>France</td>
<td>558</td>
</tr>
<tr>
<td>6</td>
<td>Hill AF</td>
<td>La Trobe University</td>
<td>18</td>
<td>2,226</td>
<td>123.67</td>
<td>10</td>
<td>Valadi H</td>
<td>Sweden</td>
<td>525</td>
</tr>
<tr>
<td>7</td>
<td>Breakefield XO</td>
<td>Harvard Medical School</td>
<td>15</td>
<td>5,142</td>
<td>342.80</td>
<td>13</td>
<td>Yuyama K</td>
<td>Japan</td>
<td>377</td>
</tr>
<tr>
<td>8</td>
<td>Ikezu T</td>
<td>Mayo Clinic Florida</td>
<td>15</td>
<td>1,255</td>
<td>83.67</td>
<td>8</td>
<td>Colombo M</td>
<td>Italy</td>
<td>367</td>
</tr>
<tr>
<td>9</td>
<td>Carter BS</td>
<td>Massachusetts General Hospital</td>
<td>14</td>
<td>4,796</td>
<td>342.57</td>
<td>13</td>
<td>Fruhbeis C</td>
<td>Germany</td>
<td>353</td>
</tr>
<tr>
<td>10</td>
<td>Zhang J</td>
<td>University of Washington</td>
<td>14</td>
<td>930</td>
<td>66.43</td>
<td>5</td>
<td>van Niel G</td>
<td>France</td>
<td>352</td>
</tr>
</tbody>
</table>
The dual-map overlay of journals reveals the distribution of relationships among journals, with the cited journals on the right and the citing journals on the left. The colored paths in the middle represent the citation relationships. As illustrated in Fig. 5C, there was only one main citation path in this study. It implied that the publications of exosomes-related CNS research were mainly focused on Molecular/Biology/Immunology.

Fig. 5. (A) The network visualization map of journals’ co-occurrence involved in exosomes-related central nervous system (CNS) research. (B) The network visualization map of journal co-citation analysis involved in exosomes-related CNS research. The size of the node represents the citation frequency, and the line between 2 nodes means that both were cited by 1 journal. (C) A dual-map overlay of journals involved in exosomes-related CNS research.

Table 5. Top 10 journals publishing the most articles in exosomes-related central nervous system research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Journal</th>
<th>Count</th>
<th>Country</th>
<th>Citations</th>
<th>Average article citations</th>
<th>H-index</th>
<th>IF (2021)</th>
<th>JCR (2021)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>International Journal of Molecular Sciences</td>
<td>102</td>
<td>Switzerland</td>
<td>2,521</td>
<td>24.72</td>
<td>27</td>
<td>6.208</td>
<td>Q1/Q2</td>
</tr>
<tr>
<td>2</td>
<td>Scientific Reports</td>
<td>54</td>
<td>UK</td>
<td>2,696</td>
<td>49.93</td>
<td>24</td>
<td>4.996</td>
<td>Q2</td>
</tr>
<tr>
<td>3</td>
<td>PLoS One</td>
<td>44</td>
<td>USA</td>
<td>2,380</td>
<td>54.09</td>
<td>26</td>
<td>3.752</td>
<td>Q2</td>
</tr>
<tr>
<td>4</td>
<td>Frontiers in Neuroscience</td>
<td>42</td>
<td>Switzerland</td>
<td>1,791</td>
<td>42.64</td>
<td>25</td>
<td>5.152</td>
<td>Q2</td>
</tr>
<tr>
<td>5</td>
<td>Cells</td>
<td>36</td>
<td>Switzerland</td>
<td>658</td>
<td>18.28</td>
<td>14</td>
<td>7.666</td>
<td>Q2</td>
</tr>
<tr>
<td>6</td>
<td>Frontiers in Cell and Developmental Biology</td>
<td>36</td>
<td>Switzerland</td>
<td>378</td>
<td>10.50</td>
<td>10</td>
<td>6.081</td>
<td>Q1/Q2</td>
</tr>
<tr>
<td>7</td>
<td>Journal of Extracellular Vesicles</td>
<td>32</td>
<td>UK</td>
<td>1,167</td>
<td>36.47</td>
<td>22</td>
<td>17.337</td>
<td>Q1</td>
</tr>
<tr>
<td>8</td>
<td>Stem Cell Research Therapy</td>
<td>32</td>
<td>UK</td>
<td>1,029</td>
<td>32.16</td>
<td>18</td>
<td>8.079</td>
<td>Q1</td>
</tr>
<tr>
<td>9</td>
<td>Journal of Alzheimer’s Disease</td>
<td>29</td>
<td>Netherlands</td>
<td>762</td>
<td>26.28</td>
<td>16</td>
<td>4.160</td>
<td>Q2</td>
</tr>
<tr>
<td>10</td>
<td>Frontiers in Cellular Neuroscience</td>
<td>28</td>
<td>Switzerland</td>
<td>1,797</td>
<td>64.18</td>
<td>19</td>
<td>6.147</td>
<td>Q1</td>
</tr>
</tbody>
</table>

IF, impact factor; JCR, Journal Citation Reports.
Table 6. Top 10 most cited references involved in exosomes-related central nervous system research

<table>
<thead>
<tr>
<th>Rank</th>
<th>First author</th>
<th>Title</th>
<th>Year</th>
<th>Source</th>
<th>Citations</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skog et al.</td>
<td>Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers</td>
<td>2008</td>
<td>Nature Cell Biology</td>
<td>3,342</td>
<td>Glioblastoma tumor-derived microvesicles may provide diagnostic information and aid in therapeutic decisions for cancer patients through a blood test.</td>
</tr>
<tr>
<td>2</td>
<td>Alvarez-Erviti et al.</td>
<td>Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes</td>
<td>2011</td>
<td>Nature Biotechnology</td>
<td>2,589</td>
<td>Exosomes-endogenous nano-vesicles can deliver siRNA to the brain in mice to induce the strong knockdown of BACE1, a therapeutic target in Alzheimer disease.</td>
</tr>
<tr>
<td>3</td>
<td>Hoshino et al.</td>
<td>Tumor exosome integrins determine organotropic metastasis</td>
<td>2015</td>
<td>Nature</td>
<td>2,536</td>
<td>Tumor-derived (brain, lung, liver) exosomes uptaken by organ-specific cells prepared the pre-metastatic niche, and exosomal integrins could be used to predict organ-specific metastasis.</td>
</tr>
<tr>
<td>4</td>
<td>van der Pol et al.</td>
<td>Classification, Functions, and Clinical Relevance of Extracellular Vesicles</td>
<td>2012</td>
<td>Pharmacological Reviews</td>
<td>1,077</td>
<td>Extracellular vesicles are likely to be a highly efficient, robust, and economic manner of exchanging information between cells, and they have a myriad of potential clinical applications, ranging from biomarkers to anticancer therapy.</td>
</tr>
<tr>
<td>5</td>
<td>Siravegna et al.</td>
<td>Integrating liquid biopsies into the management of cancer</td>
<td>2017</td>
<td>Nature Reviews Clinical Oncology</td>
<td>927</td>
<td>The molecular profiles gathered from ctDNA can be further complemented with those obtained through analysis of circulating tumor cells, as well as RNA, proteins, and lipids contained within exosomes.</td>
</tr>
<tr>
<td>6</td>
<td>Haney et al.</td>
<td>Exosomes as drug delivery vehicles for Parkinson's disease therapy</td>
<td>2015</td>
<td>Journal of Controlled Release</td>
<td>876</td>
<td>A new exosomal-based delivery system for a potent antioxidant, catalase, to treat Parkinson’s disease has been developed, and exosome-based catalase formulations have a potential to be a versatile strategy to treat inflammatory and neurodegenerative disorders</td>
</tr>
<tr>
<td>7</td>
<td>Rajendran et al.</td>
<td>Alzheimer's disease beta-amyloid peptides are released in association with exosomes</td>
<td>2006</td>
<td>Proceedings of The National Academy of Sciences of The United States of America</td>
<td>871</td>
<td>Exosomal proteins were found to accumulate in the plaques of Alzheimer disease patients’ brains, suggesting a role in the pathogenesis of Alzheimer's disease.</td>
</tr>
<tr>
<td>8</td>
<td>Zhang et al.</td>
<td>Treatment of Brain Inflammatory Diseases by Delivering Exosome Encapsulated Anti-inflammatory Drugs From the Nasal Region to the Brain</td>
<td>2011</td>
<td>Molecular Therapy</td>
<td>807</td>
<td>Intranasal administration led to rapid delivery of exosome encapsulated drug to the brain, and may provide a noninvasive and novel therapeutic approach for treating brain inflammatory-related diseases.</td>
</tr>
<tr>
<td>9</td>
<td>Asai et al.</td>
<td>Depletion of microglia and inhibition of exosome synthesis halt tau propagation</td>
<td>2015</td>
<td>Nature Neuroscience</td>
<td>773</td>
<td>Inhibition of exosome synthesis significantly reduced tau propagation in vitro and in vivo. Microglia and exosomes contribute to the progression of tauopathy, and the exosome secretion pathway may be a therapeutic target in Alzheimer disease.</td>
</tr>
</tbody>
</table>

siRNA, short interfering RNA; ctDNA, circulating tumor DNA; PTEN, phosphatase and tensin homolog.
gy journals, while the most cited papers were published in Molecular/Biology/Genetics journals (z = 9.38905, f = 33,428).

5. References, Co-cited References, and References Burst

The top 10 most cited exosomes-related articles in the CNS field were listed in Table 6. Nature and its subjournals had a substantial scientific impact on this field, with 6 of the top 10 highly cited papers published in these journals. All the top 10 references were cited more than 700 times. The study published in Nature Cell Biology by Skog J et al. in 2008 was the most cited article (3,342 times) in this field up to now.

Co-citation analysis aims to measure the degree of association between references in a specific field of research. We created a network map of the co-cited references with a total of more than 100 times by VOSviewer (Fig. 6A). In addition, the top 10 most co-cited articles were summarized in Table 7. The most co-cited reference was entitled “Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells,” which was published in Nature Cell Biology with a co-citation number of 523. Overall, these studies mainly focused on the characteristics and biological functions of exosomes and their diagnostic and therapeutic role in CNS diseases.

The references with the strongest citation bursts were explored by CiteSpace software, and the top 25 references were displayed in Fig. 6B. References with citation bursts first appeared in 2010, and the burst was attributed to a publication in 2009. Most of the references had citation bursts between 2012 and 2017. Notably, the study entitled “Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes,” which was published in Nature Biotechnology, was the strongest burst reference (2012–2016, strength 48.34). The latest reference with a citation burst emerged in 2019, and the burst is continuing.

6. Keywords Analysis of Research Hotspots

Through the analysis of keywords, including keywords co-occurrence and bursts, as well as keyword clustering and timeline view analysis, the research hotspots and scientific trends of exosomes-related studies in the CNS field have been revealed. As illustrated in Fig. 7A, after merging the keywords with similar meanings, a network visualization map of 90 keywords with occurrence more than 50 times has been summarized in Table 8.

Cluster analysis of the included keywords can demonstrate the knowledge structure of a particular field. The cluster network map of keywords was generated by CiteSpace software and was shown in Fig. 7B. There were 164 nodes and 540 links with a modularity Q of 0.8203 and a mean silhouette score of 0.9355. All the included keywords were classified into 13 clusters: Cluster #0 "Drug delivery" (LLR 110.93, 1.0E-4; Silhouette value 0.898), Cluster #1 "Biogenesis" (LLR 21.28, 1.0E-4; Silhouette value 0.900), Cluster #2 "Parkinson’s disease" (LLR 67.47, 1.0E-4; Silhouette value 0.979), Cluster #3 "Exosomes" (LLR 70.8, 1.0E-4; Silhouette value 0.988), Cluster #4 "Cerebrospinal fluid" (LLR 48.91, 1.0E-4; Silhouette value 0.889), Cluster #5 "Bionarker" (LLR 60.29, 1.0E-4; Silhouette value 0.949), Cluster #6 "Alzheimer’s disease" (LLR 123.69, 1.0E-4; Silhouette value 1.000), Cluster #7 "Extracellular vesicles" (LLR 72.68, 1.0E-4; Silhouette value 0.914), Cluster #8 "Functional recovery" (LLR 94.05, 1.0E-4; Silhouette value 1.000).
### Table 7. Top 10 most co-cited references involved in exosomes-related central nervous system research

<table>
<thead>
<tr>
<th>Rank</th>
<th>First author</th>
<th>Title</th>
<th>Year</th>
<th>Source</th>
<th>Citations</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Valadi et al.</td>
<td>Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells</td>
<td>2007</td>
<td>Nature cell biology</td>
<td>523</td>
<td>Exosomes contain both mRNA and microRNA, which can be delivered to another cell, and can be functional in this new location. They propose that this RNA is called “exosomal shuttle RNA.”</td>
</tr>
<tr>
<td>2</td>
<td>Alvarez-Erviti et al.</td>
<td>Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes</td>
<td>2011</td>
<td>Nature Biotechnology</td>
<td>510</td>
<td>Exosomes-endogenous nano-vesicles can deliver siRNA to the brain in mice to induce the strong knockdown of BACE1, a therapeutic target in Alzheimer’s disease.</td>
</tr>
<tr>
<td>3</td>
<td>Raposo and Stoorvogel</td>
<td>Extracellular vesicles: Exosomes, microvesicles, and friends</td>
<td>2013</td>
<td>Journal of Cell Biology</td>
<td>366</td>
<td>In this review, they focused on the characterization of extracellular vesicles and on currently proposed mechanisms for their formation, targeting, and function.</td>
</tr>
<tr>
<td>4</td>
<td>Skog et al.</td>
<td>Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers</td>
<td>2008</td>
<td>Nature Cell Biology</td>
<td>340</td>
<td>Glioblastoma tumor-derived microvesicles may provide diagnostic information and aid in therapeutic decisions for cancer patients through a blood test.</td>
</tr>
<tr>
<td>5</td>
<td>Théry et al.</td>
<td>Isolation and characterization of exosomes from cell culture supernatants and biological fluids</td>
<td>2006</td>
<td>Current Protocols in Cell Biology Chapter 3</td>
<td>317</td>
<td>This study described different approaches for exosome purification from various sources, and discussed methods to evaluate the purity and homogeneity of the purified exosome preparations.</td>
</tr>
<tr>
<td>6</td>
<td>Théry et al.</td>
<td>Exosomes: Composition, biogenesis and function</td>
<td>2002</td>
<td>Nature Reviews Immunology</td>
<td>299</td>
<td>This study described the physical properties that define exosomes as a specific population of secreted vesicles, and summarized their biological effects, particularly on the immune system, and discussed the potential roles that secreted vesicles could have as intercellular messengers.</td>
</tr>
<tr>
<td>7</td>
<td>Colombo et al.</td>
<td>Biogenesis, Secretion, and Intercellular Interactions of Exosomes and Other Extracellular Vesicles</td>
<td>2014</td>
<td>Annual Review of Cell and Developmental Biology</td>
<td>284</td>
<td>This review focused on the definition of exosomes and other secreted extracellular vesicles. Their biogenesis, their secretion, and their subsequent fate were also discussed.</td>
</tr>
<tr>
<td>8</td>
<td>Rajendran et al.</td>
<td>Alzheimer’s disease beta-amyloid peptides are released in association with exosomes</td>
<td>2006</td>
<td>Proceedings of the National Academy of Sciences of the United States of America</td>
<td>270</td>
<td>Exosomal proteins were found to accumulate in the plaques of Alzheimer’s disease patients’ brains, suggesting a role in the pathogenesis of Alzheimer’s disease.</td>
</tr>
<tr>
<td>9</td>
<td>Zhuang et al.</td>
<td>Treatment of Brain Inflammatory Diseases by Delivering Exosome Encapsulated Anti-inflammatory Drugs From the Nasal Region to the Brain</td>
<td>2011</td>
<td>Molecular Therapy</td>
<td>270</td>
<td>Intransal administration led to rapid delivery of exosome encapsulated drug to the brain, and may provide a noninvasive and novel therapeutic approach for treating brain inflammatory-related diseases.</td>
</tr>
<tr>
<td>10</td>
<td>Théry et al.</td>
<td>Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines</td>
<td>2018</td>
<td>Journal of Extracellular Vesicles</td>
<td>237</td>
<td>The MISEV2018 guidelines included tables and outlines of suggested protocols and steps to follow to document specific EV-associated functional activities. Besides, a checklist was provided with summaries of key points.</td>
</tr>
</tbody>
</table>
Bibliometrics Analysis of Exosomes in CNS Research

Zhuo Y., et al.

https://doi.org/10.14245/ns.2244988.494

Top 25 Keywords with the Strongest Citation Bursts

<table>
<thead>
<tr>
<th>Keywords</th>
<th>Year Strength-Begin End</th>
<th>2001 - 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenchymal stem cells</td>
<td>2001 1.10.2009 2016</td>
<td>1.10.2009</td>
</tr>
</tbody>
</table>

Table 8. Top 12 keywords involved in exosomes-related central nervous system research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Keywords</th>
<th>Occurrences</th>
<th>Centrality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exosomes</td>
<td>1,794</td>
<td>0.58</td>
</tr>
<tr>
<td>2</td>
<td>Extracellular vesicles</td>
<td>978</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>Brain</td>
<td>469</td>
<td>0.64</td>
</tr>
<tr>
<td>4</td>
<td>miRNA</td>
<td>445</td>
<td>0.15</td>
</tr>
<tr>
<td>5</td>
<td>Biomarker</td>
<td>407</td>
<td>0.10</td>
</tr>
<tr>
<td>6</td>
<td>Alzheimer's disease</td>
<td>384</td>
<td>0.61</td>
</tr>
<tr>
<td>7</td>
<td>Expression</td>
<td>366</td>
<td>0.24</td>
</tr>
<tr>
<td>8</td>
<td>Microvesicles</td>
<td>306</td>
<td>0.26</td>
</tr>
<tr>
<td>9</td>
<td>Cerebrospinal fluid</td>
<td>268</td>
<td>0.64</td>
</tr>
<tr>
<td>10</td>
<td>Cells</td>
<td>263</td>
<td>0.72</td>
</tr>
<tr>
<td>11</td>
<td>Mesenchymal stem cells</td>
<td>226</td>
<td>0.62</td>
</tr>
<tr>
<td>12</td>
<td>Blood-brain barrier</td>
<td>221</td>
<td>0.28</td>
</tr>
</tbody>
</table>

28.96, 1.0E-4; Silhouette value 0.912), Cluster #9 “Mesenchymal stem cells” (LLR 64.94, 1.0E-4; Silhouette value 1.000), Cluster #10 “Spinal cord injury” (LLR 105.27, 1.0E-4; Silhouette value 0.897), Cluster #11 “Tumor growth” (LLR 32.05, 1.0E-4; Silhouette value 0.987), Cluster #12 “miRNA” (LLR 19.47, 1.0E-4; Silhouette value 1.000). On this basis, in order to clarify the relationship between exosomes and CNS research, we grouped these clusters into 5 categories in accordance with the commonality of research hotspots, which were listed in Table 9. The timeline view, designed based on the mutations and interactions among keywords, can be used to explore the stage characteristics and evolutionary track in exosomes-related CNS research. As shown in Fig. 7C, from 2005 to 2007, CNS research related to exosomes was still in its infancy. From 2008 to 2016, research in this field significantly increased, and more attention was paid to the characteristics of exosomes, and their intracellular and extracellular functions, leading to a profound impact on later research. From 2017 to 2021, deep mechanism research accelerated, and the topic scope was broadened. The trends in research have gradually shifted from experimental studies to clinical treatments.

The keywords with the strongest citation bursts were dis-
played in Fig. 7D, aiming to reflect research frontiers and developing trends. The strongest burst keyword was "multivesicular body (2006–2016, strength 13.74)". The citation bursts time of keywords "survival", "contribute", and "diagnosis" has continued from 2019 to 2021.

DISCUSSION

1. General Information

The presence of exosomes was proved by Johnstone et al. more than 4 decades ago. However, exosomes were initially thought to be waste products excreted by cells and did not receive much attention from researchers. In the field of CNS, Fauré et al. first described the release of exosomes by cortical neurons in vitro. Recently, exosomes have been found to be a novel form of information exchange between cells. Communication among cells in the CNS includes intercellular and extracellular interactions. Specifically, intracellular interactions act via ions, while extracellular interactions are mainly composed of wiring transmission and volume transmission. Synapses are the primary vehicle for wiring transmission, while exosomes and transmitters appear to play a critical role in volume transmission. Therefore, the contribution of exosomes under physiological or pathological conditions in the CNS has become a research hotspot and has shown great promise.

2. Detailed Information

Bibliometrics and visualization analysis can be employed to characterize the current situation and forecast future research trends in an area of research. Our study revealed that there has been a marked increase in the number of publications and the quality of studies from the perspective of exosomes-related CNS research during the past 2 decades. Combining the results of Figs. 2 and 7C, the period between 2001 and 2007 can be characterized as the embryonic stage of exosomes-related CNS research due to its relatively small number of publications and citations, as well as low output of high-impact keywords; the period between 2008 and 2016 can be regarded as the steady growth stage, which produced a lot of high-quality research and laid the necessary groundwork for future directions; the period between 2017 and 2021 can be described as high growth stage, the number of relevant studies focusing on various hotspots from different perspectives increased significantly. Predictably, the topic of exosomes is likely to remain a research hotspot in the CNS field in the future.

From the results of Fig. 3A-D and Tables 1-3, European and American countries, as well as China, were the main participants, with many academic institutions, funding agencies, and scholars making essential contributions to exosomes-related CNS research. In more detail, the United States was undoubtedly the leader in this field, with the largest number of publications and citations, as well as the highest impact. This was in
large part because the United States had the largest number of academic institutions involved and the most significant amount of funding in this field. Comparatively, China also had a vast number of publications and the second-highest ranking of participating institutions and funding agencies. However, the number of average article citations in China was the lowest among the top 10 productive countries. Besides, the centrality of both China and Chinese institutions was relatively below average. It is reasonable to suggest that the impact and quality of related research in China must be improved. Considering the late start of China, and the noninclusion of many Chinese studies not written in English, China has much more potential in this field of research to some extent. Besides, active international collaboration is particularly crucial for all countries and regions.

In our study, Harvard University was the top research institution in this field, with the highest value of H-index and centrality. Scholars interested in exosomes-related CNS research may cooperate with this institution. From the results of Fig. 4A-B, and Table 4, the top 4 most prolific authors were all from United States institutions, indicating that these scholars and their teams have been at the forefront of the research and were most likely to achieve breakthrough outcomes. Théry was the only one to have been co-cited more than 1,000 times. The main contributions of Théry were listed as follows: (1) Describing different approaches for the isolation and purification of exosomes from various sources; (2) Explaining the composition, biogenesis, and function of exosomes; (3) Publishing a position statement of the International Society for Extracellular Vesicles and updating the MISEV2014 guidelines as a critical participant. Notably, Goetzl EJ ranked in the top 4 in both the number of publications and co-citation frequency, suggesting that Goetzl et al. were leading in exosomes-related CNS research with significant quantity and quality. His main achievements focused on the role of exosomes derived from various sources in neurodegenerative disorders, especially Alzheimer disease.

The journal analysis in our study was shown in Fig. 5A-B, and Table 5. All the high-quality journals came from developed countries. It was evident that the journal with the most publications in this field is the International Journal of Molecular Sciences, while Proceedings of the National Academy of Sciences of the United States of America ranked first in co-citations. Thus, these journals had a considerable impact, and more attention should be paid to the research published on them. As shown in Fig. 5C, only one main citation path was available in this study, suggesting that multidisciplinary cooperation is badly needed in exosomes-related CNS research in the future.

The reference analysis can help identify core literature and thereby better understand the developmental history and scientific frontier in exosomes-related CNS research. From the results of Fig. 6A, and Tables 6-7, the most cited study in this field was published in Nature Cell Biology and was also listed as the third most co-cited paper. It mainly introduced glioblastoma-derived microvesicles that delivered genetic information (i.e., RNA) and proteins to recipient cells, promoting tumor growth and providing diagnostic biomarkers. This work not only provided strong evidence of the involvement of tumor cell-derived exosomes in disease pathology but also revealed that the cargo of exosomes could assist in the diagnosis. Besides, Alvarez-Erviti et al., published in Nature Biotechnology in 2011, ranked second in terms of citation and co-citation frequency, demonstrating the therapeutic potential of exosomes-mediated siRNA delivery in the treatment of Alzheimer disease (AD). Similarly, Rajendran et al., published in 2006, both ranked in the top 10 in terms of citation and co-citation frequency, which suggested the critical role of exosomes in the pathogenesis of AD. Remarkably, Théry contributed 3 of the top 10 most highly co-cited references, which was the main reason why he was listed as the most highly co-cited author.

References burst refers to research that is frequently cited over a certain time period. As seen in Fig. 6B, most of the references with citation bursts appeared between 2012 and 2017, which was generally in line with the steady growth stage of exosomes-related CNS research summarized above. The first burst reference was published in 2009 by Théry et al., which focused on the role of exosomes in the communication between immune cells and tumor cells. It is worth noting that there are 5 references still in burstness, showing that this topic has gained sustained interest in recent years.

The keywords analysis can be used to identify the current direction of exosomes-related CNS research. As displayed in Fig. 7B, 13 clusters were generated after cluster analysis of the included keywords. As listed in Table 9, these clusters were divided into 5 categories based on the commonality of research hotspots.

(I) Cluster #0 "Drug delivery" mainly reflected the role of exosomes as drug delivery carriers in treating CNS diseases. It is well-known that the BBB excludes almost 100% of large-molecule therapeutic drugs and at least 98% of small-molecule drugs from the brain. However, exosomes can cross BBB with the advantage of nano-size, low immunogenicity, and homing capacity. It has been found that exosomes can steadily transport their cargo to target cells due to the structure of mem-

https://doi.org/10.14245/ns.2244988.494
brane-enclosed vesicles for therapeutic purposes. Yang et al. have discovered that anticancer drugs delivered by brain cell-derived exosomes across the BBB significantly reduced the number of markers of tumor growth and transplanted cancer cells. Thus, exosomes have been considered natural carriers for the delivery of therapeutic molecules.

(II) Cluster #1 "Biogenesis" and Cluster #9 "Mesenchymal stem cells" mainly reflected the sources of exosomes. The nomenclature of mesenchymal stem cells (MSCs) was formalized by Caplan in the 1990s. Nowadays, MSC-exosomes have gained great attention because of their regenerative and immunomodulatory functions. In addition, exosomes can be released by almost all cells in the body, exosomes derived from dissimilar sources have different biological functions and characteristics depending on their origin. For instance, Hoshino et al. found that the lung, liver, and brain-tropic tumor cell-derived exosomes can fuse preferentially with resident cells at their predicted destination.

(III) Cluster #2 "Parkinson’s disease", Cluster #6 "Alzheimer’s disease", Cluster #8 "Functional recovery", Cluster #10 "Spinal cord injury", and Cluster #11 "Tumor growth" mainly represented several CNS diseases that were closely related to exosomes research. Evidence from the other studies also supported our findings, exosomes have played an essential role in the research of Parkinson disease, AD, functional recovery after stroke, spinal cord injury, and tumor growth.

(IV) Cluster #3 "Exosomes" and Cluster #7 "Extracellular vesicles" mainly discussed the definition and classification of exosomes. Currently, vesicular bodies with a bilayer membrane structure secreted from cells or separated from the cell membrane are collectively defined as extracellular vesicles (EVs). In fact, EVs can be categorized as microvesicles (200–1,000 nm), exosomes (40–100 nm), and apoptotic bodies (0.5–3.0 μm) depending on their size. However, exosomes as a subtype of EVs are by far the most widely researched, and the term EVs is used to refer just to exosomes in some articles.

(V) Cluster #4 "Cerebrospinal fluid", Cluster #5 "Biomarker", and Cluster #12 "miRNA" mainly embodied the role of exosomes in the diagnosis of CNS diseases. Early diagnosis of CNS disorders has long been a challenge, it has been demonstrated that exosomes from CNS can be identified in peripheral body fluids and cerebrospinal fluid, and their cargo changes with disease. As exosomes can cross the BBB in highly stable conditions, it has an attractive prospect to choose exosomes to monitor disease progression and enable early diagnosis of CNS diseases. Lai et al. suggested miR-193b-3p was differentially expressed in the plasma exosomes of the patients with subarachnoid hemorrhage (SAH), then they found exosomes/miR-193b-3p treatment alleviated neurobehavioral impairments and neuroinflammation following SAH. Therefore, exosomal miRNAs are involved in the occurrence and development of various CNS diseases, playing a vital role in the early diagnosis and targeted therapy in this field.

The keywords burst analysis in Fig. 7D showed that “multivesicular body” was the keyword with the strongest citation bursts. Exosomes are produced within multivesicular bodies and released into the extracellular space by a merging of the multivesicular body with the plasma membrane. Notably, the time period for the citation burst of “survival,” “contribute,” and “diagnosis” has lasted from 2019 to 2021, implying the diagnostic and therapeutic roles of exosomes in CNS disease have the potential to become significant research hotspots in the future.

3. Summary

Exosomes are vesicles released by multiple cells, and containing various biological materials such as lipids, metabolites, proteins, and nucleic acids. Exosomes are involved in a wide range of physiological and pathological processes in the CNS, including propagation of neuroinflammation, synaptic plasticity, neuroprotection, regulation of neuronal firing, and so on. In summary, there are 3 main aspects of exosomes-related CNS research. The first aspect concerns the methodology for the isolation and identification of exosomes, and their biological characteristics in the CNS. The second aspect concerns the potential of exosomes as diagnostic and prognostic biomarkers for CNS diseases, mainly including brain tumor, neurodegenerative disease, cerebrovascular disease, and spinal cord injury. The last aspect is about the application of exosomes as drug delivery carriers loaded with specific agents in the CNS, among which the delivery of siRNA and miRNA has received more attention. The most common method of loading is electroporation.

In fact, the 3 aspects mentioned above interact with each other and deepen gradually, reflecting the shift in focus of exosomes-related CNS research from experimental studies to clinical application. Nowadays, with the further development of experimental techniques, more attention has been paid to biological tissue-derived exosomes and engineered exosomes. Therefore, it is reasonable to assume that the clinical application of these techniques in CNS diseases will be hotspots in future research.
4. Strengths and Limitations
The literature on exosomes-related CNS research evaluated in our study was obtained from the WosCC database, which was the most utilized database in the bibliometric analysis and the most exhaustive collection of high-quality medical research. As far as we know, it is the first-ever bibliometric study to provide a systematic analysis of exosomes-related CNS research combined with visualized mapping. Despite our efforts to ensure the objectivity and rigor of our data analysis, several limitations do exist. First, owing to the lack of English abstracts or references in most non-English articles, the included studies were limited to publications written in English from the WosCC database. Thus, some critical studies published in other languages or from other databases such as PubMed, Scopus, and Google Scholar might have been missed. Second, this bibliometric analysis mainly focused on global scientific research and was not adjusted for social reality, such as population size, economic conditions, and other factors, which may lead to differences between actual research conditions and bibliometric results. Third, as the data in 2022 is constantly being updated, the studies published in 2022 were excluded because of the incompleteness. It may result in missing out on the latest research findings. However, we believe our study has covered the vast majority of publications in the field since 2001, and the conclusion would not be changed even with the additional small amount of updated data.

CONCLUSION
Since 2001, exosomes-related CNS research has continuously advanced qualitatively and quantitatively, it is currently in a stage of high growth. China has made significant progress, while the United States and Europe are dominating in this field. Global cooperation among countries and institutions is necessary and beneficial. Currently, exosomes-related CNS research mainly focuses on the sources and biological functions of exosomes and their promising role in diagnosing and treating CNS diseases. The topic of biogenesis, biomarker, and drug delivery will serve as hotspots in future research. Moreover, the clinical translation of the results from exosomes-related CNS research will be of great importance. These findings will assist scholars in keeping abreast of trends in exosomes-related CNS research.

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

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Author Contribution: Conceptualization: YZ, KA, HZ; Data curation: JP, JX, GZ, ZJ, RZ; Formal analysis: YZ, KH, BW; Funding acquisition: HZ, YZ; Methodology: YZ, KA, HZ; Project administration: HZ; Visualization: YZ, BW; Writing - original draft: YZ; Writing - review & editing: YZ.

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36. Johnstone RM, Bianchini A, Teng K. Reticulocyte matura-


Incidence, Risk Factors, and Management of Postoperative Hematoma Following Anterior Cervical Decompression and Fusion for Degenerative Cervical Diseases

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Objective: Studies discussed few risk factors for specific patients, such as duration of disease; or surgical factors, such as duration and time of surgery; or C3 or C7 involvement, which could have led to the formation of hematomas (HTs). To investigate the incidence, risk factors especially the factors mentioned above, and management of postoperative HTs following anterior cervical decompression and fusion (ACF) for degenerative cervical diseases.

Methods: Medical records of 1,150 patients who underwent ACF for degenerative cervical diseases at our hospital between 2013 and 2019 were identified and reviewed. Patients were categorized into the HT group (HT group) or normal group (no-HT group). Demographic, surgical and radiographic data were recorded prospectively to identify risk factors for HT.

Results: Postoperative HT was identified in 11 patients, with an incidence rate of 1.0% (11 of 1,150). HT occurred within 24 hours postoperatively in 5 patients (45.5%), while it occurred at an average of 4 days postoperatively in 6 patients (54.5%). Eight patients (72.7%) underwent HT evacuation; all patients were successfully treated and discharged. Smoking history (odds ratio [OR], 5.193; 95% confidence interval [CI], 1.058–25.493; p = 0.042), preoperative thrombin time (TT) value (OR, 1.643; 95% CI, 1.104–2.446; p = 0.014) and antiplatelet therapy (OR, 15.070; 95% CI, 2.663–85.274; p = 0.002) were independent risk factors for HT. Patients with postoperative HT had longer days of first-degree/intensive nursing (p < 0.001) and greater hospitalization costs (p = 0.038).

Conclusion: Smoking history, preoperative TT value and antiplatelet therapy were independent risk factors for postoperative HT following ACF. High-risk patients should be closely monitored through the perioperative period. Postoperative HT in ACF was associated with longer days of first-degree/intensive nursing and more hospitalization costs.

Keywords: Anterior cervical discectomy and fusion, Anterior cervical corpectomy and fusion, Risk factors, Postoperative hematoma, Reoperation

INTRODUCTION

Anterior cervical decompression and fusion (ACF) has been widely adopted by orthopedic surgeons and regarded as the classical gold standard for anterior cervical surgery.¹–⁶ These procedures often achieve very good surgical results with relatively low rates of associated complications.⁷–⁸ Postoperative hematoma (HT) is a rare complication after ACF that can lead to acute airway obstruction (AAO), paralysis and even life-threatening conditions. Therefore, postoperative HTs must be quickly iden-
tified, and effective action should be undertaken to prevent catastrophic consequences. Some large studies have shown that the incidence of postoperative HT ranges from 0.4% to 5.6%.\textsuperscript{9,18} The reported incidence of AAO caused by HT ranges from 0.2 to 1.9%.\textsuperscript{18}

Because the potential consequences of this complication are so severe, early detection and systematic evaluation of risk factors for HT are essential. If independent risk factors for HT can be identified, surgeons can explain the harm of postoperative HT and the necessity of intratracheal intubation to specific patients before surgery, undertake preventative measures during surgery to prevent the occurrence of postoperative HT, and then particular patients who might undergo close monitoring and intensive care could be identified after surgery. Therefore, identifying risk factors for HT is critical for both patients and clinicians.

Although there is considerable experience with ACF in the literature, these studies discussed few risk factors for specific patients, such as duration of disease; or surgical factors, such as duration and time of surgery; or C3 or C7 involvement, which could have led to the formation of HT. A total of 1,150 patients who underwent ACF for degenerative cervical diseases at our institution were identified and reviewed to investigate the incidence, risk factors, and management of postoperative HT following ACF.

**MATERIALS AND METHODS**

1. **Study Population**

This study was performed in the General Hospital of Northern Theater Command, a tertiary hospital in northeastern China. After obtaining approval from the Ethics Board of General Hospital of Northern Theater Command, we retrospectively reviewed the medical records of patients who underwent ACF for cervical diseases. Informed consent was waived by the Ethics Board of General Hospital of Northern Theater Command because this study was a retrospective, observational study and all of the data were anonymously collected and analyzed.

Medical records of 1,237 patients who underwent ACF at our hospital between January 2013 and December 2019 were identified and reviewed. The inclusion criteria included the following: (1) patients who underwent ACF for cervical diseases and operations performed by one senior surgeon (LX); and (2) hospitalization between January 2013 and December 2019. The exclusion criteria were: (1) patients who underwent surgery for cervical diseases, such as infection, tumor and fracture; (2) patients who also underwent thoracic or lumbar spine surgery or other unrelated procedures; and (3) patients with incomplete data. A total of 1,150 patients were ultimately included in the study (Fig. 1). Patients were categorized into the HT group or no-HT group. The definition of postoperative HT following ACF in the current study was symptomatic postoperative HT manifested as respiratory distress, neurological injury, dysphagia and other symptoms of HT which was confirmed by magnetic resonance imaging (MRI), color Doppler ultrasound or surgical evacuation. Negative pressure drainage devices (Benos Medical Device Co., LTD, Shandong, China) were used in each case in the current study throughout the study period and were generally removed 2–3 days after surgery.

2. **Preoperative Evaluation**

Demographic data, such as age, sex, smoking history, body mass index (BMI), duration of disease, American Society of Anesthesiologists (ASA) physical status (PS) classification, preoperative hemoglobin (Hb), hematocrit, thrombocytocrit, preoperative prothrombin time, international normalized ratio, thrombin time (TT), activated partial thromboplastin time, fibrinogen, and major medical comorbidities, such as diabetes, hypertension, pulmonary, and heart disease (arrhythmia and coronary heart disease), were recorded and analyzed. Anticoagulant therapy meant a history of using low-molecular weight heparin and low-molecular weight heparin should be stopped 24 hours before the operation. Antiplatelet therapy meant a his-
tory of taking aspirin and aspirin should be stopped a week before the operation. Preoperative/postoperative systolic/diastolic pressures were recorded. We used computed tomography (CT) to determine the presence of ossification of the posterior longitudinal ligament (OPLL) at the surgical level.

3. Surgical Indicators

Surgical indicators, such as the number of discs and corpectomy involved, the duration and time of surgery, such as morning (08:00–11:00), noon (11:00–13:00), and afternoon (13:00–), C3 or C7 involvement, intraoperative blood loss (IBL), postoperative drainage (PB), blood transfusion (BT), length of stay, and hospitalization costs, were recorded and analyzed.

4. Postoperative Complications

The outcome for this study was postoperative complications during hospitalization. The following events were defined as complications: postoperative dyspnoea, cerebrospinal fluid leakage, postoperative HT, poor wound healing, postoperative hypokalemia, postoperative atrial fibrillation, postoperative neurological deterioration, deep venous thrombosis, surgical site infection, pneumonia, urinary tract infection, and bacteremia. All deaths were also considered postoperative complications.

5. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). For counting data, the chi-square test or Fisher exact probability test was used. For measurement data, the Shapiro-Wilk method was used for the normality test, and Student t-test and the Mann-Whitney rank-sum test were used for comparisons. We selected the factors which suggested as risk factors for postoperative HT in previous studies and factors such as duration of disease, surgical factors (duration and time of surgery) and C3 or C7 involvement.

Fig. 2. A 66-year-old man developed postoperative hematoma after C6 anterior cervical corpectomy and fusion (case No. 11). (A, B) Preoperative radiography findings (x-ray and computed tomography) showed a hyperplastic osteophyte at the edge of the vertebral body, which resulted in spinal stenosis. (C-E) Preoperative magnetic resonance imaging (MRI) findings showed spinal stenosis. (F-I) Muscle strength of the patient weakened 2 hours after the operation, emergency MRI was performed. Postoperative MRI findings showed an epidural hematoma, and then muscle strength returned to normal after MRI examination, so the patient received conservative treatment including close observation, detumescence and steroids, and then the patient could walk normally 3 days after operation. (J) Postoperative x-ray showed the good position of internal fixation.
Table 1. Patients who developed postoperative hematomas

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>BMI (kg/m²)</th>
<th>Smoking</th>
<th>OPLL</th>
<th>Procedure</th>
<th>Time to HT</th>
<th>Clinical manifestations</th>
<th>Treatment</th>
<th>Location of injured vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>M</td>
<td>21.2</td>
<td>Yes</td>
<td>No</td>
<td>C5/6 ACDF</td>
<td>3 Day</td>
<td>Respiratory distress after POD</td>
<td>Hematoma evacuation</td>
<td>Internal opening of drainage tube</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>M</td>
<td>21.5</td>
<td>Yes</td>
<td>No</td>
<td>C3/4 ACDF</td>
<td>41 Hr</td>
<td>Respiratory distress with DIP</td>
<td>Hematoma evacuation</td>
<td>Lateral wall muscles</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>M</td>
<td>28.3</td>
<td>Yes</td>
<td>No</td>
<td>C4/5 ACDF, C6 ACCF</td>
<td>2 Hr</td>
<td>Respiratory distress with DIP after a bad cough</td>
<td>Hematoma evacuation</td>
<td>Longus cervicalis</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>M</td>
<td>26.0</td>
<td>Yes</td>
<td>No</td>
<td>C4/5 ACDF</td>
<td>5 Day</td>
<td>Swelling, dysphagia and blood oozing from the incision after POD</td>
<td>Conservative treatment</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>M</td>
<td>28.4</td>
<td>Yes</td>
<td>Yes</td>
<td>C5 ACCF</td>
<td>10 Hr</td>
<td>Respiratory distress with DIP</td>
<td>Hematoma evacuation</td>
<td>Internal opening of drainage tube</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>M</td>
<td>20.2</td>
<td>Yes</td>
<td>No</td>
<td>C4/5 ACDF, C6 ACCF</td>
<td>4 Day</td>
<td>Swelling, dysphagia and blood oozing from the incision after POD</td>
<td>Conservative treatment</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>M</td>
<td>21.8</td>
<td>Yes</td>
<td>No</td>
<td>C5/6 ACDF</td>
<td>10 Hr</td>
<td>Respiratory distress with DIP</td>
<td>Hematoma evacuation</td>
<td>Lateral wall muscles</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>M</td>
<td>22.9</td>
<td>Yes</td>
<td>No</td>
<td>C5 ACCF</td>
<td>44 Hr</td>
<td>Respiratory distress with DIP</td>
<td>Hematoma evacuation</td>
<td>Lateral wall muscles</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>M</td>
<td>24.8</td>
<td>No</td>
<td>Yes</td>
<td>C3/4 ACDF, C5 ACCF</td>
<td>5 Day</td>
<td>Respiratory distress after POD</td>
<td>Hematoma evacuation</td>
<td>Internal opening of drainage tube</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>M</td>
<td>26.0</td>
<td>No</td>
<td>No</td>
<td>C4/5 ACDF, C6 ACCF</td>
<td>18 Hr</td>
<td>Respiratory distress with DIP</td>
<td>Hematoma evacuation</td>
<td>Longus cervicalis</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>M</td>
<td>22.8</td>
<td>Yes</td>
<td>No</td>
<td>C6 ACCF</td>
<td>2 Hr</td>
<td>Muscle strength weakened temporarily</td>
<td>Conservative treatment</td>
<td>-</td>
</tr>
</tbody>
</table>

BMI, body mass index; OPLL, ossification of the posterior longitudinal ligament; HT, hematoma; ACDF, anterior cervical discectomy and fusion; ACCF, anterior cervical corpectomy and fusion; POD, pulling out drainage; DIP, drain in place.
Table 2. Demographic characteristics of all patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with IBL</th>
<th>No hematoma (n = 1,139)</th>
<th>χ²/z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>732</td>
<td>-</td>
<td>0.010†</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>407</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51.4 ± 9.5</td>
<td>53.8 ± 10.6</td>
<td>-0.842</td>
<td>0.400</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>9 (81.8)</td>
<td>773 (67.9)</td>
<td>-</td>
<td>0.518†</td>
</tr>
<tr>
<td>≥ 60</td>
<td>2 (18.2)</td>
<td>366 (32.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 2.9</td>
<td>24.5 ± 3.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>7 (63.6)</td>
<td>674 (59.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>25–30</td>
<td>4 (36.4)</td>
<td>407 (35.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>0 (0)</td>
<td>58 (5.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
<td></td>
<td>-0.538</td>
<td>0.590</td>
</tr>
<tr>
<td>&lt; 3 Months</td>
<td>5 (45.5)</td>
<td>481 (42.2)</td>
<td>-</td>
<td>&gt; 0.999†</td>
</tr>
<tr>
<td>3 Months–1 year</td>
<td>3 (27.3)</td>
<td>279 (24.5)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1 Year–5 years</td>
<td>3 (27.3)</td>
<td>267 (23.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 Years</td>
<td>0</td>
<td>112 (9.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ASA PS classification grade</td>
<td>1.6 ± 0.7</td>
<td>1.5 ± 0.6</td>
<td>0.834</td>
<td>0.404</td>
</tr>
<tr>
<td>I–II</td>
<td>10 (90.9)</td>
<td>1066 (93.6)</td>
<td>-</td>
<td>0.520†</td>
</tr>
<tr>
<td>III–IV</td>
<td>1 (9.1)</td>
<td>73 (6.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Trauma history</td>
<td>1 (9.1)</td>
<td>292 (25.6)</td>
<td>-</td>
<td>0.307†</td>
</tr>
<tr>
<td>Smoking history</td>
<td>9 (81.8)</td>
<td>459 (40.3)</td>
<td>-</td>
<td>0.010†</td>
</tr>
<tr>
<td>Preoperative blood index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>149.1 ± 16.3</td>
<td>139.7 ± 15.3</td>
<td>1.745</td>
<td>0.081</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>41.1 ± 14.3</td>
<td>41.6 ± 4.6</td>
<td>1.535</td>
<td>0.125</td>
</tr>
<tr>
<td>PCT (%)</td>
<td>0.19 ± 0.05</td>
<td>0.18 ± 0.04</td>
<td>0.419</td>
<td>0.675</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>13.2 ± 1.0</td>
<td>12.6 ± 1.0</td>
<td>1.257</td>
<td>0.209</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.819</td>
<td>0.413</td>
</tr>
<tr>
<td>TT (sec)</td>
<td>17.8 ± 1.6</td>
<td>17.0 ± 1.3</td>
<td>1.953</td>
<td>0.051</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>34.9 ± 2.6</td>
<td>34.8 ± 4.3</td>
<td>-0.178</td>
<td>0.858</td>
</tr>
<tr>
<td>FIB (g/L)</td>
<td>2.9 ± 0.7</td>
<td>3.1 ± 0.8</td>
<td>-0.684</td>
<td>0.494</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative SP</td>
<td>127.7 ± 24.8</td>
<td>133.9 ± 16.0</td>
<td>-0.552</td>
<td>0.581</td>
</tr>
<tr>
<td>Preoperative DP</td>
<td>77.3 ± 15.1</td>
<td>81.4 ± 9.4</td>
<td>-2.198</td>
<td>0.028</td>
</tr>
<tr>
<td>Postoperative SP</td>
<td>134.1 ± 21.4</td>
<td>129.6 ± 15.8</td>
<td>0.651</td>
<td>0.515</td>
</tr>
<tr>
<td>Postoperative DP</td>
<td>77.6 ± 11.4</td>
<td>79.4 ± 28.7</td>
<td>-0.367</td>
<td>0.714</td>
</tr>
<tr>
<td>Major medical comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (27.3)</td>
<td>152 (13.3)</td>
<td>-</td>
<td>0.176†</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>1 (9.1)</td>
<td>25 (2.2)</td>
<td>-</td>
<td>0.238†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (27.3)</td>
<td>235 (20.6)</td>
<td>-</td>
<td>0.707†</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1 (9.1)</td>
<td>45 (4.0)</td>
<td>-</td>
<td>0.363†</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (9.1)</td>
<td>88 (7.7)</td>
<td>-</td>
<td>0.589†</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>2 (18.2)</td>
<td>20 (1.8)</td>
<td>-</td>
<td>0.017†</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>1 (9.1)</td>
<td>49 (4.3)</td>
<td>-</td>
<td>0.388†</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
IBL, intraoperative blood loss; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; Hb, hemoglobin; HCT, hematocrit; PCT, thrombocytocrit; PT, preoperative prothrombin time; INR, international normalized ratio; TT, thrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; SP, systolic pressure; DP, diastolic pressure.
†Fisher exact test.
which we thought could have led to the formation of HT. Univariate analysis and multivariate logistic regression analysis was further used to analyze risk factors with a significant difference. A p < 0.05 was regarded to be significantly different.

RESULTS

1. Incidence and Management of Postoperative HT

A total of 1,150 patients with ACF met the inclusion criteria, and 11 patients (1.0%) had postoperative HT. The incidence was 0.9% (10 of 1,150) in postoperative retropharyngeal HTs and 0.1% (1 of 1,150) in spinal epidural HTs. The incidence of AAO caused by a HT was 0.7% (8 of 1,150). HT occurred within 24 hours postoperatively in 5 patients (45.5%), while it occurred at an average of 4 days postoperatively in 6 patients (54.5%). Eight patients (72.7%) underwent HT evacuation, and the other 3 patients underwent conservative treatment, such as close observation, detumescence, and steroids. Among all of the patients, the complications were divided into cerebrospinal fluid leakage (2.5%, 29 of 1,150), postoperative HT (1.0%, 11 of 1,150), poor wound healing (1.4%, 16 of 1,150), neurological deterioration (0.3%, 4 of 1,150), respiratory failure (0.3%, 3 of 1,150), pneumonia (0.2%, 2 of 1,150), atrial fibrillation (0.2%, 2 of 1,150), infection (0.1%, 1 of 1,150) and hypokalemia (0.1%, 1 of 1,150). All patients were successfully treated and discharged (Table 1, Fig. 2).

2. Difference Between the HT Group and the No-HT Group

There were no significant differences in age, BMI, duration

Table 3. Surgery-related factors, length of stay and hospitalization costs of all the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with IBL</th>
<th>Patients without IBL</th>
<th>χ²/z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of discs involved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0 ± 0.9</td>
<td>1.9 ± 0.8</td>
<td>0.521</td>
<td>0.602</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>7 (63.6)</td>
<td>897 (78.8)</td>
<td>-</td>
<td>0.262†</td>
</tr>
<tr>
<td>3–5</td>
<td>4 (36.4)</td>
<td>242 (21.2)</td>
<td>1.688</td>
<td>0.091</td>
</tr>
<tr>
<td>Corpectomy</td>
<td>0.6 ± 0.5</td>
<td>0.4 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (36.4)</td>
<td>711 (62.4)</td>
<td>-</td>
<td>0.115†</td>
</tr>
<tr>
<td>1–2</td>
<td>7 (63.6)</td>
<td>428 (37.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>123.7 ± 33.5</td>
<td>113.0 ± 35.1</td>
<td>1.344</td>
<td>0.179</td>
</tr>
<tr>
<td>&lt;150</td>
<td>9 (81.8)</td>
<td>969 (85.1)</td>
<td>-</td>
<td>0.674†</td>
</tr>
<tr>
<td>≥150</td>
<td>2 (18.2)</td>
<td>170 (14.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08:00–11:00</td>
<td>7 (63.6)</td>
<td>752 (66.0)</td>
<td>-</td>
<td>0.814†</td>
</tr>
<tr>
<td>11:00–13:00</td>
<td>1 (9.1)</td>
<td>162 (14.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13:00-</td>
<td>3 (27.3)</td>
<td>225 (19.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative blood loss</td>
<td>124.5 ± 162.0</td>
<td>121.6 ± 155.3</td>
<td>-0.178</td>
<td>0.859</td>
</tr>
<tr>
<td>Postoperative drainage</td>
<td>107.2 ± 67.7</td>
<td>112.0 ± 116.5</td>
<td>0.161</td>
<td>0.872</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0 (0)</td>
<td>13 (1.1)</td>
<td>-</td>
<td>&gt;0.999†</td>
</tr>
<tr>
<td>C3 involved</td>
<td>2 (18.2)</td>
<td>324 (28.4)</td>
<td>-</td>
<td>0.738†</td>
</tr>
<tr>
<td>C7 involved</td>
<td>4 (36.4)</td>
<td>315 (27.7)</td>
<td>-</td>
<td>0.509†</td>
</tr>
<tr>
<td>OPLL among the surgical level</td>
<td>2 (18.2)</td>
<td>75 (6.6)</td>
<td>-</td>
<td>0.165†</td>
</tr>
<tr>
<td>Complications</td>
<td>11 (100)</td>
<td>53 (4.7)</td>
<td>-</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>FN (day)</td>
<td>5.0 ± 1.9</td>
<td>3.4 ± 2.6</td>
<td>4.195</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>LOS (day)</td>
<td>15.5 ± 6.7</td>
<td>14.4 ± 4.9</td>
<td>0.228</td>
<td>0.820</td>
</tr>
<tr>
<td>Cost (*10⁴ RMB)</td>
<td>8.2 ± 1.6</td>
<td>7.2 ± 1.6</td>
<td>2.070</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
IBL, intraoperative blood loss; OPLL, ossification of the posterior longitudinal ligament; FN, first-degree/intensive nursing; LOS, length of stay; RMB, ren min bi.
†Fisher exact test.
of disease, ASA PS classification, trauma history, preoperative coagulation indices, blood pressure, or history of most major medical comorbidities between the 2 groups (Table 2). There were no significant differences in the number of discs and corpectomy involved, duration of operation, time of operation, IBL, PB, BT, C3 involvement, C7 involvement or OPLL at the surgical level (Table 3).

Patients in the HT group presented with a significantly higher frequency of male sex (p = 0.01), smoking history (p = 0.01), and antiplatelet therapy (p = 0.017), a significantly lower preoperative diastolic pressure (p = 0.028) compared with those in the no-HT group (Table 2). Patients with postoperative HT had a higher frequency of complications (p < 0.001), longer days of first-degree/intensive nursing (p < 0.001) and higher hospitalization costs (p = 0.038) (Table 3).

3. Risk Factor Analysis

Univariate analysis showed that smoking history (odds ratio [OR], 6.667; 95% confidence interval [CI], 1.434–30.996; p = 0.016), preoperative Hb (OR, 1.046; 95% CI, 1.002–1.093; p = 0.042), preoperative TT (OR, 1.520; 95% CI, 1.0456–2.210; p = 0.028), and antiplatelet therapy (OR, 12.433; 95% CI, 2.524–61.257; p = 0.002) were risk factors for HT.

Our multivariate logistic regression analysis revealed that smoking history (odds ratio [OR], 5.193; 95% confidence interval [CI], 1.058–25.493; p = 0.042), preoperative TT value (OR, 1.643; 95% CI, 1.104–2.446; p = 0.014), and antiplatelet therapy (OR, 15.070; 95% CI, 2.663–85.274; p = 0.002) remained significant predictors of HT (Table 4).

DISCUSSION

1. Incidence and Risk Factors for Postoperative HT

Postoperative HT after ACF is a rare but potentially catastrophic complication. Some large studies have shown that the incidence of postoperative HT ranges from 0.4% to 5.6%.9–18 The reported incidence of AAO caused by an HT ranges from 0.2% to 1.9%.18 In the largest single-surgeon series of ACF operations, we reviewed 1,150 patients and found that 11 patients (1.0%) had postoperative HT, which was consistent with previous reports.5–18 However, these studies discussed few risk factors for specific patients, such as duration of disease; or surgical factors, such as duration and time of surgery; or C3 or C7 involvement, which could have led to the formation of HTs. In the current study, duration of disease was divided into less than 3 months, 3 months–1 year, 1 year–5 years, and over 5 years, duration of operation was divided into < 150 minutes and ≥ 150 minutes, time of operation was divided into morning (08:00–11:00), noon (11:00–13:00), and afternoon (13:00–), 2 specific cervical spines are mentioned such as C3 and C7.

Risk factors for postoperative HTs included male sex, age older than 65, smoking, higher/lower BMI, anemia, more medical comorbidities, the presence of diffuse idiopathic skeletal hyperostosis, OPLL, therapeutic heparin levels, ASA PS classification grades of III or greater, longer operative times, multiple surgical levels, and increased IBL.11–14,19 A total of 37,261 anterior cervical discectomy and fusion patients were identified, of whom 148 (0.40%) developed a HT requiring reoperation.11 Risk factors for the development of HT requiring reoperation were multilevel procedures, a preoperative international normalized ratio > 1.2, lower BMI, ASA PS classification grades of III or greater, preoperative anemia, and male sex.11 There were no significant differences between the HT group and the no-HT group in the distributions of duration of disease, duration of operation, time of operation, C3 or C7 involvement. Therefore, we speculated that the duration of disease and operation has little influence on the occurrence of postoperative HT. No matter at what time stage (morning, noon, or afternoon) of the operation, the surgeon can complete the operation conscientiously, and does not affect the occurrence of postoperative HT. Different anterior cervical surgery segment, especially C3 or C7 exposure didn't affect the occurrence of postoperative HT.

In the current study, risk factors for the development of such HTs included smoking history, preoperative TT value and anti-

### Table 4. Univariate analysis and multivariate logistic regression analysis of the risk factors for hematoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Smoking history</td>
<td>6.667 (1.434–30.996)</td>
<td>0.016</td>
</tr>
<tr>
<td>Preoperative Hb</td>
<td>1.046 (1.002–1.093)</td>
<td>0.042</td>
</tr>
<tr>
<td>Preoperative TT</td>
<td>1.520 (1.0456–2.210)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; Hb, hemoglobin; TT, thrombin time.
Postoperative Hematoma


platelet therapy. We routinely assayed the TT as part of a coagulation screen for the preoperative patients. Based on the results obtained from this paper, we recommend preoperative TT measurements for patients undergoing ACF. We found that 18.2% of patients in the HT group and 1.8% of patients in the non-HT group had received preoperative antiplatelet therapy in our study, and antiplatelet therapy was an independent risk factor for HT. Because the p-value of gender was 0.010 by Fisher exact probability test in Table 2, we speculated male gender was enough a risk factor for postoperative HT. We speculated the reason why gender was omitted was because gender did not result in a risk factor for HT by univariate and multivariate analysis by the statistical problem due to the zero count cell (female with HT) for a 2 × 2 contingency table. These identified risk factors could help surgeons and nurses to plan treatment and case lists. For example, patients at risk for developing HT should be given focused attention to maximize the length of postoperative observation. Postoperative HT in the ACF was associated with a higher frequency of complications, longer days of first-degree/intensive nursing and greater hospitalization costs. These findings are especially important for patient postoperative management and counselling.

2. Time of Presentation of the HT

It is interesting to discuss the timing of HT in our study. HTs are generally considered to occur mainly within the first few hours after surgery. There were 17 occurrences (0.7%) of postoperative HT in 2,375 ACF procedures. HT occurred within 24 hours postoperatively in 11 patients (65%), while it occurred at an average of 6 days postoperatively in 6 patients (35%). In a series of AAOS following anterior cervical corpectomy and fusion, 1.15% of patients (9 of 785) developed postoperative HTs. Of these cases, 66.7% (6 of 9) occurred within 24 hours of surgery, while 33.3% (3 of 9) presented at an average of 72 hours postoperatively. A previous study showed that 37% of HTs requiring reoperation occurred after discharge from the hospital. This finding suggests that surgeons should have heightened awareness of this complication throughout the entire 30-day postoperative period and not only during hospitalization.11

The definition of postoperative HT following ACF in the current study was symptomatic postoperative HT manifested as respiratory distress, neurological injury, dysphagia and other symptoms of HT which was confirmed by MRI, color Doppler ultrasound or surgical evacuation. In the current study, 1 patient with postoperative muscle strength weakened was diagnosed postoperative HT through MRI, 2 patients were diagnosed through color Doppler ultrasound, and other patients underwent emergency exploratory operation and HT evacuation because of respiratory distress. There is a specific type of HT called postoperative delayed HT, which is defined by the progression of neurological deterioration because HTs are observed after more than 3 days. Sokolowski et al.21 reported a case with symptom onset 13 days after the initial surgery. In the current study, HT occurred within 24 hours postoperatively in 5 patients (45.5%), others occurred at an average of 3 days postoperatively in the 6 patients (54.5%), and 4 patients (36.4%) presented with delayed HT. Although HTs were more common in the acute postoperative period in previous studies, the occurrence of HTs should be considered for at least 2 weeks after surgery.

Drains were used in each case in the current study throughout the study period and were generally removed 2–3 days after surgery. It is important to note that the placement of drains did not prevent postoperative HT.14 In the current study, drains were in place at the time of HT formation in 63.6% (7 of 11) of patients, and the HT formed shortly (several hours) after drain removal in 9.1% (1 of 11) of patients. Although a HT can form before the drain is removed, it should be noted that removal of the drain could damage vessels or the muscle bed and contribute to HT formation.12 Therefore, we recommend close monitoring of the patient’s vital signs, especially breathing, for several hours after the drain is removed.

3. Causes of HTs

Some researchers have noted that vascular injury and intramuscular bleeding are the main causes of HT.22-25 Incorrect and insufficient hemostasis of the vessels has been identified as one of the main causes of postoperative HT. There have been some reports of dyspnoea being caused by delayed bleeding associated with arterial aneurysms and venous thrombosis.22,26 In a previous study, surgeons were able to identify a discrete source of bleeding upon secondary surgery in up to 75% of cases in some series.21 In the current study, the rate was 62.5%, and we found vessel injury in 5 patients (internal opening of the drainage tube in 3 patients and longus cervicalis in 2 patients) upon the secondary operation. We also found that HT could develop without any injury to specific vessels in 3 patients (blood oozing from the lateral wall muscle surface).

Bleeding from exposed cancellous bone after removing ventral osteophytes and dorsal intraspinal canal osteophytes of the spine as well as the site of distractor pin should be taken seriously during operation, we can use bone wax and gelatin sponge to
effectively control severe bleeding from exposed cancellous bone during operation. Previous studies have shown that the presence of OPLL was a significant risk factor for HT.\textsuperscript{10,12,13} Patients with OPLL usually require extensive osteophyte resection, which can result in greater exposure of cancellous bone, leading to HT formation. Vascular injury occurs during or after surgery and can result in additional bleeding. Therefore, strategies to reduce the incidence of postoperative HT must address multiple potential areas of hemorrhage, including blood vessels, muscles, and exposed cancellous bone. Effective hemostasis and avoidance of excessive intraoperative traction are important for all patients.

4. Management of Postoperative HT

The incidence of AAO reported in previous studies ranged from 0.2% to 1.9%.\textsuperscript{14} Eight patients (0.7%) presented with AAO caused by HT in the current study. An effective and timely treatment is required to obtain a better therapeutic effect and prognosis of HT-related AAO. The patient’s respiratory status can be assessed by carefully evaluating the condition of the neck and the patient’s behavior.\textsuperscript{15} The behavior of patients with controlled dyspnoea or impaired breathing must be closely evaluated. Specifically, spontaneous relief of dyspnoea is impossible when the patient is anxious. Therefore, it is very important to send anxious patients to the operating room immediately to remove the HT, find the cause of bleeding and adopt appropriate hemostatic methods. Patients without fear or anxiety can be treated with oxygen and be closely observed. However, if the patient’s condition deteriorates, the HT should be removed.\textsuperscript{15,18}

Postoperative respiratory difficulty caused by AAO after ACF is very risky situation because the intratracheal intubation is very difficult. When postoperative respiratory difficulty happens, the first step is to open the incision and relieve the pressure of HT on airway. At the same time, high-flow oxygen inhalation increases the patient’s oxygen reserve, to create the conditions for intubation. If the patient cooperates calmly, intubation may be performed while the patient is awake. Under the condition of adequate preparation, the vast majority of patients can be quickly induced and successfully intubated with visual laryngoscope.

According to our experience, postoperative oedema mostly causes eating difficulties and will not cause AAO. Most patients with AAO experience postoperative HT rather than oedema. In the current study, 8 patients presented with swelling of the incision site and respiratory distress, fear and anxiety, so we chose HT evacuation. The preoperative symptoms of all patients resolved immediately or within hours of HT evacuation. Conservative management with steroid treatment was initiated before neurosurgical decompression, resulting in improved neurologic outcomes for patients presenting with mild neurological deterioration.\textsuperscript{27,28} We examined 3 cases with conservative treatment, one of which received steroid therapy because his muscle strength weakened temporarily, and it returned to normal approximately 30 minutes later.

Our study has several limitations. First, the retrospective nature of the study can affect the accuracy. Second, factors such as Pack-years for smoking, spinal degeneration, alignment and bone fragility were not discussed in the current study. We will pay much attention to these factors in future prospective studies. Third, the associations between the HT and hemostatic materials were not discussed. We have used bone wax to stop the bleeding from exposed cancellous bone, used gelatin sponge and surgical hemostatic gauze to stop the bleeding from the surface of dura, and all the ACF operations were performed by one senior surgeon (LX), so we were able to rule out the bias caused by the different hemostatic methods and procedures of different surgeons. Forth, the results might have been affected by the relatively limited sample size and nonrandomized design. A multicentre, prospective study with a more detailed assessment of risk factors might be needed.

CONCLUSION

Smoking history, preoperative TT value and antiplatelet therapy were significant risk factors for postoperative HT following ACF. Postoperative HT in ACF was associated with longer days of first-degree/intensive nursing and greater hospitalization costs. Although HT occurring in the acute postoperative period can be detected and handled in a timely manner, we believe that HT might be a possible cause of airway obstruction even after the acute postoperative period because 54.5% of postoperative HTs occurred in a delayed fashion.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: HW, HY, NZ, LX; Data curation: NZ; Formal analysis: HW, HY, LX; Funding acquisition: HW; Methodology: HY, NZ, LX; Visualization: HW,
REFERENCES


Perioperative Clinical Features and Long-term Prognosis After Oblique Lateral Interbody Fusion (OLIF), OLIF With Anterolateral Screw Fixation, or OLIF With Percutaneous Pedicle Fixation: A Comprehensive Treatment Strategy for Patients With Lumbar Degenerative Disease

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Objective: To compare the efficacy of oblique lateral interbody fusion (OLIF), OLIF combined with anterolateral screw fixation (OLIF-AF), and OLIF combined with percutaneous pedicle screw fixation (OLIF-PF) in the treatment of single-level or 2-level degenerative lumbar disease.

Methods: Between January 2017 and 2021, 71 patients were treated with OLIF and combined OLIF. The demographic data, clinical outcomes, radiographic outcomes, and complications were compared among the 3 groups.

Results: The operative time and intraoperative blood loss in the OLIF (p < 0.05) and OLIF-AF (p < 0.05) groups were lower than in the OLIF-PF group. Posterior disk height improvement in the OLIF-PF group was better than in the OLIF (p < 0.05) and OLIF-AF (p < 0.05) groups. In terms of foraminal height (FH), the OLIF-PF group was significantly better than the OLIF group (p < 0.05), but there was no significant difference between the OLIF-PF and OLIF-AF groups (p > 0.05) or between the OLIF and OLIF-AF groups (p > 0.05). There were no significant differences in fusion rates, the incidence of complications, lumbar lordosis, anterior disc height, and cross-sectional area among the 3 groups (p > 0.05). The OLIF-PF group had significantly lower rates of subsidence than the OLIF group (p < 0.05).

Conclusion: OLIF remains a viable option with similar patient-reported outcomes and fusion rates compared with surgeries that include lateral and posterior internal fixation while greatly reducing the financial burden, intraoperative time, and intraoperative blood loss. OLIF has a higher subsidence rate than lateral and posterior internal fixation, but most subsidence is mild and has no adverse effect on clinical and radiographic outcomes.

Keywords: Lumbar vertebrae, Spinal fusion, Spinal stenosis, Pedicle screws, Patient Reported Outcome Measures, Prognosis
INTRODUCTION

Lumbar fusion has been widely used in treating lumbar degenerative diseases. Oblique lateral interbody fusion (OLIF), an anterior, minimally invasive lumbar fusion, has received widespread attention in clinical practice.1-3 He et al.4 suggested that OLIF and OLIF with percutaneous pedicle screw fixation (OLIF-PF) have equivalent clinical and radiographic outcomes and similar complication rates. Guo et al.5 reported that OLIF with anterolateral screw fixation (OLIF-AF) had the same Oswestry Disability Index (ODI) score, imaging findings, and complication rates as OLIF-PF in the treatment of single-segment lumbar degenerative disease.

Current literature,⁴⁻⁷ due to small sample sizes, heterogeneity of research objectives, short follow-up times, and low levels of evidence, is insufficient to determine whether OLIF or combined methods are superior. Thus, it is difficult for clinicians to choose the most appropriate method. In this study, which to our knowledge is the first to include OLIF, OLIF-AF, and OLIF-PF as comparison groups, we evaluate the clinical and radiographic outcomes of OLIF and OLIF-AF and OLIF-PF and analyze the differences among the 3 groups from multiple perspectives to provide recommendations on choosing the most appropriate approach in clinical practice.

MATERIALS AND METHODS

This study was reviewed and approved by the ethics commit-
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Intraoperatively, antibiotic saline was repeatedly rinsed, bipolar physiological lordosis was restored, and slippage was reduced. When fluoroscopy showed that the cage was centered, the intervertebral space was spread, the nucleus pulposus was removed according to routine procedures, followed by C-arm fluoroscopy of the screw position.

2. Clinical Indicators

Relevant descriptive information such as age, body mass index, operative time, intraoperative blood loss, postoperative hospital stay, complications, and operative stage, was collected and analyzed. The visual analogue scale (VAS) and the ODI were used for preoperative, postoperative, and final follow-up. The final follow-up was at least 12 months after surgery. At this visit, computed tomography (CT) was used to assess pedicle screw position and fusion rate and to measure Hounsfield units. A combination of CT and magnetic resonance imaging (MRI) was used to assess the degree of decompression.

3. Imaging Parameter Measurement

All patients underwent lumbar x-ray, CT, and MRI at preoperative, postoperative, and final follow-up (Fig. 2). The sagittal angle of lumbar lordosis (LL) was measured by x-ray in the Picture Archiving Communication System (Fig. 3). Foraminal height (FH), cross-sectional area of the intervertebral foramina (CSAF), anterior disc height (ADH), and posterior disc height (PDH) were measured on the CT sagittal view (Fig. 4). The cross-sectional area (CSA) of the spinal canal was measured in the axial sections of T2-weighted imaging (Fig. 5). The degree of subsidence was graded using the grading system reported by Marchi et al.,9 where grades 0 and I were referred to as low-grade and grades II and III as the high-grade subsidence.

4. Statistical Analysis

The normal distribution of parameters was compared between the 2 groups using a t-test and expressed as mean ± standard deviation, while 1-way analysis of variance was employed for comparing the data among multiple groups. If there was a statistically significant difference between the groups, a post hoc comparison was performed using Bonferroni correction. Parametrics with nonnormal distribution were statistically described by the median. The Mann-Whitney U-test was used for assessing data between the 2 groups, and for multiple groups, the Kruskal-Wallis
H-test was used. If the difference between the groups was statistically significant, a post hoc comparison was performed using Bonferroni correction. Categorical data were represented by frequency. The chi-square test or Fisher exact test was used to compare data between the 2 or more groups. If the differences between the groups were statistically significant, the chi-square test or Fisher exact test was further used for multiple comparisons, and the corresponding p-value was corrected using Bonferroni correction. Multivariate analysis was performed using linear regression for linear variables and logistic analysis for categorical data.
variables. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome were included in multivariate analysis. Statistical analysis was performed using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Demographic Data

The demographics data of the patients was shown in Table 1. A total of 71 patients (48 women and 23 men) were enrolled in the study, and the mean patient age was 64.8 ± 10.6 years (range, 34–88 years). 51 cases had at least 12 months of follow-up, 12 cases had at least 24 months of follow-up, and 8 cases had at least 36 months of follow-up.
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Fig. 5. The magnetic resonance imaging (MRI) presentation in an operative patient. (A–C) The patient underwent OLIF. (D–F) The patient underwent OLIF-AF. (G–I) The patient underwent OLIF-PF. Three groups in MRI before the operation, at postoperative 1 day, and at last follow-up. The yellow arrow points to the sagittal segment corresponding to the axial MRI image. OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

Table 1. The demographic data of the patients of OLIF, OLIF-AF, and OLIF-PF groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 71)</th>
<th>OLIF (n = 25)</th>
<th>OLIF-AF (n = 19)</th>
<th>OLIF-PF (n = 27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.8 ± 10.6 (34–88)</td>
<td>65.2 ± 10.9 (34–88)</td>
<td>66.9 ± 8.7 (48–84)</td>
<td>62.8 ± 11.4 (43–85)</td>
<td>0.424</td>
</tr>
<tr>
<td>Female sex</td>
<td>48</td>
<td>18 (72)</td>
<td>18 (94.7)</td>
<td>12 (44.4)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Overweight, BMI &gt; 25 kg/m²</td>
<td>36</td>
<td>14 (56)</td>
<td>9 (47.4)</td>
<td>13 (48)</td>
<td>0.804</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>7 (28)</td>
<td>2 (10.5)</td>
<td>5 (18.5)</td>
<td>0.346</td>
</tr>
<tr>
<td>Smoker</td>
<td>9</td>
<td>2 (8)</td>
<td>1 (5)</td>
<td>6 (22)</td>
<td>0.160</td>
</tr>
<tr>
<td>Bone density† (CT H &gt; 120)</td>
<td>28</td>
<td>11 (44)</td>
<td>3 (15.8)</td>
<td>14 (51.8)</td>
<td>0.075</td>
</tr>
<tr>
<td>Levels fused</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2–3 included (%)</td>
<td>6</td>
<td>4 (16)</td>
<td>2 (10.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>L3–4 included (%)</td>
<td>29</td>
<td>10 (40)</td>
<td>9 (47)</td>
<td>10 (37)</td>
<td></td>
</tr>
<tr>
<td>L4–5 included (%)</td>
<td>59</td>
<td>21 (84)</td>
<td>18 (94)</td>
<td>20 (74)</td>
<td></td>
</tr>
<tr>
<td>Follow-up‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year (%)</td>
<td>51</td>
<td>12 (48)</td>
<td>14 (73.4)</td>
<td>25 (92.5)</td>
<td></td>
</tr>
<tr>
<td>2-Year (%)</td>
<td>12</td>
<td>11 (44)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3-Year (%)</td>
<td>8</td>
<td>2 (8)</td>
<td>4 (21)</td>
<td>2 (7.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation, median (range), or percentages.

OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation; BMI, body mass index; CT HU, computed tomography Hounsfield units.

*Statistically significant at p < 0.05. †The bone density was presented as continuous variable based on lumbar CT HU value. ‡Time from discharge to final follow-up (mo).
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2. Clinical Outcomes

Forty patients underwent single-level surgery, and 31 patients underwent double-level surgery; the operation time of the OLIF group (p < 0.05) and OLIF-AF group (p < 0.05) was shorter than that of the OLIF-PF group. The intraoperative blood loss in the OLIF group (p < 0.05) and OLIF-AF group (p < 0.05) was also less than that in the OLIF-PF group. The OLIF, OLIF-AF, and OLIF-PF groups showed no significant difference in VAS and ODI scores (p > 0.05), recorded preoperatively, 1 week postoperatively, and final follow-up, respectively (Table 2).

3. Radiographic Outcomes

There was no significant difference in preoperative and postoperative ADH, PDH, FH, the CSAF, and CSA, LL among the OLIF, OLIF-AF, and OLIF-PF groups (p > 0.05). During follow-up, the improvement of PDH in the OLIF-PF group was superior to that in the OLIF (p < 0.05) and OLIF-AF groups (p < 0.05) (Table 3). In terms of FH, the OLIF-PF group was significantly better than the OLIF group (p < 0.05), but there was no statistical difference between the OLIF-PF group and the OLIF-AF group (p > 0.05) or between the OLIF group and the OLIF-AF group (p > 0.05). In the improvement of CSAF, the OLIF-PF group (p < 0.05) and OLIF-AF group (p < 0.05) were better than the OLIF group. There were 38 surgical segments in the OLIF group and 32 achieved bony fusion, with a fusion rate of 84.2% (32 of 38); 29 surgical segments in the OLIF-AF group involving 25 cases of bony fusion at a fusion rate of 86.2% (25 of 29), and a total of 35 segments were operated in the OLIF-PF group.

Table 2. The clinical outcome data of the patients of OLIF, OLIF-AF, and OLIF-PF groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>OLIF (n = 25)</th>
<th>OLIF-AF (n = 19)</th>
<th>OLIF-PF (n = 27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fused segments</td>
<td>12</td>
<td>9</td>
<td>19</td>
<td>0.175</td>
</tr>
<tr>
<td>Single</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>97.2 ± 37.9</td>
<td>118.3 ± 48.0</td>
<td>195.8 ± 45.5</td>
<td>0.000*</td>
</tr>
<tr>
<td>Intraoperative blood loss (mL)</td>
<td>20 (5–60)</td>
<td>40 (10–100)</td>
<td>50 (40–150)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Hospitalization (day)</td>
<td>8.8 ± 2.4</td>
<td>8.0 ± 2.0</td>
<td>8.5 ± 2.1</td>
<td>0.413</td>
</tr>
<tr>
<td>Complications</td>
<td>16</td>
<td>10</td>
<td>13</td>
<td>0.503</td>
</tr>
<tr>
<td>Revision</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Cage-associated infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Cage migration</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Subsidence</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>0.010*</td>
</tr>
<tr>
<td>Pedicle screw breakage</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-VAS of low back</td>
<td>5.0 (2.0–7.0)</td>
<td>5.0 (0–7.0)</td>
<td>5.0 (0–8.0)</td>
<td>0.699</td>
</tr>
<tr>
<td>Post-VAS of low back</td>
<td>2.0 (1.0–4.0)</td>
<td>3.0 (0–4.0)</td>
<td>2.0 (0–3.0)</td>
<td>0.694</td>
</tr>
<tr>
<td>Follow-up VAS of low back</td>
<td>1.0 (0–2.0)</td>
<td>1.0 (0–2.0)</td>
<td>1.0 (0–3.0)</td>
<td>0.316</td>
</tr>
<tr>
<td>Delta VAS of low back</td>
<td>4.0 (2.0–6.0)</td>
<td>4.0 (0–6.0)</td>
<td>3.5 (0–5.0)</td>
<td>0.259</td>
</tr>
<tr>
<td>Pre-VAS of leg</td>
<td>4.0 (0–6.0)</td>
<td>3.5 (0–6.0)</td>
<td>2.5 (0–7.0)</td>
<td>0.540</td>
</tr>
<tr>
<td>Post-VAS of leg</td>
<td>1.0 (0–3.0)</td>
<td>1.5 (0–3.0)</td>
<td>1.0 (0–4.0)</td>
<td>0.687</td>
</tr>
<tr>
<td>Follow-up VAS of leg</td>
<td>0 (0–2.0)</td>
<td>1.0 (0–2.0)</td>
<td>0 (0–3.0)</td>
<td>0.686</td>
</tr>
<tr>
<td>Delta VAS of leg</td>
<td>3.0 (0–5.0)</td>
<td>3.0 (0–5.0)</td>
<td>2.5 (0–5.0)</td>
<td>0.418</td>
</tr>
<tr>
<td>Pre-ODI (%)</td>
<td>44.0 (22.0–60.0)</td>
<td>46.5 (21.0–57.0)</td>
<td>43.5 (24.0–58.0)</td>
<td>0.101</td>
</tr>
<tr>
<td>Post-ODI (%)</td>
<td>16.0 (9.0–28.0)</td>
<td>21.0 (10.0–23.0)</td>
<td>16.5 (7.0–23.0)</td>
<td>0.459</td>
</tr>
<tr>
<td>Follow-up ODI (%)</td>
<td>7.0 (4.0–17.0)</td>
<td>10.0 (5.0–22.0)</td>
<td>8.0 (4.0–18.0)</td>
<td>0.115</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or median (range).
OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation; VAS, visual analogue scale; ODI, Oswestry Disability Index; NA, not available.

*Statistically significant at p < 0.05. †The delta VAS of low back/leg was calculated as the pre-VAS score minus follow-up VAS.
of which 33 achieved bony fusion, with a fusion rate of 94.3% (33 of 35). There were no significant differences in fusion rates among the OLIF, OLIF-AF, and OLIF-PF groups (p > 0.05).

4. Complications

There were no vascular, ureteral, lumbar plexus, sympathetic nerve, abdominal organ injuries, or other serious complications in the 3 groups. There were 38 surgical segments in the OLIF group including 25 segments showing subsidence. Of which, 68% (17 of 25) patients had grades 0–I and 32% (8 of 25) cases exhibited grades II–III subsidence. There were 29 surgical segments in the OLIF-AF group, and a total of 13 segments showed subsidence. Of which, 70% (9 of 13) cases reported grades 0–I, and 30% (4 of 13) presented grade II. A total of 35 segments were operated in the OLIF-PF group, and a total of 11 segments showed subsidence with grades 0–I. In the subsidence rates, OLIF-PF was superior to the OLIF group (p < 0.05), and there was no significant difference between the OLIF and OLIF-AF groups (p > 0.05), or the OLIF-AF and OLIF-PF groups (p > 0.05). One patient who underwent OLIF was found to have cage displacement 2 weeks postoperatively without symptoms and was treated with posterior percutaneous pedicle screw fixation. Two patients who underwent OLIF-PF had cage displacement, but they were asymptomatic and did not receive treatment. One patient with OLIF-PF was found to have screw fractures at their final follow-up visit, but they were asymptomatic and required no treatment.

5. Subgroup Analysis

We conducted subgroup analysis based on numbers of fused surgical segments (single vs. double) (Supplementary Table 1), gender (male vs. female) (Supplementary Table 2), and age (≤ 65 years old vs. > 65 years old) (Supplementary Table 3). However, there was no significant prognostic difference in these subgroups, which indicating the operation of OLIF, OLIF-AF, and OLIF-PF may have similar prognostic outcomes, regardless of numbers of fused surgical segments, gender, and age.

6. Multivariate Regression Analysis

Univariate analysis was explored to evaluate improvement of

<table>
<thead>
<tr>
<th>Variable</th>
<th>OLIF (n = 25)</th>
<th>OLIF-AF (n = 19)</th>
<th>OLIF-PF (n = 27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-LL (°)</td>
<td>25.3 (2.4–57.4)</td>
<td>25.4 (4.6–52.8)</td>
<td>30.4 (2.1–46.5)</td>
<td>0.562</td>
</tr>
<tr>
<td>Post-LL (°)</td>
<td>26.6 (2.5–48.5)</td>
<td>25.1 (5.4–53.8)</td>
<td>25.7 (3.9–60.6)</td>
<td>0.985</td>
</tr>
<tr>
<td>Follow-up LL (°)</td>
<td>27.9 (2.2–56.0)</td>
<td>28.9 (5.7–48.5)</td>
<td>25.9 (7.9–49.4)</td>
<td>0.801</td>
</tr>
<tr>
<td>Pre-ADH (cm)</td>
<td>0.80 ± 0.24</td>
<td>0.83 ± 0.26</td>
<td>0.89 ± 0.29</td>
<td>0.394</td>
</tr>
<tr>
<td>Post-ADH (cm)</td>
<td>1.16 ± 0.18</td>
<td>1.14 ± 0.27</td>
<td>1.17 ± 0.21</td>
<td>0.794</td>
</tr>
<tr>
<td>Follow-up-ADH (cm)</td>
<td>0.98 ± 0.22</td>
<td>1.01 ± 0.23</td>
<td>1.09 ± 0.20</td>
<td>0.084</td>
</tr>
<tr>
<td>Pre-PDH (cm)</td>
<td>0.51 ± 0.15</td>
<td>0.58 ± 0.18</td>
<td>0.61 ± 0.21</td>
<td>0.108</td>
</tr>
<tr>
<td>Post-PDH (cm)</td>
<td>0.81 ± 0.18</td>
<td>0.81 ± 0.20</td>
<td>0.92 ± 0.25</td>
<td>0.058</td>
</tr>
<tr>
<td>Follow-up-PDH (cm)</td>
<td>0.61 ± 0.14</td>
<td>0.68 ± 0.29</td>
<td>0.83 ± 0.21</td>
<td>0.000*</td>
</tr>
<tr>
<td>Pre-FH (cm)</td>
<td>1.59 ± 0.22</td>
<td>1.67 ± 0.24</td>
<td>1.61 ± 0.23</td>
<td>0.261</td>
</tr>
<tr>
<td>Post-FH (cm)</td>
<td>1.88 ± 0.21</td>
<td>1.89 ± 0.29</td>
<td>1.93 ± 0.24</td>
<td>0.575</td>
</tr>
<tr>
<td>Follow-up-FH (cm)</td>
<td>1.68 ± 0.21</td>
<td>1.72 ± 0.25</td>
<td>1.86 ± 0.27</td>
<td>0.008*</td>
</tr>
<tr>
<td>Pre-CSAF (cm²)</td>
<td>1.03 ± 0.26</td>
<td>1.17 ± 0.29</td>
<td>1.14 ± 0.27</td>
<td>0.083</td>
</tr>
<tr>
<td>Post-CSAF (cm²)</td>
<td>1.41 ± 0.29</td>
<td>1.54 ± 0.31</td>
<td>1.46 ± 0.34</td>
<td>0.252</td>
</tr>
<tr>
<td>Follow-up-CSAF (cm²)</td>
<td>1.15 ± 0.24</td>
<td>1.35 ± 0.28</td>
<td>1.45 ± 0.35</td>
<td>0.000*</td>
</tr>
<tr>
<td>Pre-CSA (cm²)</td>
<td>1.32 ± 0.45</td>
<td>1.21 ± 0.42</td>
<td>1.35 ± 0.46</td>
<td>0.351</td>
</tr>
<tr>
<td>Post-CSA (cm²)</td>
<td>1.71 ± 0.44</td>
<td>1.56 ± 0.57</td>
<td>1.67 ± 0.46</td>
<td>0.405</td>
</tr>
<tr>
<td>Follow-up-CSA (cm²)</td>
<td>1.63 ± 0.46</td>
<td>1.50 ± 0.55</td>
<td>1.80 ± 0.52</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or mean ± standard deviation. OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation; LL, lumbar lordosis; ADH, anterior disc height; PDH, posterior disc height; FH, foraminal height; CSAF, cross-sectional area of the intervertebral foramina; CSA, cross-sectional area. *Statistically significant at p < 0.05.
Comparison of Different OLIF Fixation Methods

Zhang X, et al.

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Table 4. Univariate analysis of radiographic outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Fused condition (yes or no)</th>
<th>p-value</th>
<th>Subsidence condition (yes or no)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>0.654</td>
<td></td>
<td>0.043*</td>
</tr>
<tr>
<td>OLIF</td>
<td>25</td>
<td>21/4</td>
<td></td>
<td>17/8</td>
<td></td>
</tr>
<tr>
<td>OLIF-AF</td>
<td>19</td>
<td>17/2</td>
<td></td>
<td>10/9</td>
<td></td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>27</td>
<td>25/2</td>
<td></td>
<td>9/18</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td>0.773</td>
<td></td>
<td>0.390</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>30</td>
<td>27/3</td>
<td></td>
<td>17/13</td>
<td></td>
</tr>
<tr>
<td>≤ 65</td>
<td>41</td>
<td>36/5</td>
<td></td>
<td>19/22</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.259</td>
<td></td>
<td>0.177</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>19/4</td>
<td></td>
<td>9/14</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>44/4</td>
<td></td>
<td>27/21</td>
<td></td>
</tr>
<tr>
<td>Fused segment</td>
<td></td>
<td></td>
<td>0.766</td>
<td></td>
<td>0.397</td>
</tr>
<tr>
<td>Single</td>
<td>39</td>
<td>35/4</td>
<td></td>
<td>18/21</td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td>32</td>
<td>28/4</td>
<td></td>
<td>18/14</td>
<td></td>
</tr>
<tr>
<td>Bone density†</td>
<td></td>
<td></td>
<td>0.662</td>
<td></td>
<td>0.432</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>26/2</td>
<td></td>
<td>12/16</td>
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</tr>
<tr>
<td>Low</td>
<td>43</td>
<td>37/6</td>
<td></td>
<td>25/18</td>
<td></td>
</tr>
</tbody>
</table>

OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

*Statistically significant at p < 0.05. †The bone density was presented as continuous variable based on lumbar computed tomography Hounsfield units value.

clinical outcomes (Supplementary Table 4) and radiographic outcomes (Table 4). We found that age, gender, numbers of fused surgical segments, and bone mineral density did not show statistically significant differences in clinical outcomes and radiological outcomes, and the choice of internal fixation did not show statistically significant differences in the improvement of clinical outcomes, but the choice of posterior internal fixation was significantly better than OLIF in terms of avoiding subsidence in the radiological outcomes (p < 0.05). Using multivariate analysis, compared with the OLIF group, the risk of subsidence in the OLIF-PF group was lower (odds ratio, 0.272; 95% confidence interval, 0.082–0.904; p < 0.05). In the other words, the choice of posterior internal fixation was an independent protective factor in terms of avoiding subsidence (Table 5), while there were no factors independently associated with clinical outcomes (Supplementary Table 5).

DISCUSSION

With the development of the OLIF technique, OLIF and OLIF combined with internal fixation have been widely used and have achieved satisfactory results (Table 6). Nevertheless, research comparing the advantages of OLIF and OLIF combined with different internal fixations is urgently needed. To our knowledge, this is the first retrospective study to date which evaluate outcomes in the OLIF, OLIF-AF, and OLIF-PF. In our study, we used a multivariate analysis to investigate the effects of age, gender, and single or double surgical level on clinical and radiological outcomes. In addition, the follow-up time in this study is longer than that reported in similar literature.

Our study found that the OLIF group and OLIF-AF group outperformed the OLIF-PF group in terms of shorter operation duration and less intraoperative blood loss. Similar findings have been reported in the previous studies. Because patients in the OLIF-PF group must be adjusted from the lateral position to the prone position, the surgical procedure is longer. Without the need for a change in position or an extra incision, the OLIF-AF group's total operation time and blood loss were reduced. Because of enhanced recovery after surgery, there was no significant difference in the length of hospital stays across the 3 groups.

In our study, low-grade subsidence was observed in all 3 groups but high-grade subsidence was only observed in the OLIF group. By implanting an interbody fusion device, OLIF
can restore the height of the intervertebral space, achieve indirect decompression, and alleviate neurological symptoms.\(^{20}\) Subsidence, on the other hand, may impede the effects of indirect decompression by restoring disc height and result in discomfort, nonfusion, and other negative effects. In OLIF, the problem of the loss of interbody height brought on by fusion subsidence cannot be avoided.\(^{21,22}\) Subsidence has been demonstrated to be a significant predictor of revision after OLIF.\(^{23}\) Putzen et al.\(^{24}\) show that the use of posterior fixation can boost axial compressive strength, which lowers the likelihood of subsidence. According to Ge et al.,\(^{19}\) additional lateral plate fixation is ineffective at preventing subsidence. In this study, we found that posterior internal fixation is superior to lateral fixation in avoiding subsidence, and lateral fixation outperforms OLIF alone, which is consistent with the findings of Guo et al.\(^{5}\) and He et al.\(^{4}\)

We found that the fusion rate of OLIF-PF was better than that of OLIF-AF and OLIF, but not significantly so. This indicates that OLIF-PF may be superior at fostering fusion and maintaining intervertebral stability. We suggest that posterior percutaneous pedicle screw internal fixation can effectively maintain the stability of the 3 columns, restrict flexion and extension of the operative segment, distribute the stress of the fusion device, and establish a stable external environment for bone graft fusion.\(^{23}\) The lateral screw also promotes fusion and lowers the likelihood of subsidence because it can greatly lessen the stress on the fusion device, even if it is not as effective as the posterior bilateral pedicle screw.\(^{18}\)

In the present study, we found improvements in VAS and ODI after surgery and at follow-up in all 3 groups, while there were no statistically significant differences in ODI and VAS scores between groups. We hypothesize that the recurrence of symptoms after OLIF is due to excessive loss of reconstructed intervertebral height caused by subsidence. Intervertebral fusion may prevent the occurrence of these symptoms. Recent studies have also shown that fusion is associated with better clinical outcomes.\(^{25,26}\) In all 3 groups, the fusion rate rose as time passed after surgery, which led to an improvement in symptoms.

Although OLIF has the advantage of indirect decompression fusion and causes little damage to the posterior anatomical structure of the lumbar spine, the risk of injury to abdominal organs, great vessels, psoas major muscle, and lumbar plexus nerve from this approach cannot be ignored.\(^{20,27,28}\) However, in our cohort, there were no serious complications, and there was no statistically significant difference in the probability of com-

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Table 5. Logistic regression analysis of radiological outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Fused condition (yes or no)</th>
<th>Subsidence condition (yes or no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF</td>
<td>25</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>OLIF-AF</td>
<td>19</td>
<td>1.083 (0.150–7.808)</td>
<td>0.937</td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>27</td>
<td>3.649 (0.519–25.647)</td>
<td>0.193</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td>30</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≤ 65</td>
<td>41</td>
<td>1.542 (0.310–7.677)</td>
<td>0.597</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>4.552 (0.687–30.150)</td>
<td>0.116</td>
</tr>
<tr>
<td>Fused segment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>39</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Double</td>
<td>32</td>
<td>0.563 (0.106–2.996)</td>
<td>0.501</td>
</tr>
<tr>
<td>Bone density(^{†})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low</td>
<td>43</td>
<td>1.280 (0.210–7.819)</td>
<td>0.789</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

\(^{†}\)The bone density was presented as continuous variable based on lumbar computed tomography Hounsfield units value.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Properties (mean follow-up)</th>
<th>Subjects</th>
<th>Group (n)</th>
<th>Results</th>
<th>Limitations of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujibayashi et al.</td>
<td>A prospective consecutive clinical study</td>
<td>Degenerative lumbar diseases</td>
<td>28 in OLIF-PF</td>
<td>Significant improvement in DH, SDA, JOA score Fusion rate: 100%</td>
<td>The study population was heterogeneous with different lumbar levels and pathologies.</td>
</tr>
<tr>
<td>Sato et al.</td>
<td>A prospective study, 12 months</td>
<td>Degenerated spondylolisthesis</td>
<td>20 in OLIF-PF</td>
<td>Significant improvement in VAS, ODI, DH, CSA, FH</td>
<td>The sample size was small, the follow-up time was short, and bone fusion was not evaluated.</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>A retrospective study, 7 months for all patients</td>
<td>Degenerative lumbar disease</td>
<td>22 in OLIF</td>
<td>Significant improvement in VAS, ODI, SF-36</td>
<td>There was no comparison between OLIF and fixed follow-up, no statistical fusion, and the follow-up time was short.</td>
</tr>
<tr>
<td>Sardhara et al.</td>
<td>A retrospective study, 5.7 months for all patients</td>
<td>Lumbar spondylolisthesis</td>
<td>8 in OLIF-PF, 5 in OLIF-LF, 2 in OLIF-RPSF</td>
<td>Fusion rate: 57% in OLIF-PF, and 100% in OLIF-LLF</td>
<td>The follow-up time is short and the sample size is small.</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>A preliminary retrospective study, 9.7 months for OLIF-AF</td>
<td>Degenerative spine deformity</td>
<td>11 in OLIF-AF</td>
<td>Similar changes in coronal Cobb angle, LL, PT, PI-LL mismatch, CSVL, and SVA, VAS for back pain and ODI score Fusion rate: 100%</td>
<td>The number of cases was small, patients had selection bias, and the follow-up time was short.</td>
</tr>
<tr>
<td>Xie et al.</td>
<td>A retrospective analysis, 15.0 months for OLIF-AF</td>
<td>Lumbar degenerative disc disease</td>
<td>65 in OLIF-AF</td>
<td>Significant improvement in ODI score, VAS, cross-sectional area, disk height, foraminal height Fusion rate at 12 months: 93.8%</td>
<td>There is no distinction between segments resulting in differences.</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>A retrospective study, 21 months for all patients</td>
<td>Degenerative lumbar diseases</td>
<td>14 in OLIF-AF</td>
<td>Significant improvement in DH, FA, and CSA, VAS, ODI Fusion rate at follow-up months: 95%</td>
<td>The sample size was small.</td>
</tr>
<tr>
<td>Luo et al.</td>
<td>A retrospective study, 31.8 months for all patients</td>
<td>Lumbar polymicrobial spondylodiscitis</td>
<td>7 in OLIF-PF</td>
<td>Significant improvement in VAS, ODI Fusion rate at 24 months: 100%</td>
<td>The sample size was small.</td>
</tr>
<tr>
<td>He et al.</td>
<td>A retrospective study, 24 months for OLIF, 24 months for OLIF-PF</td>
<td>Spondylolisthesis</td>
<td>32 in OLIF, 41 in OLIF-PF</td>
<td>Similar changes in VAS score, posterior disc height, foraminal height, foraminal width OLIF was superior to OLIF-PF in operation time, intraoperative blood loss. Fusion rate at 24 months: 93.8% in OLIF and 100% in OLIF-PF</td>
<td>Prognosis assessment was incomplete and there was no multivariate analysis.</td>
</tr>
<tr>
<td>Cheng et al.</td>
<td>A retrospective study, 23.3 months for all patients</td>
<td>Degenerative lumbar diseases</td>
<td>48 in OLIF-PF, 15 in OLIF-PF, 16 in OLIF-AF</td>
<td>Similar changes in VAS, ODI, the DH, SL, LL, CSA, PT, and PI-LL mismatch had also improved by final follow-up.</td>
<td>The study population was heterogeneous with different lumbar levels and pathologies. The fusion rate, operative time, bleeding and other differences between the 3 groups were not compared.</td>
</tr>
</tbody>
</table>

(Continued)
Table 6. Literature review of the clinical and radiologic outcomes of OLIF compared to other lumbar interbody fusion (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Properties (mean follow-up)</th>
<th>Subjects</th>
<th>Group (n)</th>
<th>Results</th>
<th>Limitations of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo et al.18 2021</td>
<td>A retrospective analysis,</td>
<td>Single-segment mild degenerative lumbar diseases</td>
<td>24 in OLIF-AF; 27 in OLIF-PF</td>
<td>Similar changes in ODI score, anterior and posterior disc heights, foraminal height, fusion rate, and incidence of complications; OLIF-AF was superior to OLIF-PF in anesthesia time, operation time, intraoperative blood loss, number of intraoperative fluoroscopy, and VAS score. Fusion rate at 18 months: 87.5% in OLIF-AF and 92.6% in OLIF-PF</td>
<td>The effect of double segments was not included, the number of cases was small and the follow-up time was short.</td>
</tr>
<tr>
<td>Zhang et al.7 2022</td>
<td>A retrospective analysis,</td>
<td>Lumbar spondylolisthesis</td>
<td>25 in OLIF-ASRSF; 28 in OLIF-PF</td>
<td>Significant improvement in VAS, FH, LL, DH. OLIF-ASRSF was superior to OLIF-PF in ODI at 24 months postsurgery. Fusion rate at 24 months: 100% in OLIF-ASRSF; 100% in OLIF-PF</td>
<td>The sample size was small and there was no independent evaluation based on surgical level, the patients were young with ideal bone quality, and elderly patients were not counted.</td>
</tr>
</tbody>
</table>

OLIF, oblique lateral interbody fusion; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation; OLIF-AF, OLIF combined with anterolateral screw fixation; DH, disc height; SDA, segmental disc angle; JOA score, Japanese Orthopaedic Association; VAS, visual analogue scale; ODI, Oswestry Disability; SF-36, Short Form health survey; FH, foraminal height; OLIF-RPSF, OLIF combined with reverse pedicle screw fixation; OLIF-LLF, OLIF combined with lateral lumbar intervertebral fixation; LL, lumbar lordotic angle; PT, pelvic tilt; PI-LL, pelvic incidence minus lumbar lordosis; CSVL, central sacral vertical line; SVA, sagittal vertical axis; SLL, segmental lumbar lordotic angle; FA, foramen area; CSA, cross-sectional area.

CONCLUSION

For 2 or fewer surgical levels, we believe that OLIF remains a viable option. This technique has similar patient-reported outcomes and fusion rates as compared with the addition of lateral and posterior instrumentation, but the advantages of OLIF are the avoidance of posterior pedicle instrumentation, the percutaneous nature of the technique, and the substantial reduction in operating time. The subsidence rate of OLIF is higher than that of lateral and posterior internal fixation, but most of the subsidence is mild and has no adverse effect on clinical and radiographic outcomes. The long-term effects of OLIF are still under evaluation, but early data suggest that OLIF remains a safe and effective option for the treatment of lumbar degenerative diseases.

NOTES

Supplementary Materials

Supplementary Tables 1-5 can be found via https://doi.org/10.14245/ns.2244954.477.

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Supplementary Information

www.e-neurospine.org sidered.

Zhang Y, et al.
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### Supplementary Table 1. Subgroup analysis of prognosis in patients with single/double fused segment

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Delta VAS of low back †</th>
<th>p-value</th>
<th>Delta VAS of leg †</th>
<th>p-value</th>
<th>Fused (yes/no)</th>
<th>p-value</th>
<th>Subsidence (yes/no)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single segment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF</td>
<td>13</td>
<td>4.0 (3.0–6.0)</td>
<td>0.262</td>
<td>3.0 (0–5.0)</td>
<td>0.592</td>
<td>11/2</td>
<td>0.811</td>
<td>8/5</td>
<td>0.440</td>
</tr>
<tr>
<td>OLIF-AF</td>
<td>7</td>
<td>3.0 (0–4.0)</td>
<td>4.0 (0–4.0)</td>
<td>7/0</td>
<td>0.592</td>
<td>11/2</td>
<td>0.811</td>
<td>8/5</td>
<td>0.440</td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>19</td>
<td>3.0 (0–5.0)</td>
<td>3.0 (0–6.0)</td>
<td>17/2</td>
<td>0.761</td>
<td>17/2</td>
<td>0.582</td>
<td>12/7</td>
<td>0.228</td>
</tr>
<tr>
<td><strong>Double segments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF</td>
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<td>0.458</td>
<td>3.0 (0–4.0)</td>
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<td>0.648</td>
<td>9/3</td>
<td>0.091</td>
</tr>
<tr>
<td>OLIF-AF</td>
<td>12</td>
<td>4.0 (1.0–6.0)</td>
<td>2.0 (0–5.0)</td>
<td>10/2</td>
<td>0.648</td>
<td>10/2</td>
<td>0.648</td>
<td>7/5</td>
<td>0.091</td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>8</td>
<td>4.0 (2.0–4.0)</td>
<td>2.5 (0–4.0)</td>
<td>8/0</td>
<td>0.761</td>
<td>8/0</td>
<td>0.582</td>
<td>6/2</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Values are presented as median (range).

VAS, visual analogue scale; OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

†The delta VAS of low back/leg was calculated as the pre-VAS score minus follow-up VAS.
## Supplementary Table 2. Subgroup analysis of prognosis in male and female patients

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Delta VAS of low back&lt;sup&gt;†&lt;/sup&gt;</th>
<th>p-value</th>
<th>Delta VAS of leg&lt;sup&gt;†&lt;/sup&gt;</th>
<th>p-value</th>
<th>Fused (yes/no)</th>
<th>p-value</th>
<th>Subsidence (yes/no)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF</td>
<td>7</td>
<td>4.5 (3.0–6.0)</td>
<td>0.272</td>
<td>3.0 (1.0–5.0)</td>
<td>0.865</td>
<td>5/2</td>
<td>0.640</td>
<td>4/3</td>
<td>0.620</td>
</tr>
<tr>
<td>OLIF-AF</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1/0</td>
<td>0.865</td>
<td>0/1</td>
<td>0.906</td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>15</td>
<td>3.0 (0–5.0)</td>
<td>3.0 (0–6.0)</td>
<td>13/2</td>
<td>13/2</td>
<td>5/10</td>
<td>0.620</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>OLIF</td>
<td>18</td>
<td>4.0 (2.0–5.0)</td>
<td>0.310</td>
<td>3.0 (0–4.0)</td>
<td>0.375</td>
<td>16/2</td>
<td>0.660</td>
<td>13/5</td>
<td>0.111</td>
</tr>
<tr>
<td>OLIF-AF</td>
<td>18</td>
<td>4.0 (0–6.0)</td>
<td>3.0 (0–5.0)</td>
<td>16/2</td>
<td>16/2</td>
<td>10/8</td>
<td>0.660</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>12</td>
<td>4.0 (2.0–4.0)</td>
<td>2.0 (0–4.0)</td>
<td>12/0</td>
<td>12/0</td>
<td>4/8</td>
<td>0.660</td>
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<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range).

VAS, visual analogue scale; OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

<sup>†</sup>The delta VAS of low back/leg was calculated as the pre-VAS score minus follow-up VAS.
## Supplementary Table 3. Subgroup analysis of prognosis in elderly patients

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Delta VAS of low back†</th>
<th>p-value</th>
<th>Delta VAS of leg†</th>
<th>p-value</th>
<th>Fused (yes/no)</th>
<th>p-value</th>
<th>Subsidence (yes/no)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More than 65 yr</strong></td>
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<td></td>
</tr>
<tr>
<td>OLIF</td>
<td>11</td>
<td>4.0 (2.0-6.0)</td>
<td>0.153</td>
<td>3.0 (0-4.0)</td>
<td>0.524</td>
<td>9/2</td>
<td>0.621</td>
<td>8/3</td>
<td>0.423</td>
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<tr>
<td>OLIF-AF</td>
<td>10</td>
<td>4.0 (3.0-6.0)</td>
<td>2.5 (1.0-4.0)</td>
<td>10/0</td>
<td></td>
<td>5/5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>9</td>
<td>4.0 (0-5.0)</td>
<td>4.0 (0-6.0)</td>
<td>8/1</td>
<td></td>
<td>4/5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Less than 65 yr</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF</td>
<td>14</td>
<td>4.0 (3.0-5.0)</td>
<td>0.445</td>
<td>3.0 (0-5.0)</td>
<td>0.603</td>
<td>12/2</td>
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</tr>
<tr>
<td>OLIF-AF</td>
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<td>4.0 (0-5.0)</td>
<td>3.0 (0-5.0)</td>
<td>7/2</td>
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<td>5/4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>18</td>
<td>4.0 (0-5.0)</td>
<td>2.5 (0-4.0)</td>
<td>17/1</td>
<td></td>
<td>5/13</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range).

VAS, visual analogue scale; OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

†The delta VAS of low back/leg was calculated as the pre-VAS score minus follow-up VAS.
Supplementary Table 4. Univariate analysis of clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Delta VAS of low back$^1$</th>
<th>p-value</th>
<th>Delta VAS of leg$^1$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>OLIF</td>
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<td>0.102</td>
<td>3.0 (0–5.0)</td>
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<tr>
<td>OLIF-AF</td>
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<td></td>
</tr>
<tr>
<td>OLIF-PF</td>
<td>27</td>
<td>3.0 (0–5.0)</td>
<td></td>
<td>3.0 (0–6.0)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
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<td></td>
<td>0.147</td>
<td></td>
<td>0.477</td>
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<tr>
<td>&gt; 65</td>
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<td>4.0 (0–5.0)</td>
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<td>3.0 (0–5.0)</td>
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</tr>
<tr>
<td>≤ 65</td>
<td>41</td>
<td>4.0 (0–6.0)</td>
<td></td>
<td>3.0 (0–6.0)</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
<td>0.239</td>
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<td>Male</td>
<td>23</td>
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<td></td>
<td>3.0 (0–6.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>4.0 (0–6.0)</td>
<td></td>
<td>3.0 (0–5.0)</td>
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</tr>
<tr>
<td>Fused segment</td>
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<tr>
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<td>3.0 (0–6.0)</td>
<td></td>
</tr>
<tr>
<td>Double</td>
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<td></td>
<td>3.0 (0–5.0)</td>
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<tr>
<td>Bone density$^1$</td>
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<td>0.268</td>
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<td>3.0 (0–5.0)</td>
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<tr>
<td>Low</td>
<td>43</td>
<td>4.0 (0–5.0)</td>
<td></td>
<td>3.0 (0–6.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range).

VAS, visual analogue scale; OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

$^1$The bone density was presented as continuous variable based on lumbar computed tomography Hounsfield units value.$^1$The delta VAS of low back/leg was calculated as the pre-VAS score minus follow-up VAS.
## Supplementary Table 5. Multivariate linear regression analysis of clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Delta VAS of low back&lt;sup&gt;†&lt;/sup&gt;</th>
<th>Delta VAS of leg&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \beta )</td>
<td>SE</td>
</tr>
<tr>
<td>Surgery</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>OLIF</td>
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<td>1.00</td>
</tr>
<tr>
<td>OLIF-AF</td>
<td>19</td>
<td>-0.170</td>
<td>0.371</td>
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<tr>
<td>OLIF-PF</td>
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<td>-0.259</td>
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</tr>
<tr>
<td>Age (yr)</td>
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<td>&gt; 65</td>
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<td>1.00</td>
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<tr>
<td>( \leq 65 )</td>
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<td>Sex</td>
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<td>1.00</td>
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<td>Fused segment</td>
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<td>Single</td>
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<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Double</td>
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<tr>
<td>Bone density&lt;sup&gt;†&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Low</td>
<td>43</td>
<td>0.165</td>
<td>0.391</td>
</tr>
</tbody>
</table>

VAS, visual analogue scale; SE, standard error; OLIF, oblique lateral interbody fusion; OLIF-AF, OLIF combined with anterolateral screw fixation; OLIF-PF, OLIF combined with percutaneous pedicle screw fixation.

<sup>†</sup>The bone density was presented as continuous variable based on lumbar computed tomography Hounsfield units value. <sup>‡</sup>The delta VAS of low back/leg was calculated as the pre-VAS score minus follow-up VAS.
Commentary on “Perioperative Clinical Features and Long-term Prognosis After Oblique Lateral Interbody Fusion (OLIF), OLIF With Anterolateral Screw Fixation, or OLIF With Percutaneous Pedicle Fixation: A Comprehensive Treatment Strategy for Patients With Lumbar Degenerative Disease”

Chang Il Ju
Department of Neurosurgery, College of Medicine, Chosun University, Gwangju, Korea

Till now, lumbar interbody fusion remains an effective surgical treatment option for a variety of lumbar spinal disorders including degenerative spinal disease, deformity, trauma, infection, and neoplasia. In particular, recently, various surgical methods such as the posterior lumbar interbody fusion, transforaminal lumbar interbody fusion (TLIF), anterior lumbar interbody fusion, oblique lumbar interbody fusion (OLIF), and the minimal endoscopic approach have been introduced.

OLIF was first introduced by Mayer1 in 1997 as a surgical method called the prepsous approach, and in 2012, Silvestre et al.3 used the term OLIF for the first time and reported it as a new minimally invasive surgical technique. They analyzed complications and morbidity in 179 patients undergoing OLIF surgery, and initial data showed that bleeding, operative time, and postoperative recovery were favorable compared to conventional surgery.3 Today, this approach is being extended to include minimally invasive surgical treatment of spinal deformities and is used to treat a variety of degenerative spinal diseases.4

As with other minimally invasive spinal surgeries, OLIF has advantages such as minimal exposure of the surgical site, less soft tissue damage, less intraoperative bleeding and postoperative pain, as well as shorter operation time, faster recovery, and shorter hospital stay.5,6 However, like minimally invasive surgery, OLIF also has its disadvantages. A narrow and small surgical field of view does not allow a full vision of the surrounding anatomy, which can lead to complications such as disorientation, unintentional damage to anatomy, and wrong level of surgery. In addition, surgery in a narrow space makes it difficult to operate, if not much experience, the operation time and learning curve may be prolonged.
Therefore, these minimally invasive surgeries require accurate surgical site orientation and rely more frequently on fluoroscopic guidance for confirmation.  

Fortunately, these problems are becoming possible to be solved by advanced surgical equipment being introduced in spinal surgery. And, among them, representative ones are the introduction of navigation systems and robotic surgery.  

Pham et al.\(^8\) reported the use of robotic guidance for bilateral iliac fixation in a single lateral position as a way to gain advantages in terms of time savings and efficiency could significantly reduce surgical and anesthesia time without the need to turn the patient over.  

Overall rates and types of complications after OLIF surgery were relatively low and within the expected range for an OLIF procedure. These results suggest that navigation-assisted OLIF is safe and effective with the benefit of significantly reducing radiation exposure.  

In addition, Bae et al.\(^9\) reported that using the method using transumbilical retroperitoneal lumbar interbody fusion, although technically difficult, both the treatment of degenerative spinal diseases and satisfactory cosmetic results could be achieved.  

Zhang et al.\(^7\) reported, compared with minimally invasive TLIF radiographically, OLIF was more effective in restoring disc height (DH) and better in the subsidence. Also, the fusion rate, improving the disc angle and lumbar lordosis was similar in both groups.  

However, like any other surgery, complications associated with OLIF are inevitable. For example, cage subsidence has been one of the most commonly reported complications in several studies, leading to loss of DH and recurrence of neuromuscular impingement.\(^11\)  

Zhang et al.\(^12\) reported the posterior DH, foraminal height and subsidence rate of OLIF with percutaneous pedicle screw fixation were better than that of OLIF with anterolateral screw fixation and OLIF but fusion rate was no significant. This indicates that OLIF- posterior percutaneous pedicle screw internal fixation may be superior at fostering fusion and maintaining intervertebral stability. Among other methods, additional posterior percutaneous pedicle screw internal fixation after OLIF surgery effectively maintains the stability of the 3 pillars, limits flexion and extension of the surgical segment, dissipates the stress of the fusion device, and provides a stable exterior for bone graft fusion.  

For successful surgical results of OLIF, it is very important to reduce the cage subsidence and increase the fusion rate. To achieve this goal, internal factors such as the patient’s bone mineral density are also important, but the surgical method is also an important factor. Considering that the screw fixation method can also be an important factor along with the cage insertion method.  

Clinically, the results reported by Zhang et al.\(^12\) that OLIF with percutaneous pedicle fixation can be better for promoting union and maintaining intervertebral stability make it possible to expect more successful surgery of OLIF in the future.  

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

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https://doi.org/10.14245/ns.2346608.304


Mini-Open Intercostal Retroperitoneal Approach for Upper Lumbar Spine Lateral Interbody Fusion

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2Department of Neurosurgery, Pusan National University School of Medicine, Yangsan, Korea

Objective: Conventional oblique lumbar interbody fusion (OLIF) approach is possible from the L2/3 to L4/5 levels. However, obstruction of the lower ribs (10th–12th) makes it difficult to maintain disc parallel maneuvers or orthogonal maneuvers. To overcome these limitations, we proposed an intercostal retroperitoneal (ICRP) approach to access the upper lumbar spine. This method does not expose the parietal pleura or require rib resection and employs a small incision.

Methods: We enrolled patients who underwent a lateral interbody procedure on the upper lumbar spine (L1/2/3). We compared the incidence of endplate injury between conventional OLIF and ICRP approaches. In addition, by measuring the rib line, the difference in endplate injury according to rib location and approach was analyzed. We also analyzed the previous period (2018–2021) and the year 2022, when the ICRP has been actively applied.

Results: A total of 121 patients underwent lateral interbody fusion to the upper lumbar spine (OLIF approach, 99 patients; ICRP approach, 22 patients). Endplate injuries occurred in 34 of 99 (34.3%) and 2 of 22 patients (9.1%) during the conventional and ICRP approaches, respectively (p = 0.037; odds ratio, 5.23). When the rib line was located at the L2/3 disc or L3 body, the endplate injury rate was 52.6% (20 of 38) for the OLIF approach but 15.4% (2 of 13) for the ICRP approach. Since 2022, the proportion of OLIF including L1/2/3 levels has increased 2.9-fold.

Conclusion: The ICRP approach is effective in reducing the incidence of endplate injury in patients with a relatively lower rib line, without pleural exposure or rib resection.

Keywords: Lumbar vertebrae, Spinal stenosis, Spinal fusion, Intercostal muscle

INTRODUCTION

Oblique lumbar interbody fusion (OLIF) has recently been in the spotlight owing to its advantages of indirect decompression and minimal invasiveness. In particular, the advantages of a short operation time and less bleeding volume are emphasized in multilevel surgery rather than in single-level surgery. Direct lateral interbody fusion (DLIF) is a similar approach to OLIF, but DLIF is only applied in limited range of lumbar spines owing to obstructions of the rib and pelvis. In contrast, OLIF can be applied in a relatively wide range because it can gain access despite interference of the pelvis.2–4

The OLIF approach can reach L2–5 levels. However, L1/2 is inaccessible owing to rib obstruction, and in some patients, L2/3 is also difficult to access. If the procedure is forcibly performed even with rib obstruction, an endplate injury is common because performing a procedure parallel to the disc is impossible, as shown in Fig. 1.
Endplate injury is one of the more concerning complications of OLIF, which is mainly aimed at indirect decompression. In case of failure of disc height restoration owing to endplate injury, indirect decompression may be inadequate, resulting in incomplete surgical outcomes or the need for additional laminectomy.

When OLIF is performed for deformity correction, endplate preservation is important for scoliosis correction and sagittal alignment restoration. Endplate injuries result in insufficient correction, leading to additional fusion or suboptimal outcomes. In this regard, best efforts are needed to reduce endplate injuries when performing OLIF on the upper spine.

The upper lumbar spine can also be fixed using posterolateral fusion (PLF) or posterior lumbar interbody fusion (PLIF). However, since OLIF mainly uses percutaneous pedicle screws (PPS) for posterior fixation, the combination of OLIF and PLF/PLIF has limitations, such as additional incisions in the posterior back, muscle injuries, more bleeding, and longer operation times. In this regard, accessing the upper lumbar spine from the same lateral position has advantages in that it reduces operation time and bleeding and enables the use of PPS.

Previous studies have focused on the approach of upper lumbar spine corpectomy, which requires rib resection. Studies of OLIF access to the upper lumbar spine are limited, and the recently published paper by Mitsui et al. is the only search result. In this study, the location of the rib varied from patient to patient, particularly for thoracic kyphosis and scoliosis. The authors reported that a considerable number of patients required rib resection to access the upper lumbar spine. However, complications following rib resection, such as chronic pain in the chest wall, pneumothorax, and chest tube insertion are a burden to spine surgeons. Therefore, we considered ways of accessing the upper lumbar spine without rib resection and have devised an approach.

We noted the location of the lower ribs and parietal pleura. As shown in Fig. 2, the parietal pleura descends posteriorly to the 12th rib, but it descends laterally to the 10th rib. In the lateral position, the distal intercostal space between the 10th and 12th ribs is a space without parietal pleura. If we approach this area, we can reach the retroperitoneal space through dis-
Intercostal Retroperitoneal Approach for Upper Lumbar Spine

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In this study, we provided a detailed description of the surgical technique and complications associated with the ICRP approach. In addition, we compared the endplate injury rate of the upper lumbar spine between the conventional OLIF and ICRP approaches according to the rib position.

MATERIALS AND METHODS

The Institutional Review Board (IRB) of our institution approved the study protocol and waived the requirement for informed consent owing to the retrospective nature of this study (IRB number: 05-2022-214). All procedures involving human participants were performed according to the ethical standards of the IRB of the hospital.

1. Patient Enrollment

Our institution performed 677 OLIF procedures between April 2018 and December 2022. Among them, we enrolled patients as follows: (1) Degenerative lumbar stenosis, spondylolisthesis, degenerative scoliosis, degenerative kyphosis, or adjacent segment disease that did not respond to medications and conservative treatments for more than 6 weeks, (2) demineralized bone matrix (DBM) filling polyetheretherketone (PEEK) cage, (3) OLIF was performed on the upper lumbar spine (L1/2 or L2/3 or L1/2/3), (4) OLIF was extended form the upper lumbar spine (L1/2 or L2/3 or L1/2/3) to the lower lumbar spine (L3/4/5/S1) (Fig. 3). We excluded patients as following exclusion criteria: (1) surgery due to infection, trauma, or tumor, (2) using interbody material other than PEEK+DBM, (3) among multilevel fusions, simple posterior fixation of the upper lumbar spine without OLIF (L1/2 or L2/3 or L1/2/3), (4) patients in whom additional surgeries at the index level during the follow-up period were excluded. Demographic data such as body mass index (BMI), bone mineral density (BMD), American Society of Anesthesiologists (ASA) physical status classification grade, past medical history, operation time, estimated blood loss (EBL), and history of previous lumbar spine surgery were collected. In addition, the diagnosis that led to the operation was classified as follows: adjacent segmental disease (ASD), scoliosis, multiple stenosis with/without sagittal deformity, and focal stenosis.

2. Surgical Technique (Supplementary video)

1) Preoperative planning

When planning the ICRP approach for the upper lumbar spine, the extent of descent of the left costophrenic recess was evaluated using preoperative x-ray and computed tomography (CT) images. This evaluation was valuable because in patients in whom the OLIF L1/2/3 approach is obstructed by the ribs, the rib cage is located considerably downward, but the costophrenic recess...
2) Skin incision

The disc level of L1/2 or L2/3 was marked using the C-arm. The ribs were marked by palpation around the disc level. An incision of approximately 4 cm was made between the anterior and posterior axillary lines (Fig. 5A).

3) Dissection of the chest wall

The subcutaneous skin, external intercostal muscles, internal intercostal muscles, innermost intercostal muscles, and diaphragm were exposed in sequence. This layer-by-layer approach involves spreading each muscle bundle. The diaphragm was incised to visualize the retroperitoneal fat (Fig. 5B–E). We should pay attention about the exposure of pleura in the space between the innermost intercostal muscles and diaphragm.

4) Retroperitoneal approach

After retroperitoneal fat is retracted to the medial side, the psoas muscle is exposed. When the psoas muscle was retracted dorsally, the disc space was exposed. During this process, attention should be paid to the sympathetic chain, which is located close to the psoas muscle in the upper lumbar spine. When the path of the sympathetic chain overlapped with the annulotomy margin, the sympathetic chain was medially dissected and retracted (Fig. 5F). At this time, the commercially available OLIF25 retractor was inserted between the ribs (Fig. 5G). When the retractor was distracted between the ribs, sufficient fixation force was obtained without pinning (Fig. 5H).

5) Cage insertion

After confirming the annulotomy margin through the C-arm, annulotomy, discectomy using a shaver, contralateral annulus release, trial placement, endplate preparation, and cage insertions were performed as in conventional OLIF. The contralateral annulus release process requires attention. When a sharp device, such as a curette, enters deeply during the contralateral annulus release, it can cause damage to the renal vessels, since the kidneys are located on the right side of the upper lumbar spine (Fig. 4B, D).

6) Closure

The diaphragm aponeurosis was tightly sutured, and the internal/external intercostal muscles were also closed layer by layer.

3. Radiological Parameters

We measured radiologic parameters using preoperative x-ray, intraoperative C-arm, postoperative 1-week x-ray, postoperative 1-week magnetic resonance (MR). Endplate injury was defined as any endplate disruption (> 1 mm) occurred in the postoperative MR T2 sagittal images (Fig. 6). We measured the depth of the endplate defect using postoperative MR T2 sagittal images.

The occurrence of pneumothorax and diaphragmatic herniation was evaluated using serial chest x-ray.

The rib line was defined as a line connecting the distal ends of ribs 10, 11, and 12 in the L-spine lateral image, and the level of the lumbar spine where this rib line crosses was measured (Fig. 4, red dotted line).

4. Statistical Analysis

Among the continuous variables, age, operative time, and BMD were normally distributed (using the Shapiro-Wilk test), whereas length of hospital stay, BMI, and EBL were not. The
Fig. 5. Mini-open intercostal retroperitoneal approach. (A) Incision line (red dot line) is designed at the intercostal space; 3-dimensional reconstruction image indicates L2/3 disc space is identified between ribs. (B-E) Dissection of the chest wall: (B) External intercostal muscles; (C) Internal intercostal muscles; (D) Innermost intercostal muscles; and (E) Diaphragm are identified, and the pleura is not exposed. Opening this layer exposes the retroperitoneal space. The white arrow indicates the direction of the muscle bundle. (F) The sympathetic nerve is directly anterior to the psoas muscle. The blue arrow indicates the direction of retraction. Dissection and retraction of the psoas muscle to the dorsal side and the sympathetic nerve to the ventral side.

(Continued)
RESULTS

A total of 121 patients underwent lateral interbody fusion of the upper lumbar spine. The conventional OLIF approach was employed in 99 patients (conventional group), and the ICRP approach was applied in 22 patients (ICRP group). OLIF at the L1/2 level was performed in 10 cases, and 2-level ICRP (L1/2/3) was performed in 2 cases (Fig. 2). There was no difference between the 2 groups regarding patients’ demographic characteristics such as BMI, BMD, ASA physical status classification grade, previous lumbar spine operation history, and disease entity (Table 1).

The ICRP group underwent longer-level fusion. Regarding surgical indications, multiple level stenosis with/without sagittal deformity was the most common (49 patients), followed by ASD according to the previous fusion (37 patients) (Table 1). Endplate injury occurred in 34 of 99 patients (34.3%) in the conventional group and 2 of 22 (9.1%) patients in the ICRP group. There was a significant difference in the incidence of endplate injuries between the 2 groups (p = 0.020; odds ratio, 5.23). In the conventional group, the average endplate defect depth was 1.28 ± 2.20 mm, whereas that in the ICRP group was 0.27 ± 0.94 mm (p = 0.037) (Table 1).

When comparing the year 2022 (when ICRP was actively applied) and the previous period (2018–2021), OLIF for L1/2/3 level was further increased among all OLIF patients. In 2022, the fusion level increased significantly, and OLIF was more applied even when the rib line was low. The endplate injury rate and endplate injury depth were partially reduced, but there was independent T-test or Mann-Whitney test was performed to compare the 2 groups of continuous variables according to the normal distribution. Fisher exact test was used to compare categorical variables between the 2 groups. In addition, to measure the clinical changes after the active application of ICRP, the level of fusion and endplate injury between the previous period (2018–2021) and 2022 were compared. All analyses were performed using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA).
The rib line was diversely distributed from the L1/2 disc space to the L3 vertebra; L2 vertebra - L2/3 disc level (80.2%), L1/2 disc level (9.9%), and L3 vertebra level (9.9%) (Table 1). When the rib line was high (L1/2 disc, L2 vertebra level), the conventional approach and ICRP showed no significant difference in endplate injury and endplate injury depth, but when the rib line was low (L2/3 disc, L3 vertebra level), ICRP was related with significantly lower endplate injury and endplate injury depth (Table 3).

Complications of the ICRP approach included 1 case of minimal endplate injury and 2 cases of transient sympathetic nerve injury. There was 1 case of pleura laceration and pneumothorax, which was described separately in the case. No other com-

**Table 1. Operative details**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICRP (n = 22)</th>
<th>Conventional (n = 99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.55 ± 9.26</td>
<td>69.39 ± 6.34</td>
<td>0.261</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>11:11</td>
<td>36:63</td>
<td>0.333</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.39 ± 4.68</td>
<td>26.15 ± 3.84</td>
<td>0.066</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>0.26 ± 1.82</td>
<td>0.16 ± 1.70</td>
<td>0.809</td>
</tr>
<tr>
<td>ASA PS classification grade, I:II:III</td>
<td>3:14:5</td>
<td>5:82:12</td>
<td>0.110</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>64</td>
<td>0.230</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>30</td>
<td>0.304</td>
</tr>
<tr>
<td>Smoking</td>
<td>2</td>
<td>10</td>
<td>1.000</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0</td>
<td>5</td>
<td>0.583</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1</td>
<td>8</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0</td>
<td>3</td>
<td>1.000</td>
</tr>
<tr>
<td>Cured cancer history</td>
<td>0</td>
<td>7</td>
<td>0.348</td>
</tr>
<tr>
<td>Previous lumbar spine operation, none:nonfusion:fusion</td>
<td>10:3:9</td>
<td>54:11:34</td>
<td>0.744</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>497.50 ± 187.55</td>
<td>420.86 ± 136.34</td>
<td>0.029</td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>500.00 ± 320.34</td>
<td>391.41 ± 253.55</td>
<td>0.087</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>20.83 ± 11.97</td>
<td>17.35 ± 6.70</td>
<td>0.918</td>
</tr>
<tr>
<td>Disease entity</td>
<td></td>
<td></td>
<td>0.479</td>
</tr>
<tr>
<td>ASD</td>
<td>6</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>3</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Multiple stenosis</td>
<td>12</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Focal stenosis</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Fusion level</td>
<td>3.32 ± 1.17</td>
<td>2.52 ± 0.86</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Rib line, L1:2:2.3:2:3:3</td>
<td>2.7:6:7</td>
<td>10:51:33:5</td>
<td>0.002</td>
</tr>
<tr>
<td>Endplate injury</td>
<td>2/22 (9.1)</td>
<td>34/99 (34.3)</td>
<td>0.020</td>
</tr>
<tr>
<td>Endplate injury depth (mm)</td>
<td>0.27 ± 0.94</td>
<td>1.28 ± 2.20</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). ICRP, intercostal retroperitoneal approach; BMI, body mass index; BMD, bone mineral density; ASA PS, American Society of Anesthesiologists physical status; EBL, estimated blood loss; ASD, adjacent segmental disease.

**Table 2. Comparison of endplate injury and subsidence according to period**

<table>
<thead>
<tr>
<th>Variable</th>
<th>2018–2021</th>
<th>2022</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/exclusion</td>
<td>49/369 (13.3)</td>
<td>72/187 (38.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fusion level</td>
<td>2.31 ± 0.96</td>
<td>2.90 ± 0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>Approach, ICRP/conventional</td>
<td>3/49 (6.1)</td>
<td>19/72 (26.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Rib line, low/total</td>
<td>15/49 (30.6)</td>
<td>36/72 (50.0)</td>
<td>0.030</td>
</tr>
<tr>
<td>Endplate injury/total</td>
<td>19/49 (38.8)</td>
<td>17/72 (23.6)</td>
<td>0.105</td>
</tr>
<tr>
<td>Endplate injury depth (mm)</td>
<td>1.53 ± 2.49</td>
<td>0.81 ± 1.67</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. ICRP, intercostal retroperitoneal approach. Rib line low: rib line at L2/3 disc or L3 vertebra level.
Table 3. Endplate injury incidence according to rib line and different approach

<table>
<thead>
<tr>
<th>Rib line</th>
<th>ICRP</th>
<th>Conventional</th>
<th>p-value (ICRP vs. conventional)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endplate, injury/total</td>
<td>Endplate injury depth (mm)</td>
<td>Endplate, injury/total</td>
</tr>
<tr>
<td>L1/2</td>
<td>0/2 (0)</td>
<td>0 (0)</td>
<td>2/10 (20.0)</td>
</tr>
<tr>
<td>L2</td>
<td>0/7 (0)</td>
<td>0 (0)</td>
<td>12/51 (23.5)</td>
</tr>
<tr>
<td>L2/3</td>
<td>1/6 (16.7)</td>
<td>0.33 ± 0.82</td>
<td>17/33 (51.5)</td>
</tr>
<tr>
<td>L3</td>
<td>1/7 (14.3)</td>
<td>0.57 ± 1.51</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Total</td>
<td>2/22 (9.1)</td>
<td>0.27 ± 0.94</td>
<td>34/99 (34.3)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation.
ICRP, intercostal retroperitoneal approach.
†Mann-Whitney test.

Fig. 7. Case illustration of pneumothorax. (A) Conventional OLIF L2/3/4/5 and ICRP L1/2 was performed. Red dotted line indicates incision line of ICRP. (B, C) Extralayer between innermost intercostal muscle and diaphragm. (D, E) Postoperative chest computed tomography, pneumothorax (red arrows). OLIF, oblique lumbar interbody fusion; ICRP, intercostal retroperitoneal approach.

Complications, including diaphragmatic hernia, rib fracture, contralateral root, vessel, or organ injury, were observed.

1. Case: Pleural Laceration and Pneumothorax

We encountered the first pneumothorax case (15th ICRP approach). L1–5 OLIF was performed to correct degenerative scoliosis in a 74-year-old female patient. After conventional OLIF for L2/3/4/5, we could not access the L1/2 level because of lower ribs. In this case, the ICRP incision line was designed quite posteriorly (Fig. 7A). And during the dissection, we found one
extra layer between innermost and diaphragm. This layer is tough, membrane-like layer without muscle (Fig. 7B, C). Postoperative chest CT showed pneumothorax (Fig. 7D, E). Since there was no lung or visceral pleura injury, it was absorbed naturally. We guess that the cause of the pneumothorax was the posterior location of the incision. Since the parietal pleura descends to the lower rib posteriorly, there is a risk of pneumothorax injury if the incision is designed posteriorly to the midaxillary line (Fig. 2).

DISCUSSION

The ICRP approach for upper lumbar spine OLIF has some advantages over the existing approach involving rib resection. Because the pleura is exposed at the posterior part of the lower rib, an incision between the anterior and posterior axillary lines can avoid exposure of the parietal pleura. In addition, the ICRP approach is free of rib resection-related complications. Since the commercial retractor can be fixed in the intercostal space without pinning, no risk of pin-site complications such as segmental vessel injury or ureter injury, is present. The most important advantage of ICRP is the lower risk of endplate injury because we can insert a surgical device parallel to the disc space.

We analyzed differences in surgical trends after use of ICRP by comparing 2022 and previous period (2018–2021). Compared to the past, we performed L1/2/3 level surgery in much more cases in 2022. Even in the similar disease entity at the 2 timepoints, we believe that the difference in fusion level is due to following reasons; (1) In the past, when the rib line was low, we could not approach the upper lumbar spine; (2) The endplate was severely damaged when approaching excessively with the conventional approach; (3) With the development of ICRP, we can perform OLIF on the upper spine while reducing endplate injury even a lower rib line. Through these changes, we can reduce the back muscle injury, EBL, and additional time for posterior fusion of the upper lumbar spine. In addition, our experience showed that, through ICRP, even a spine surgeon who has no experience in chest wall surgery can easily extend the range of OLIF to the upper lumbar spine.

However, the ICRP approach requires an additional incision, which leads to prolonged surgical time. In this regard, if the rib line is higher than the L2/3 disc level, the conventional approach is preferred over the ICRP approach. If the rib line is L2/3 or lower, the ICRP approach is a good option (Table 3). We also noted that the ICRP approach may be difficult to perform in patients with large rib cages.

Unlike the conventional OLIF approach, the ICRP approach requires an understanding of 4 specific anatomical structures. First: intercostal muscle layers. Four layers of intercostal muscles were visualized during the ICRP approach: the external intercostal muscles, internal intercostal muscles, innermost intercostal muscles, and diaphragm. In the process of exposing each muscle layer, dissection too close to the inferior border of the rib may damage the intercostal nerves or vessels. If a structure other than the muscle layer is identified during the dissection process, determining whether air bubbles are formed after filling the operative corridor with saline is necessary. Second: sympathetic nerves. The thoracic sympathetic nerve descends below the diaphragm (at the L2 level) and becomes the abdominal sympathetic nerve, which is located at the anterior border of the psoas muscle at the L2 level. Going distally, it runs ventral (to the aorta) and away from the psoas muscle.24 As shown in Fig. 5E, the sympathetic nerve is likely included in the range of annulotomy at L1/2 or L2/3. In such cases, sufficient medial retraction of the sympathetic nerve is necessary before annulotomy. Third: contralateral vessels and organs. As shown in Fig. 4, the L1/2 or 2/3 level is close to the right kidney or renal vessel. Hence, careful maneuvering during contralateral annulotomy is advisable. In particular, the use of a blunt device, rather than a sharp one (such as a curette), is recommended for annulotomy. We should also avoid inserting these devices too deep. Finally: rib line and parietal pleura. Every patient has a considerably different rib line due to thoracic kyphosis, and aging.20,25 However, the costophrenic recess is constantly positioned irrespective of the rib line. The parietal pleura descends to the 12th rib in the midscapular line, 10th rib in the midaxillary line, and 8th rib in the midclavicular line.21 Therefore, the lateral minimal incision is less likely to expose the parietal pleura than an incision extending posteriorly (Fig. 2). However, serial follow-up chest x-rays are required to evaluate minor injuries of the parietal pleura that are not recognized during surgery.

This study had several limitations. First, selection bias inevitably existed in patients who chose the conventional and ICRP approaches. However, in our study, ICRP was performed in patients with a lower rib line. The selection bias was more unfavorable for ICRP, yet it presented better results. Second, our study did not describe the clinical outcomes. This is because most of the enrolled patients underwent multisegment surgery for different disease entities, and a simple comparison of clinical results is not meaningful. Third, the fusion rate was not evaluated in our study because we did not have long-term follow-up data, and no follow-up CT evaluations were performed. How-
ever, this study focused on the introduction of a new surgical technique and its short-term complications. In addition, we assumed that this approach may have little effect on the fusion rate because ICRP does not require rib resection and has a lower incidence of endplate injury. Fourth, we evaluated endplate injury by MR rather than x-ray. As shown in Fig. 5A, it is difficult to evaluate endplate injury at all levels in patients with scoliosis using only L-spine x-ray lateral images. Therefore, we measured the presence and depth of endplate injury using postoperative MR T2 sagittal images. For this reason, the endplate injury rate was significantly higher than that of previous OLIF endplate injury related studies.26,27

CONCLUSION

The ICRP approach is effective in reducing the incidence of endplate injuries in patients with a relatively low rib line. In addition, this approach has the advantage of a smaller incision, without pleural exposure or rib resection, compared to the conventional upper lumbar spine approach. However, the possible risks of sympathetic nerve and contralateral side injuries should be considered.

NOTES

Supplementary Material: Supplementary video clip 1 can be found via https://doi.org/10.14245/ns.2244960.480.

Video clip 1. Mini-open intercostal retroperitoneal approach for upper lumbar spine.

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: SHL, DWS; Data curation: SHL, JSL, YHK; Formal analysis: SHL, SHB; Methodology: SHL, SHB, DWS; Project administration: DWS, GSS; Visualization: SHL; Writing - original draft: SHL, DWS; Writing - review and editing: SHL, DWS, SHB, JSL, YHK, SKS, SWL, GGS.

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Commentary on “Mini-Open Intercostal Retroperitoneal Approach for Upper Lumbar Spine Lateral Interbody Fusion”

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Multiple minimally invasive anterior and lateral operative techniques have been developed to achieve indirect decompression and arthrodesis of the lumbar spine. Amongst them is the oblique lateral lumbar interbody fusion (OLIF) which utilizes a left-sided anterior-to-psoas window to access the disc space. This minimally invasive approach was designed to allow direct access to the anterolateral lumbar spine, through the retroperitoneal space, and lessen the retraction on the psoas muscle and lumbar plexus as compared to the relatively similar direct lumbar interbody fusion, which utilizes a transpsoas approach. Both of these lateral approaches allow for placement of larger interbody cages across the lumbar intervertebral spaces as compared to traditional posterior based interbody fusion such as the transfemoral lumbar interbody fusion. Both the direct and oblique lateral approaches are clinically beneficial for select cases of spinal canal stenosis as the large graft expands foraminal height as well as increases the spinal canal diameter by stretching the ligamentum flavum, a process referred to as indirect decompression. This indirect decompression may lose its effectiveness if there is cage subsidence, which is commonly a result of bony endplate injury during the discectomy. A central technical tenet of the OLIF technique is to align the retractor in parallel with the disc space to both aid in the discectomy and interbody placement as well as lessen the chance of this endplate injury as the decompression is completed and prepared for arthrodesis. While this parallel retractor placement can be achieved more easily in the lower lumbar spine, even under the iliac crest for L4–5 access, OLIF at the upper lumbar levels may be obstructed by the 10th, 11th and 12th ribs. To overcome this rib impediment, many surgeons resect the anterior portions of these ribs to access the thoracolumbar junction during the OLIF approach in order to obtain the necessary parallel retractor placement.

This issue of Neurospine features the article “Mini-Open Intercostal Retroperitoneal Approach for Upper Lumbar Spine Lateral Interbody Fusion” which describes a novel adaptation of the OLIF technique that obviates the need for rib resection and maintains parallel access to the disc spaces. The authors describe a dissection of the intercostal muscles over the top of the ribs to allow sufficient space to open the retractor. By avoiding the traditional rib resection at these levels, the author postulate that the rate of pneumothorax, chest wall pain and chest tube insertion would be lower than in the traditional approach. The present study examines 121 total patients; 99 of whom had traditional OLIF approaches to the L1–2...
or L2–3 disc spaces and 22 patients who had the intercostal retroperitoneal approach (ICRP). The disc removal, endplate preparation and interbody placement in the groups were similar. The rib line, as measured by a line connecting the distal tips of the 10th, 11th and 12th ribs were also measured. There was significantly less endplate injury in the ICRP group (9.1%) as compared to the traditional OLIF approach (34.3%) as measured by postoperative magnetic resonance imaging. In patients with low rib lines (caudal to the L2–3 disc). The advantage of the ICTR was maintained with a comparative rate of endplate injury of 15.4% versus 52.6%. This low rib line anatomy can make traditional OLIF even more challenging. Although the long-term follow-up in patients was not included in the report, it could be inferred that the higher rates of endplate injury in the traditional OLIF group may result in higher subsidence and less clinical benefit. While the study's small size and biases are explained by the authors, it should not detract from the important technical nuances that are presented.

Lateral surgery of the upper lumbar spine and thoracolumbar junction requires anatomical knowledge of this complex region. Either (or both) the retroperitoneal and retropleural cavities may need to be entered, as these 2 cavities are essentially contiguous aside from the separating diaphragm. The diaphragm may need to be opened or reflected in order to access the disc space. Since the lateral attachments of the diaphragm are typically between the inferior edge of the 10th rib and superior edge of the 12th rib, skin incision lines above the 10th rib have traditionally been used for retroperitoneal approaches and below the 12th rib for retropleural approaches. While these incision placement recommendations are good general guidelines, there is significant variability in the diaphragmatic attachments in different patients, and surgeons may need to mobilize the diaphragm even if anticipating a purely retroperitoneal approach. In addition, the parietal pleura may be encountered in upper lumbar retroperitoneal approaches as the parietal pleura descends posteriorly to the 12th rib but laterally to the 10th rib. Therefore, even though the approach is started in the retroperitoneal space, it may transgress the retropleural space, especially when these lower ribs are resected. Mitsui et al. recently published on the need for rib resection specifically in the OLIF approach to upper lumbar retroperitoneal approaches as the parietal pleura descends posteriorly to the 12th rib but laterally to the 10th rib. Therefore, even though the approach is started in the retroperitoneal space, it may transgress the retropleural space, especially when these lower ribs are resected. Mitsui et al. recently published on the need for rib resection specifically in the OLIF approach to upper lumbar retroperitoneal fusion (L1–2 and L2–3). In the study of Mitsui et al., factors affecting the need for rib resection were studied postoperatively. The decision for rib resection was made intraoperatively based on a true lateral fluoroscopic image. While these authors concluded that thoracolumbar kyphosis and the location of the apex of a coronal lumbar deformity were the independent risk factors associated with the need for rib resection during OLIF. With the standard OLIF technique, the rate of endplate injury was higher in the nonrib resection group and the rate of pleural violation was higher in the rib resection group. These secondary results of the (endplate injury and pleural violation) support the utility and value of an approach such as the ICRP OLIF.

Balancing the need to obtain a parallel view of the disc space with the associated risks of rib resection required in many upper lumbar OLIF was the basis of the development of the ICRP technique. The authors did report a pleural laceration and pneumothorax complication with the ICRP approach which they postulated was secondary to a posteriorly biased incision and the posterior and dorsal descent of the parietal pleura. It will be interesting to see the longer term results of the ICRP approach, and whether these selected complications continue to be lower than with traditional OLIF approaches. Based on the variable anatomy of the diaphragm, caudal ribs and soft tissue structures at the thoracolumbar junction, it is unlikely that any lateral access approach will eliminate the risks of complications. The authors should be commended for their description of this novel technique and their critical investigation. While larger scale studies of ICRP OLIF are certainly forthcoming to validate these early results, the ICRP approach does provide lateral surgeons with an additional strategy to avoid potential complications and improve outcomes in this crowded and challenging region of the spine.

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

REFERENCES


Overall Survival of Non-Small Cell Lung Cancer With Spinal Metastasis: A Systematic Review and Meta-Analysis

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Objective: The long-term survival data of lung cancer patients with spinal metastases are crucial for informed treatment decision-making. However, most studies in this field involve small sample sizes. Moreover, survival benchmarking and an analysis of changes in survival over time are required, but data are unavailable. To meet this need, we performed a meta-analysis of survival data from small studies to obtain a survival function based on large-scale data.

Methods: We performed a single-arm systematic review of survival function following a published protocol. Data of patients who received surgical, nonsurgical, and mixed modes of treatment were meta-analyzed separately. Survival data were extracted from published figures with a digitizer program and then processed in R. Median survival time was used as an effect size for moderator analysis to explain the heterogeneity.

Results: Sixty-two studies with 5,242 participants were included for pooling. The survival functions showed a median survival of 6.72 months for surgery (95% confidence interval [CI], 61.9–7.01; 2,367 participants; 36 studies), 5.99 months for nonsurgery (95% CI, 5.33–6.47; 891 participants; 12 studies), and 5.96 months for mixed (95% CI, 5.67–6.43; 1,984 participants; 18 studies). Patients enrolled since 2010 showed the highest survival rates.

Conclusion: This study provides the first large-scale data for lung cancer with spinal metastasis that allows survival benchmarking. Data from patients enrolled since 2010 had the best survival and thus may more accurately reflect current survival. Researchers should focus on this subset in future benchmarking and remain optimistic in the management of these patients.

Keywords: Carcinoma, Non-small cell lung, Survival analysis, Metastasis, Spine

INTRODUCTION

Survival benchmarking is fundamental in cancer management. First, the survival of spine metastases of lung cancer is highly diverse as it is affected by age, functional status, molecular profiles such as epidermal growth factor receptor (EGFR) mutation, and many difficult-to-measure variables. When the survival outcome of this highly diverse population is derived from a small number of cases, the likelihood of misleading conclusions can be high. Zairi et al.1 studied 53 surgical patients with lung cancer with spine metastasis and concluded that surgery is not recommended on account of short life expectancy and frailty. Although employing a large sample size would potentially avoid this, small sample size studies such as this are common in the current literature. One potential solution is to use data from the Global Cancer Observatory,2 which provides
large-scale survival data for lung cancer that inform cancer control, research, and survival benchmarking. Although lung cancer data are available in this format, data regarding patients with spine metastases are not. This defect should be filled in the current era of big data-oriented cancer statistics.

Second, surgeons typically consider fixation or fusion instrumentation appropriate for patients who survive for longer than 1 year after surgical treatment. Wide excision is also considered for patients who survive longer. However, decompression alone or vertebroplasty can be used as alternative treatments for patients with limited survival. Therefore, when treating patients with recurrent lesions after local treatment, surgeons and radio-oncologists need expected survival data for treatment decision-making.

Furthermore, the influence of time is significant and includes progressing aging demographics and the advancement of multimodal oncological treatments. Therefore, survival is not constant but could subtly improve over time. Following the introduction of targeted therapies (such as TKIs) in early 2000, the survival rates of patients with lung cancer have gradually improved. Accordingly, improved survival is also expected among patients with spinal metastasis; however, this assumption has not been substantiated. The Global Spinal Tumour Study Group attempted—but failed—to statistically demonstrate improved survival among patients with spinal metastasis of lung cancer. Although this multinational collaborative study included 263 patients, the confidence intervals of the survival curves were wide, and statistically significant differences could not be established (Fig. 1).

One solution to the above problem is a meta-analysis, which can help obtain a survival function based on large-scale data. Two types of patient populations need to be addressed separately: those who underwent surgery and those who received nonsurgical treatments. In a randomized study conducted in 2005, Patchell et al. reported that surgery provided a clear advantage in metastatic epidural spinal cord compression. Since then, surgery has become the first option for patients who can physically tolerate it. Moreover, the surgical community seems to fully accept this conclusion, as no other randomized studies have been reported in this field since the study was published. However, patients who are unlikely to tolerate surgery are considered to have a poorer baseline condition, regardless of cord compression or spinal instability. Therefore, the surgical treatment itself may act as a selection criterion that differentiates the baseline condition. To separately accommodate the 2 types of patients, the current study meta-analyzed each group separate-
ly. This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines.6

MATERIALS AND METHODS

All data are provided within the article and are freely available from the Open Science Framework.6 The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021256577) on July 8, 2021.

This single-arm meta-analysis analyzed the survival function of non-small cell lung cancer (NSCLC) patients with spinal metastasis. Pathologies other than NSCLC and patients without spinal metastasis were excluded. The patient population was divided into 3 groups: surgery, nonsurgery, and mixed. Surgery was defined as patients undergoing operative treatment such as palliative decompression, debulking, total vertebrectomy, separation surgery, or any form of minimally invasive surgery. Nonsurgery was defined as treatments such as radiotherapy, vertebroplasty, chemotherapy, or palliative care. The mixed category contained combined survival data of surgical and nonsurgical patients. Only studies with extractable survival data were included. Studies with unextractable data, those that included non-NSCLC pathologies or nonspinal metastases, and those that did not report the total number of events were excluded. The context was restricted to clinical settings such as tertiary institutions, medical centers, and oncological centers. There were no restrictions on the type of study (randomized controlled trials or nonrandomized studies) as long as the data were extractable.

1. Finding and Assessing Individual Studies

We searched MEDLINE, Embase, and Google Scholar, as illustrated in Supplementary material 1. We also included the survival data of 172 patients from our institution (the Spine Oncology Registry of National Taiwan University Hospital). The search strategy for each database is detailed in Supplementary material 2. The search was performed on June 26, 2021. There were no restrictions on language. Study titles, abstracts, and full text were independently screened for inclusion by 2 authors (CLC and FYT), and discrepancies were resolved based on a consensus with a third author (JPJ). To facilitate transparency and reproducibility, we used a prepiloted form (Supplementary material 3) in the process of study inclusion and data extraction. No automation tool was used.

For qualitative data, the bias in the body of evidence was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) version dedicated to prognostic factors.7 As the current GRADE framework has no dedicated version to accommodate single-arm reviews, we narrowed the definitions according to the fundamental intention of the assessment (Supplementary material 4). The risk of bias (study limitations) in individual studies was assessed according to the respective GRADE items. All 3 outcomes were determined a priori, as presented in a summary of findings table. The GRADE level was independently judged by CLC and FYT, and discrepancies were resolved based on a consensus with JPJ.

2. Synthesizing the Body of Evidence

Data extraction was straightforward for studies that provided the survival data of each patient within the publication. For studies that provided a Kaplan–Meier curve, we used WebPlotDigitizer4 to obtain the approximate coordinates in the image. The coordinates were processed using the IPDfromKM package8 in R statistical software (R Development Core Team 2020, www.r-project.org) to obtain the survival data of each patient. Survival time was measured in months.

The survival data of individuals were pooled to estimate the survival function separately for the surgery, nonsurgery, and mixed groups. The data were also grouped chronologically to facilitate the assessment of changes over time. However, we did not predetermine the exact date of the partition. Moderator analysis was applied to explore the sources of statistical heterogeneity in study-level covariates, with median survival as the effect size. The 5 predetermined study-level covariates were as follows: mean age; starting date of study/subgroup inclusion; surgery or alternative treatment; and proportions of patients who received tyrosine kinase inhibitor (TKI), had an EGFR mutation, or had synchronous/metachronous malignancies. Conventional definitions were used for the confidence interval (95% confidence interval [CI]), heterogeneity ($I^2$ < 40%: unimportant; 30%–60%: moderate; 50%–90%: substantial, 75%–100%: considerable), and p-value (< 0.05: significant). The online GRADEproGDT software was utilized for GRADE assessment. The R packages survival, survminer, metafor, and metaCART were used for analysis.

RESULTS

A total of 2,244 studies were identified and screened (Supplementary material 1), of which 196 studies were assessed for eligibility and 62 were included in the meta-analysis. We document-
ed the reasons for excluding 134 eligible studies (Supplementary material 5). Three studies were exclusively obtained from Google Scholar, one from the National Taiwan University Hospital Spine Oncology Registry, and the remaining 58 from either MEDLINE or Embase. The characteristics of included studies, including individual citations, are detailed in Supplementary material 6. The interreviewer agreement using Cohen kappa was 0.927 (96.9% agreement; Supplementary material 7). Among the included studies, one§ was in Chinese, one¶ in German, and one¶ in Japanese; the rest were in English.

1. Survival Between Treatment Types

The summary of findings table and the pooled survival function of the 3 outcomes are shown in Table 1 and Fig. 2A, respectively. The pooled survival function estimated from the data of multiple studies (Fig. 2A) showed a median survival time of 6.72 months in the surgery group (95% CI, 61.9–7.01; 2,367 participants; 36 studies), 5.99 months in the nonsurgery group (95% CI, 5.33–6.47; 891 participants; 12 studies), and 5.96 months in the mixed group (95% CI, 5.67–6.43; 1,984 participants; 18 studies).

The large-scale survival data narrowed the CI significantly compared to those shown in Fig. 1. Sections of the curves where the CIs did not overlap suggested a meaningful difference in the survival times of patients between the surgery and nonsurgery groups. The nonsurgery group showed a lower survival probability in the period between 6 months and 30 months. Although a log-rank test indicated significant differences (p = 0.012) between the surgery, nonsurgery, and mixed, the curves began to merge at 30 months and overlapped significantly thereafter (Fig. 2A).

2. Survival Changes Over Time

Although the study protocol was designed to allow the analysis of potential survival differences over time, the data classification was not predetermined. Therefore, we partitioned the data a posteriori so as to evenly distribute the number of studies into 5 groups (Fig. 2B). The partition in 1999 was determined based on moderator analysis, as discussed below. Because the studies had been conducted across varying time spans, a clean partition was impossible. As a compromise, the data were sorted in ascending order according to the time of initial recruitment in each study. We admit that this is an a posteriori classification. However, the partitions can be further investigated and refined, as the data are freely available from the Open Science Framework.⁸

Table 1. Summary table of findings

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute number of patients survival* (95% CI)</th>
<th>Median overall survival (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Months</td>
<td>1 Year</td>
<td>2 Years</td>
<td>survival</td>
</tr>
<tr>
<td>Surgery ⁹</td>
<td>5.3 per</td>
<td>3.2 per</td>
<td>1.4 per</td>
<td>6.72 Months</td>
</tr>
<tr>
<td></td>
<td>10 (5.1–5.5)</td>
<td>10 (3.0–3.4)</td>
<td>10 (1.2–1.5)</td>
<td>(6.19–7.01)</td>
</tr>
<tr>
<td>Nonsurgery ¹</td>
<td>4.9 per</td>
<td>2.5 per</td>
<td>1.2 per</td>
<td>5.99 Months</td>
</tr>
<tr>
<td></td>
<td>10 (4.6–5.3)</td>
<td>10 (2.3–2.8)</td>
<td>10 (1.0–1.4)</td>
<td>(5.33–6.47)</td>
</tr>
<tr>
<td>Mixed cohorts ³</td>
<td>5.0 per</td>
<td>3.0 per</td>
<td>1.4 per</td>
<td>5.96 Months</td>
</tr>
<tr>
<td></td>
<td>10 (4.7–5.2)</td>
<td>10 (2.8–3.2)</td>
<td>10 (1.2–1.5)</td>
<td>(5.67–6.43)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

*The absolute data is estimated from the percentage of survival (and its 95% confidence interval). 1 Decompression, instrumentation, en-bloc, anterior/posterior approaches, or combinations. 2 Radiotherapy, stereotactic body radiontherapy, chemotherapy, vertebroplasty, etc. 3 Varying proportion of surgical and nonsurgical data integrated into a single survival function.

Patient or population: Populations diagnosed with non-small cell lung cancer that presents with spinal metastasis.

Setting: Tertiary institutions, medical centers, oncological centers.

Exposure: There is no designated intervention or exposure in this study because the aim of this review is obtain the survival curve.

Comparison: There is no designated comparator.

GRADE Working Group grades of evidence risk associated with the prognostic factor.

High certainty: We are very confident that the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) lies close to that of the estimate.

Moderate certainty: We are moderately confident that the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) is likely to be close to the estimate, but there is a possibility that it is substantially different.

Low certainty: Our certainty in the estimate is limited: the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) may be substantially different from the estimate.

Certainty: We have very little certainty in the estimate: the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) is likely to be substantially different from the estimate.

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There were several findings from this analysis. First, patients enrolled since 2010 had the best survival, with a nonoverlapping 95% CI. Second, the partition in 1999 was an output of the moderator analysis, which showed a large survival gap when data were separated. Third, when patients enrolled in 1989 or earlier were omitted, survival times improved in the period before 30 months. Beginning at the 30-month timepoint, all survival curves merged, and the survival probability ranged from 8.5% (95% CI, 6.74%–10.79%) to 11.7% (95% CI, 9.63%–14.15%). The 30-month survival has remained seemingly constant for the recent 2 decades. Finally, starting in 1999, more studies reported TKI usage or EGFR mutation status (see Supplementary material 8).

Fig. 2. (A) Pooled survival curves of surgery, nonsurgery, and mixed study/subgroup. The solid line represents the survival function, and the semi-translucent area represents the 95% confidence interval. The p-value is the result of a log-rank test. (B) Survival over time. Survival data were pooled according to the time of initial recruitment in each study. The means by which studies were grouped is clarified in the text (see Methods and Supplementary material 8).
3. Moderator Analysis

Along with the 5 study-level covariates mentioned in the Methods section, we also accounted for the exclusiveness of NSCLC. At the stage of study inclusion, 34 studies reported the patholo-

gy as NSCLC. However, the pathology was unavailable (i.e., labeled as “lung cancer”) in 36 studies. After discussion, we decided to include both types of studies and perform moderator analysis for this covariate. We divided studies into subgroups to

Fig. 3. The survival data were separately visualized according to the result of the moderator analysis. This demonstrates the effect of covariates on the survival outcome. The p-value is the result of a log-rank test. Starting year of cohort inclusion (A), exclusiveness of non-small cell lung cancer (NSCLC) (B), mean age (C), treatment types (D), % epidermal growth factor receptor (EGFR) mutation (E), and % targeted therapy (F).
accommodate the study-level covariates. For example, one of the included studies with an ID of “Yang SZ 2017” reported 2 sets of survival data: surgery and nonsurgery. These were separated into 2 subgroups in the moderator analysis: “Yang SZ 2017-su,” and “Yang SZ 2017-no,” respectively. The subgroups and extracted covariates of all studies are listed in Supplementary material 6. The metaCART package was used to identify the point of partition that best explained the heterogeneity (see Supplementary material 9). The covariate of synchronous metastasis was not influential according to the analysis in metaCART. The influential covariates were further visualized with survival data in Fig. 3. Overall, 5 moderators (excluding the percentage of patients receiving TKIs, Fig. 3F) were significantly related to survival differences among groups.

The $R^2$ value indicates how well our separation model explains heterogeneity. As in regression analysis, $R^2$ values closer to 1 indicate a good model. Although all 6 separation models indicated a significant difference, the $R^2$ values were low (see Supplementary material 9). Thus, the analysis accounted for heterogeneity to only a limited extent, and most heterogeneity remained unexplained (residual heterogeneity). This suggests that there was serious heterogeneity in the survival data included in this review (in terms of median overall survival). Although median survival represents only one timepoint (that of 50% survival) in the survival function, this was a significant finding that downgraded several GRADE items, as discussed in the next section.

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**Fig. 4.** World map showing the distribution of studies included in this review. (A) Number of patients whose survival data were pooled. (B) Age-standardized rates (ASRs) of lung cancer incidence in males in 2018. The data have been obtained from The Cancer Atlas. One study (ID: Choi 2015) has been excluded because it analyzed patients from 10 countries.
4. GRADE Assessment
The GRADE scores of all outcomes indicated very low certainty of evidence (Table 1 and Supplementary material 4). Three main issues are summarized here. First, there was considerable heterogeneity in the data in terms of median survival. Second, studies that reported a single survival curve for surgical and nonsurgical treatments (i.e., those in the mixed category) seldom indicated their inclusion criteria or clinical severity. This can cause sampling discrepancies or bias between studies and make it difficult to define the target population, thus limiting the generalizability of outcomes. However, this issue was less severe in studies in the surgery and nonsurgery categories. Third, we considered studies from a small number of countries or regions, representing a minority of lung cancer cases (according to data from The Cancer Atlas). This may have introduced publication bias (Fig. 4).

DISCUSSION
There have been significant advancements in the treatment of lung cancer with spinal metastasis in the past decade. Biomarker-directed therapies, like Osimertinib treatment, are among the newer TKIs therapies replacing previous targeted therapies. In addition, studies of PD-1 and PD-L1 inhibitors have led to the increased use of immunotherapy with pembrolizumab since 2015. Stereotactic radiosurgery is regarded as a game-changer for spinal metastasis in other pathologies, with ongoing trials investigating different sessions. Radiosurgery has also led to the development of minimally invasive procedures like separation surgery. Despite these advancements, the durability of these treatments is not ideal. Hence, it is crucial to determine whether they translate to survival benefits, especially in patients with spinal metastasis.

1. Survival Benchmarking Is Now Possible
To date, this is the first and the largest dataset representing a collection of all currently published survival. The dataset is open source and is available in the Open Science Framework. This allows researchers to subset the dataset to complement any individual comparison. To demonstrate this, we compared the survival rates of the surgical cohort of the National Taiwan University Hospital Spine Oncology Registry against those of the dataset. For a meaningful comparison, we subset the dataset that underwent surgery beginning in 2004 (Fig. 5). A log-rank test indicated a p-value of 0.16, suggesting a similarity to those of the dataset. Furthermore, as described in the Introduction, fusion is typically considered appropriate for patients who survive for longer than 1 year. The 1-year survival of our institute was 41.3%, slightly higher than those of the (subset) dataset of 32.9%. This suggests fusion should be highly considered. Addi-

Fig. 5. Example demonstration of benchmarking against institutional data (data from the Spine Oncology Registry of National Taiwan University Hospital). NTUH, National Taiwan University Hospital.
tionally, the high heterogeneity of our dataset reasonably reflect the high diversity of this group of patients. Hence, researchers need to utilize the covariates highlighted in the moderator analysis (Fig. 3) to subset the appropriate dataset to achieve a fair and meaningful comparison.

For a highly diverse population, benchmarking with a large-scale dataset can avoid misleading conclusions, as described in the Introduction. For instance, Zairi et al. studied 53 surgical patients with lung cancer with spine metastasis and concluded that surgery is not recommended, on account of short life expectancy and frailty. Although our data suggest that the outcome of these patients is poor, it was not as poor as that described by Zairi et al. Frequently, the survival outcome deriving from a small number of cases of highly diverse population results in a Kaplan-Meier curve with large ladder steps and a wide 95% CI. Moreover, we found that the survival of surgical patients was slightly better than those of nonsurgical patients and was statistically significant (p = 0.0046) (Fig. 3D), although each was meta-analyzed separately.

2. Survival Changes Over Time

Upon analyzing survival changes over time (Fig. 2B), data from patients enrolled since 2010 had the best survival. This finding could suggest that the overall improvement of survival in lung cancer, in general, also applies to those with spinal metastasis. Although this is expected, it has not previously been presented in statistical terms. Since the data from 2010 may more accurately reflect current survival, researchers should focus on this subset in future benchmarking and remain optimistic in the management of these patients.

However, we also found that improvements were evident only prior to 30 months. The data visualization suggests a time limit of 30 months for survival analysis using this dataset, although this interpretation is not based on any statistical calculations. Our analysis also suggests that future research on comparative effectiveness should aim to reach the minimal period of 30-month follow-up before concluding superiority. On the contrary, studies that use a point estimate, commonly in conjunction with a median survival time, would be unlikely to identify the 30-month impasse. Rothrock et al. demonstrated a gradual improvement with regression of median survival time in 309 lung cancer patients from 1998 to 2017. Although these findings are consistent with this study (Fig. 2B) in terms of median survival time, the improvement in outcome at 30 months was not demonstrated. This is because the median survival only serves as a point estimate of the full survival curve and does not encapsulate trends in the first and third quartiles or at any other points of interest. Overall, due to the a posteriori classification of data, these findings can only be considered exploratory.

3. Limitations

There were significant limitations to this study. First, for survival comparisons between surgery and other groups, any causative conclusions (such as those commonly derived in comparative effectiveness research) would be inappropriate. This is because the survival data were derived from single-arm rather than double-arm trials. Although the grouped data can be illustrated side-by-side, we cannot conclude that either has a relative survival advantage. Second, there was serious heterogeneity in the data. As there is no standard technique for the assessment of heterogeneity in non-parametric survival data, we used median survival as an effect size for heterogeneity assessment; moderator analysis only accounted for a small amount of heterogeneity. Third, the findings related to survival changes over time can only be regarded as exploratory. Studies varied significantly in their follow-up durations, resulting in significant overlaps at each time span when survival data were obtained (Supplementary material 8). The sorting and partitioning of survival data (Fig. 2B) was an a posteriori attempt. Overall, this resulted in very low certainty of evidence, as assessed under the GRADE framework.

CONCLUSION

This is the first large-scale data regarding lung cancer with spinal metastasis that allows survival benchmarking. Data from patients enrolled since 2010 had the best survival and may more accurately reflect current survival. Researchers should focus on this subset in future benchmarking and remain optimistic in the management of these patients.

NOTES

Supplementary Materials: Supplementary materials 1-9 can be found via https://doi.org/10.14245/ns.2245026.513.
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REFERENCES


Floor-Mounted Robotic Pedicle Screw Placement in Lumbar Spine Surgery: An Analysis of 1,050 Screws

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Objective: To analyze the usage of floor-mounted robot in minimally invasive lumbar fusion.

Methods: Patients who underwent minimally invasive lumbar fusion for degenerative pathology using floor-mounted robot (ExcelsiusGPS) were included. Pedicle screw accuracy, proximal level violation rate, pedicle screw size, screw-related complications, and robot abandonment rate were analyzed.

Results: Two hundred twenty-nine patients were included. Most surgeries were primary single-level fusion. Sixty-five percent of surgeries had intraoperative computed tomography (CT) workflow, 35% had preoperative CT workflow. Sixty-six percent were transfornamental lumbar interbody fusion, 16% were lateral, 8% were anterior, and 10% were a combined approach. A total of 1,050 screws were placed with robotic assistance (85% in prone position, 15% in lateral position). Postoperative CT scan was available for 80 patients (419 screws). Overall pedicle screw accuracy rate was 96.4% (prone, 96.7%; lateral, 94.2%; primary, 96.7%; revision, 95.3%). Overall proximal facet and endplate violation rates were 0.4% and 0.9%. Average diameter and length of pedicle screws were 7.1 mm and 47.7 mm. Screw revision had to be done for 1 screw (0.1%). Use of the robot had to be aborted in 2 cases (0.8%).

Conclusion: Usage of floor-mounted robotics for the placement of lumbar pedicle screws leads to excellent accuracy, large screw size, and negligible screw-related complications. It does so for screw placement in prone/lateral position and primary/revision surgery alike with negligible robot abandonment rates.

Keywords: Robotics, Pedicle screw, Accuracy, Lumbar spine, Complications, Screw size

INTRODUCTION

Given that anatomical landmarks are poorly visualized or palpated in minimally invasive spine surgery (MISS), both decompression and instrumentation heavily rely on intraoperative imaging.1,2 Over the last 2 decades, there has been an evolution of newer navigation technologies in MISS with an intent to help reduce radiation exposure and increase pedicle screw accuracy.3-7 The advent and application of robotic navigation in MISS in recent years has led to an improvement in pedicle screw accuracy, mainly because of planning of the screw trajectory and size and real-time visualization during placement.6,9 The ability to plan the screw beforehand also allows placing screws with greater length and diameter, possibly increasing the stability of the construct. In addition, the robotic arm increases the reproducibility of screw placement by mitigating human error and decreasing surgeon fatigue as a result of favorable ergonomics.
For lumbar interbody fusion surgeries, the utilization of the robot has gone beyond just pedicle screw placement to also assist with the identification of the disc space, disc preparation, and planning and placement of the interbody device using the navigational system of the robot.10

Although studies have been conducted on the usage of robotic systems in MISS,11 literature regarding floor-mounted robots specifically requires more evidence to establish their utility. A floor-mounted robot does not attach to the bed or patient and hence, allows for easy in and out of the operating room (OR). Also, it better facilitates the placement of pedicle screws in the lateral position and sacral screws. The purpose of this study was to analyze the usage of a floor-mounted robotic system with integrated navigation capability and a rigid arm (ExcelsiusGPS, Globus Medical, Inc., Audubon, PA, USA) in minimally invasive lumbar spine fusion for degenerative lumbar pathology. This is the largest reported series in the literature of lumbar pedicle screw placement utilizing the ExcelsiusGPS robotic system. Our hypothesis was that the utilization of a floor-mounted robot leads to excellent accuracy of pedicle screw placement with negligible screw-related complications and robot abandonment rates.

MATERIALS AND METHODS

1. Study Design and Population

This study was an Institutional Review Board (IRB)-approved retrospective review of prospectively collected data (Hospital for Special Surgery IRB approval number: 2018-1142) that was exempt from the informed consent requirement. Consecutive patients who underwent primary or revision minimally invasive lumbar fusion for degenerative lumbar pathology in the form of transforaminal lumbar interbody fusion (TLIF), lateral lumbar interbody fusion (LLIF), anterior lumbar interbody fusion (ALIF), or a combination of interbody fusion types (irrespective of the number of levels) (Qureshi-Louie class II–V)12 using ExcelsiusGPS robotic system (Globus Medical Inc., Audubon, PA, USA) between February 2019 and November 2021 were included. ExcelsiusGPS is a current-generation floor-mounted robot with a fully integrated navigation platform that allows for K-wireless placement of pedicle screws.13 Indications of primary surgery included unstable/isthmic spondylolisthesis, up-down foraminal stenosis, degenerative scoliosis, and need for alignment/lordosis restoration. Indications for revision surgery included pseudarthrosis, adjacent segment disease, and failure of

Fig. 1. (A) Intraoperative planning of pedicle screws (trajectory, diameter, and length) and interbody placement. Pedicle screw placement through the rigid robotic arm with the patient in prone (B) or lateral (C) position. Disc preparation (D) and interbody placement (E) using robotic navigation.
prior decompression. Surgeries included were all performed by 3 fellowship-trained spine surgeons with practices dedicated to MISS (experience with the robotic platform – 3 years, 2 years, and 1 year, respectively) and the surgeons’ techniques did not change over the study course.

2. Surgical Workflow (Fig. 1)

(1) Prone or lateral positioning of the patient on the Jackson table after induction of general anesthesia.
(2) Prepping and draping in a sterile fashion.
(3) Placement of the dynamic reference base (DRB) in the right posterior superior iliac spine (PSIS) with a small stab incision.
(4) Placement of a surveillance marker in the left PSIS with a stab incision.
(5) Attachment of a temporary intraoperative computed tomography (CT) fixture to the DRB.
(6) Three-dimensional (3D) fluoroscopic spin with Ziehm Vision RFD 3D (Ziehm Imaging, Inc., Orlando, FL, USA) (intraoperative CT workflow). In cases with preoperative CT workflow, this step was not needed and instead a preoperative CT scan was performed.
(7) Transfer of images to the ExcelsiusGPS robot.
(8) Intraoperative planning of pedicle screw and interbody placement.
(9) Registration of navigated instruments with the system.
(10) Utilization of a foot pedal by the surgeon to bring the robotic arm at the desired position.
(11) Placement of headless screws through the rigid end-effector under real-time visualization.
(12) Docking of the tubular retractor through a separate incision (posterior for TLIF, lateral for LLIF) using robotic navigation.
(13) Anteroposterior and lateral x-rays to confirm the positioning of screws and tube.
(14) TLIF or LLIF was performed as described previously in the literature.14-20 Robotic navigation was utilized for disc preparation and interbody placement.
(15) Passage of rods under lateral fluoroscopy.
(16) X-rays to confirm good positioning of all hardware.
(17) For ALIF, the robot was used only for bilateral percutaneous pedicle screw placement in the prone position after anterior interbody placement was done with the patient supine.

3. Data Collection

Data was collected and managed using REDCap (Research Electronic Data Capture)21,22 hosted at Weill Cornell Medicine Clinical and Translational Science Center supported by the National Center For Advancing Translational Science of the National Institute of Health under award number: UL1 TR002384. REDCap is a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant web-based software platform designed to support data capture and data management for research studies.

Patient demographics, including age, sex, body mass index (BMI), and American Society of Anesthesiologists (ASA) physical status classification were obtained from electronic medical records. Surgical data that were analyzed included type of surgery (primary/revision), type of fusion, and number of levels operated.

The outcome measures included: (1) pedicle screw accuracy, (2) proximal level facet and endplate violation rate, (3) pedicle screw size, (4) screw-related complications, and (5) robot abandonment rate. Pedicle screw accuracy was assessed separately for placement in prone/lateral positions and primary/revision surgeries according to the CT-based Gertzbein-Robbins Scale which grades screws depending on the extent of pedicle cortical breach (grade A: 0 mm, grade B: < 2 mm, grade C: < 4 mm, grade D: < 6 mm, grade E: > 6 mm).23 Grade A and B screws were deemed as accurate and grade C, D, and E screws as inaccurate.24,25 The screws were also assessed according to the Simplified Screw Grading System (good: no pedicle, tip, facet, or endplate breach; acceptable: pedicle breach within the radiographic safe zone, ant distance of tip breach; poor: any breach outside of the radiographic safe zone i.e. ≥ 4 mm of superior/lateral breach or ≥ 2 mm of inferior/medial breach or violating the facet/endplate affecting the superior unfused level).26,27 CT scans were performed at 1-year postsurgery (as part of standard of care to assess fusion) and were evaluated for pedicle screw placement by 3 independent reviewers, an orthopedic spine fellow, and 2 orthopedic surgery residents. Operative time, recorded as time of incision to time of closure, was assessed for 1-level TLIF, LLIF, and ALIF which included insertion of pedicle screws with robotic assistance.

4. Statistical Analysis

For descriptive analysis, categorical variables were summarized as “number (percentage),” normally and nonnormally distributed continuous variables were summarized as “mean ± standard deviation” and “median (interquartile range)” respectively.
All analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA).

**RESULTS**

Two hundred twenty-nine patients were included. The mean age was 61 years and the mean BMI was 28.4 kg/m². Eighty-three percent of patients were ASA physical status classification grade II. Most surgeries were primary single-level fusion. Sixty-six percent were TLIF; 16% were LLIF; 8% were ALIF; and 10% were a combination of interbody fusion types. A total of 1,050 pedicle screws were placed with robotic assistance (85% in prone position, 15% in lateral position). Sixty-five percent of surgeries had the intraoperative CT workflow and 35% had the preoperative CT workflow. The average time for 1-level TLIF, LLIF, and ALIF including insertion of robotic screws were 104, 119, and 154 minutes, respectively (Table 1).

Postoperative CT scan was available for 80 patients (419 screws). The overall pedicle screw accuracy rate was 96.4% (screws placed in prone position: 96.7%; screws placed in lateral position: 94.2%; primary surgery: 96.7%; revision surgery: 95.3%). The overall poor screw placement rate was 2.8% (screws placed in prone position: 2.7%; screws placed in lateral position: 3.8%; primary surgery: 2.7%; revision surgery: 3.5%). The overall proximal facet and proximal endplate violation rates were 0.4% and 0.9%, respectively. These findings are detailed in Tables 2 and 3.

The average diameter and length of pedicle screws were 7.1 mm and 47.7 mm, respectively. > 50% screws had a diameter of ≥ 7.5 mm and length of ≥ 50 mm (Table 4). Return to the OR for screw revision had to be done for 1 screw (0.1%) placed in the prone position (L5 pedicle grade B inferior breach leading to neurological deficit). There was no major wound-related complication in any case. The use of the robot had to be aborted in 2 cases (0.8%) (array was bumped in one, calibration error in the other).

**DISCUSSION**

The ExcelsiusGPS robot was approved by the U.S. Food and Drug Administration in 2017. Its advantages over previously described robotic systems include K-wireless screw placement due to the rigidity of the external arm, detection of an offset > 1 mm by the surveillance marker and skiving forces by the sensor in the end-effector, fully integrated navigation capability, and portability. Studies conducted on the use of ExcelsiusGPS robotic system in spine surgery and their findings are summarized in Table 5. The current study aimed to assess the utilization of this floor-mounted robotic system in the placement of pedicle screws in the prone/lateral position and in primary/revision surgery. It also analyzed the rates of screw-related complications and robot abandonment.

### Table 1. Demographic and surgical data (n = 229)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pedicle screws</td>
<td>1,050</td>
</tr>
<tr>
<td>Prone</td>
<td>896 (85.3)</td>
</tr>
<tr>
<td>Lateral</td>
<td>154 (14.7)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61.05 ± 12.01</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>111 (48.5)</td>
</tr>
<tr>
<td>Male</td>
<td>118 (51.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.41 ± 5.56</td>
</tr>
<tr>
<td>ASA PS classification grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (6.6)</td>
</tr>
<tr>
<td>II</td>
<td>190 (83)</td>
</tr>
<tr>
<td>III</td>
<td>24 (10.5)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>161 (70.3)</td>
</tr>
<tr>
<td>Revision</td>
<td>68 (29.7)</td>
</tr>
<tr>
<td>Type of fusion</td>
<td></td>
</tr>
<tr>
<td>TLIF</td>
<td>152 (66.4)</td>
</tr>
<tr>
<td>LLIF</td>
<td>36 (15.7) (lateral, 21; prone, 15)</td>
</tr>
<tr>
<td>ALIF</td>
<td>18 (7.8)</td>
</tr>
<tr>
<td>Combination</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Operative time (min) for 1-level interbody fusion + robotic pedicle screws</td>
<td></td>
</tr>
<tr>
<td>1-Level TLIF</td>
<td>104.36 ± 19.42</td>
</tr>
<tr>
<td>1-Level LLIF</td>
<td>119.2 ± 33.7</td>
</tr>
<tr>
<td>1-Level ALIF</td>
<td>154.2 ± 42.3</td>
</tr>
<tr>
<td>Fusion levels</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>156 (68)</td>
</tr>
<tr>
<td>2</td>
<td>52 (22.7)</td>
</tr>
<tr>
<td>3</td>
<td>14 (6.1)</td>
</tr>
<tr>
<td>4</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>5</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>6</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>7</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; TLIF, transfemoral lumbar interbody fusion; LLIF, lateral lumbar interbody fusion; ALIF, anterior lumbar interbody fusion.
A floor-mounted robot has several advantages over a table-mounted robot in spine surgery. It is portable and can be shifted or moved during the surgery. It provides a more open and wider working field to the surgeon and may improve ergonomics. It better facilitates single-position surgery in the lateral position and insertion of sacral screws. One of its drawbacks is that it has a greater working distance compared to a table-mounted robot and this may lead to less accuracy in pedicle screw insertion. However, the findings of this study show that floor-mounted robotic screw insertion has excellent accuracy and negligible

Table 2. Assessment of pedicle screw placement in prone and lateral positions using robotics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lateral breach</th>
<th>Inferomedial breach</th>
<th>Accuracy (GRS)</th>
<th>Tip breach</th>
<th>Proximal facet violation</th>
<th>Proximal end-plate violation</th>
<th>SSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prone (n = 367)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr B: 18 (4.9)</td>
<td>355/367 (96.7)</td>
<td>Gr B: 10 (2.7)</td>
<td>2 (0.5)</td>
<td>3 (0.8)</td>
<td>Good: 296 (80.6)</td>
<td>Average: 61 (16.6)</td>
<td>Poor: 10 (2.7)</td>
</tr>
<tr>
<td>Gr C: 7 (1.9)</td>
<td>Gr C: 2 (0.5)</td>
<td>Gr C: 7 (1.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr D: 2 (0.5)</td>
<td>Total: 14 (3.8)</td>
<td>Gr D: 1 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr E: 1 (0.25)</td>
<td>Total: 18 (4.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 28 (7.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral (n = 52)</td>
<td></td>
<td></td>
<td>49/52 (94.2)</td>
<td>0</td>
<td></td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Gr B: 1 (1.9)</td>
<td>Gr C: 2 (3.8)</td>
<td>Gr C: 2 (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr D: 1 (1.9)</td>
<td>Total: 4 (7.6)</td>
<td>Gr D: 1 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (n = 419)</td>
<td></td>
<td></td>
<td>404/419 (96.4)</td>
<td>2 (0.4)</td>
<td>4 (0.9)</td>
<td>Good: 341 (81.4)</td>
<td>Average: 66 (15.7)</td>
</tr>
<tr>
<td>Gr B: 19 (4.6)</td>
<td>Gr C: 9 (2.2)</td>
<td>Gr C: 2 (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr D: 3 (0.7)</td>
<td>Total: 14 (3.3)</td>
<td>Gr D: 1 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr E: 1 (0.2)</td>
<td>Total: 18 (4.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 32 (7.8)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).
GRS, Gertzbein-Robbins Scale; SSGS, Simplified Screw Grading System; Gr, grade.

Table 3. Assessment of pedicle screw placement in primary and revision surgeries using robotics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lateral breach</th>
<th>Inferomedial breach</th>
<th>Accuracy (GRS)</th>
<th>Tip breach</th>
<th>Proximal facet violation</th>
<th>Proximal end-plate violation</th>
<th>SSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (n = 334)</td>
<td></td>
<td></td>
<td>323/334 (96.7)</td>
<td>Gr A: 4 (1.2)</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
<td>Good: 273 (80.6)</td>
</tr>
<tr>
<td>Gr A: 18 (5.4)</td>
<td>Gr A: 10 (2.9)</td>
<td>Gr B: 7 (2.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Average: 52 (16.6)</td>
</tr>
<tr>
<td>Gr B: 6 (1.8)</td>
<td>Gr B: 2 (0.6)</td>
<td>Gr C: 1 (0.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr C: 2 (0.6)</td>
<td>Total: 12 (3.6)</td>
<td>Gr D: 1 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr D: 1 (0.3)</td>
<td>Total: 27 (8.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revision (n = 85)</td>
<td></td>
<td></td>
<td>81/85 (95.3)</td>
<td>0</td>
<td>2 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr A: 1 (1.2)</td>
<td>81/85 (95.3)</td>
<td>Gr A: 6 (7)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gr B: 3 (3.6)</td>
<td>Total: 2 (2.3)</td>
<td>Total: 6 (7)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gr C: 1 (1.2)</td>
<td>Total: 5 (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (n = 419)</td>
<td></td>
<td></td>
<td>404/419 (96.4)</td>
<td>2 (0.4)</td>
<td>4 (0.9)</td>
<td>Good: 341 (81.4)</td>
<td>Average: 66 (15.7)</td>
</tr>
<tr>
<td>Gr A: 19 (4.6)</td>
<td>Gr A: 12 (2.9)</td>
<td>Gr B: 7 (1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr B: 9 (2.2)</td>
<td>Gr B: 2 (0.5)</td>
<td>Gr C: 1 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr C: 3 (0.7)</td>
<td>Total: 14 (3.3)</td>
<td>Gr D: 1 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr D: 1 (0.2)</td>
<td>Total: 18 (4.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 32 (7.8)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).
GRS, Gertzbein-Robbins Scale; SSGS, Simplified Screw Grading System; Gr, grade.
screw-related complications.

Pedicle screw placement using the conventional freehand and 2-dimensional fluoroscopy techniques has been reported to have comparatively higher rates of misplacement, which can in turn lead to neurovascular injury, chronic low back pain, and decreased pullout strength.\textsuperscript{37-39} Two recent meta-analyses comparing robot-assisted versus freehand or fluoroscopy-based pedicle screw placement showed superior accuracy with robotic assistance.\textsuperscript{40,41} Roser et al.\textsuperscript{42} demonstrated higher accuracy for robotic versus navigated screw placement (99% vs. 92%). Previous studies conducted on pedicle screw placement using ExcelsiusGPS robot demonstrated an accuracy ranging from 96.6% to 100% and zero screw-related intraoperative or postoperative complications.\textsuperscript{28-36} (Table 5). The current study, including screws placement both in prone and lateral positions and in primary and revision surgeries, showed similar findings with an overall pedicle screw accuracy of 96.4%, poor screw placement rate of 2.8%, and a single incident (0.1%) of screw-related complication that required a return to the OR for screw revision. One of the major issues that can compromise the accuracy of robotic screws is skiving. It can be reduced if the drill is started off of the bone and then advanced into the vertebral body until a point just beyond the end of the pedicle.\textsuperscript{37} In addition, the ExcelsiusGPS robotic platform has a unique sensor to detect excessive lateral force.\textsuperscript{13}

### Table 4. Pedicle screw diameter and length

<table>
<thead>
<tr>
<th>Diameter and length</th>
<th>No. of screws (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>5.0</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>5.5</td>
<td>70 (6.6)</td>
</tr>
<tr>
<td>6.5</td>
<td>415 (39.5)</td>
</tr>
<tr>
<td>7.5</td>
<td>407 (38.8)</td>
</tr>
<tr>
<td>8.5</td>
<td>148 (14.1)</td>
</tr>
<tr>
<td>Length (mm)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>35</td>
<td>8 (0.8)</td>
</tr>
<tr>
<td>40</td>
<td>95 (9)</td>
</tr>
<tr>
<td>45</td>
<td>418 (39.8)</td>
</tr>
<tr>
<td>50</td>
<td>382 (36.4)</td>
</tr>
<tr>
<td>55</td>
<td>129 (12.3)</td>
</tr>
<tr>
<td>60</td>
<td>16 (1.5)</td>
</tr>
</tbody>
</table>

LLIF often requires the addition of a pedicle screw construct to provide stability. Traditionally, it involves an intraoperative flip to the prone position following the lateral surgery, which, in turn, increases the operative time. Lately, the concept of single-position surgery has gained traction where screws are put in the lateral position without needing a flip. Robotics has been the main driver behind this as it enables placing screws in ergonomically difficult and unfamiliar positions (especially the down-screwed screws) by providing a defined trajectory through the rigid arm.\textsuperscript{44,45} Huntsman et al.,\textsuperscript{34} using the ExcelsiusGPS robotic system, had reported a high pedicle accuracy rate of 98% with no screw-related complications in their study of 55 patients who had undergone single-position LLIF surgery. The current study had similar findings of high pedicle screw accuracy (94.2%),

### Table 5. Studies conducted on ExcelsiusGPS-assisted spine surgery and their findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery type</th>
<th>No. of patients/ pedicle screws</th>
<th>Pedicle screw accuracy</th>
<th>Screw-related complications</th>
<th>Robot abandonment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang et al.\textsuperscript{28} (2018)</td>
<td>Posterolateral fusion</td>
<td>2/8</td>
<td>100% (8/8)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Jain et al.\textsuperscript{29} (2019)</td>
<td>TLIF, ALIF, LLIF</td>
<td>106/636</td>
<td>100% (66/66)</td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>Wallace et al.\textsuperscript{30} (2019)</td>
<td>Not specified</td>
<td>106/600</td>
<td>98.2% (589/600)</td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>Elswick et al.\textsuperscript{31} (2019)</td>
<td>Not specified</td>
<td>28/127</td>
<td>97.6% (122/125)</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Godzik et al.\textsuperscript{32} (2019)</td>
<td>MI-TLIF, ALIF, LLIF</td>
<td>28/116</td>
<td>96.6% (112/116)</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Benech et al.\textsuperscript{33} (2019)</td>
<td>Posterolateral fusion</td>
<td>54/292</td>
<td>98.3% (287/292)</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Huntsman et al.\textsuperscript{34} (2020)</td>
<td>Single-position LLIF</td>
<td>55/328</td>
<td>Not studied</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Fayad et al.\textsuperscript{35} (2020)</td>
<td>MI-TLIF, LLIF, ALIF</td>
<td>20/103</td>
<td>98.1% (101/103)</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Maalouly et al.\textsuperscript{36} (2021)</td>
<td>Interbody fusion</td>
<td>50/250</td>
<td>98% (245/250)</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Current study</td>
<td>MI-TLIF, LLIF, ALIF, combination</td>
<td>229/1050</td>
<td>96.4% (406/419)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

TLIF, minimally invasive transforaminal lumbar interbody fusion; MI-TLIF, minimally invasive TLIF; ALIF, anterior lumbar interbody fusion; LLIF, lateral lumbar interbody fusion.

ExcelsiusGPS (Globus Medical Inc, Audubon, PA).
low poor screw placement rate (3.8%), and no screw-related complication.

Placement of pedicle screws in revision surgeries can be challenging due to altered anatomy and existing instrumentation. Ando et al.46 had found a high rate of pedicle breaches when placing freehand pedicle screws in revision surgeries and concluded that due to a high potential for malposition, these screws should be placed carefully. Bederman et al.,67 on the other hand, found a high accuracy of pedicle screws in revision surgeries when using robotic guidance and concluded that it can benefit surgeons in navigating altered bony anatomy. The current study demonstrated a high pedicle screw accuracy (95.3%), low poor screw placement rate (3.5%), and no screw-related complications in revision surgeries.

Proximal unfused level violation can lead to adjacent segment disease compromising long-term clinical outcomes.27,48–50 The robot allows planning of the screw trajectory and hence, prevents violation of the superior facet joint or endplate at the upper instrumented level. Zhang et al.51 found that, compared to the freehand technique, robot-guided spinal surgery had significantly less facet joint violations (5.8% vs. 27.3%) and larger screwfacet distance (4.16 mm vs. 1.92 mm). Two meta-analyses also demonstrated decreased proximal facet joint violation with robotic assistance.41,52 Using ExcelsiusGPS, Wallace et al.30 reported no evidence of superior facet joint violation in any case. In the current study, 6 screws (1.3%) had affected the proximal unfused level by violating the facet (2 screws, 0.4%) or the endplate (4 screws, 0.9%).

Although the stability of the pedicle screw construct is largely dependent on the bone quality of the patient, screw size is also an important contributing factor. Previous studies have shown an increase in fixation strength with increasing screw diameter and length.53 Shafi et al.,27 in their comparative study of robotics and navigation, found that robotic assistance allows for placement of pedicle screws with greater diameter and length, with similarly high accuracy. The current study found that the pedicle screws had an average diameter of 7.1 mm and an average length of 47.7 mm, with >50% of screws having a diameter of ≥7.5 mm and length of ≥50 mm.

Although robotic platforms in spine surgery have been previously associated with increasing time demand, these studies do not seem to be completely reliable because of drawbacks like inconsistent definition of operative time and use of older robotic systems. The findings of this study showed that the average time for 1-level TLIF, LLIF, and ALIF including insertion of robotic screws were 104, 119, and 154 minutes, respectively. Our previously published papers demonstrated operative times of 112, 103, and 93 minutes with fluoroscopy, robotics, and navigation, respectively, for 1-level TLIF.36 There was no significant difference in the total OR time between robotics and navigation. This shows that robotics does not increase the operative time demand compared to conventional spine surgery techniques. Each surgeon goes through a learning curve when adopting a new technology and we believe that once the learning curve is over, robotics actually leads to a more efficient operative workflow than traditional techniques.

The limitations of this study include its retrospective design, lack of a control group, and unavailability of the postoperative CT scans for pedicle screw assessment for >50% of patients. The learning curve of the surgeons with robotics was unaccounted for. The results were not stratified by intraoperative/preoperative CT workflow or surgeon experience with the robotic platform. Three of the included patients had ≥5 levels of fusion and included thoracic pedicle screws that may have led to heterogeneity of the dataset. For assessing screw size, stratified analysis was not done according to specific levels. In terms of the operative time demand, we did not have the data separately for screw insertion and interbody procedure or the data for time per screw. Hence, only the overall time from incision to closure (operative time) could be calculated. Comparative studies with larger sample sizes should be conducted to assess the outcomes and cost-effectiveness of robotics in MISS.

CONCLUSION

The use of current-generation floor-mounted robot for the placement of lumbar pedicle screws leads to excellent accuracy, large screw size, and negligible screw-related complications. It does so for screw placement in prone/lateral position and primary/revision surgery alike with negligible robot abandonment rates.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: PS, SAQ; Data cu-
Floor-Mounted Robotic Pedicle Screw Placement

Shahi P, et al.

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REFERENCES


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45. Pham MH, Diaz-Aguilar LD, Shah V, et al. Simultaneous robotic single position oblique lumbar interbody fusion with
Acceptance of Early Surgery for Treatment of Spinal Cord Cavernous Malformation in Contemporary Japan

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³Department of Neurosurgery, Osaka Medical and Pharmaceutical University, Osaka, Japan

Objective: Spinal cord cavernous malformation (CM) is an intramedullary vascular lesion that may present with progressive symptoms. Surgery is recommended for symptomatic patients, but optimal timing of surgery is debatable. Some advocate waiting until plateau of neurological recovery and others support emergency surgery. There is no statistic on how commonly these strategies are utilized. We aimed to find contemporary practice pattern among neurosurgical spine centers in Japan.

Methods: A database of intramedullary spinal cord tumors assembled by Neurospinal Society of Japan was surveyed and 160 patients with spinal cord CM were identified. Neurological function, disease duration, and number of days between presentation to hospitals and surgery were analyzed.

Results: Duration of disease before presentation to hospitals ranged from 0 to 336 months (median, 4 months). Number of days between patients’ presentation and surgery ranged from 0 to 6,011 days (median, 32 days). Time from symptom onset to surgery ranged from 0 to 336.9 months (median, 6.6 months). Patients with severe preoperative neurological dysfunction had shorter duration of disease, fewer days between presentation and surgery, and shorter time between symptom onset and surgery. Patients with paraplegia or quadriplegia were more likely to improve when operated on within 3 months from onset.

Conclusion: Timing of surgery for spinal cord CM in Japanese neurosurgical spine centers generally was early, with 50% of patients undergoing surgery within 32 days after presentation. Further study is needed to clarify optimal timing of surgery.

Keywords: Spinal cord, Hemangioma, Cavernous malformation, Operative surgical procedures

INTRODUCTION

Spinal cord cavernous malformations (CM), also referred to as cavernoma,¹ cavernous angioma,² or cavernous hemangioma,³ are vascular lesions characterized by thin, sinusoidal vascular channels without intervening neural tissue. Three major patterns of clinical presentation may be observed: (1) multiple episodes of discrete neurological deterioration with varying degrees of recovery between the acute insults; (2) slow progression of neurological deterioration; (3) sudden onset of symptoms with rapid decline over hours or days or gradual worsening lasting weeks to months.⁴,⁵

Surgery is indicated in patients with significant or progressive neurological deficits, for whom complete excision should be attempted. Patients with mild or spontaneously resolving symptoms may be followed expectantly, but surgery should be considered if the lesion is exophytic.⁶,⁷ Annual hemorrhage rates range from 0% to 4.5% and should be taken into consideration.⁴

While there is a consensus on indication for surgery of spinal cord CM, the optimal timing of surgery is less clear.⁷ A litera-
ture review found that symptom duration less than 3 years is associated with higher percentage of patients improving after surgery.\(^3\) Imagama et al.\(^4\) reviewed 41 patients and reported that patients who had stable gait preoperatively had shorter preoperative disease duration and had better chance of retaining stable gait at the follow-up. He recommended early surgery for patients who have stable gait, and delayed surgery after initial rehabilitation until the plateau stage of recovery for patients with motor paresis. During this interval for recovery, a gliotic plane develops between the lesion and the spinal cord, allowing for relatively safe removal.\(^7\) On the other hand, Duan et al.\(^9\) reviewed 52 patients and found that emergency rescue surgery (within 3 days from onset in patients with acute symptom onset with rapid decline or within 7 days from onset in patients with repeating deterioration of neurological symptoms with acute onset) resulted in higher chance of neurofunctional improvement at long-term follow-up. There is no data on how commonly each of these strategies (delayed or emergency surgery) are utilized among spine surgeons. We reviewed a database of intramedullary spinal cord tumors to find the practice pattern in contemporary Japan.

### MATERIALS AND METHODS

#### 1. Ethics

This study was performed as a part of multicenter cohort study by Endo et al.\(^1\) with recognition from Neurospinal Society of Japan, an affiliate of the Japan Neurosurgical Society. The study protocol was approved by the Institutional Review Board of Tohoku University Hospital (2021-1-130) and participating centers. As this was a retrospective and noninvasive study, the requirement for written informed consent from patients was waived. Instead, a public notice that provided information on this study protocol was approved by the Institutional Review Board of Tohoku University Hospital (2021-1-130) and participating centers.

#### 2. Patient Selection

A questionnaire was sent to 58 participating neurosurgical spine centers across Japan and data on patients with intramedullary spinal cord tumors treated surgically between 2009 and 2020 were collected. Patients with spinal lipoma or myxopapillary ependymoma were excluded. Patients who had previously undergone surgery for the same lesions were also excluded.

#### 3. Baseline Characteristics

Data were collected on patients’ age, sex, histological diagnosis, types of surgery, presence of recurrence at the follow-up, duration of the disease before presenting to the hospital, and dates of presentation to the hospital and surgery. Neurological functions preoperatively and at follow-ups were graded according to modified McCormick scale (mMS) (grade I: intact neurologically, normal ambulation, minimal dysesthesia; grade II: mild motor or sensory deficit, functional independence; grade III: moderate deficit, limitation of function, independent with external aid; grade IV: severe motor or sensory deficit, limited function, dependent; grade V: paraplegia or quadriplegia, even with flickering movement).\(^12,13\) All data were anonymized.

### RESULTS

There were 160 patients (70 women and 90 men) with spinal cord CM, whose age ranged from 7 to 85 years (mean, 52.01 years; median, 52 years) (Table 1).

Duration of disease before presenting to the hospital ranged from 0 to 336 months (mean, 27.88 months; median [interquartile range], 4 [1–32]; n = 158) (Fig. 1).

Number of days between patients’ presentation to the hospital and the surgery ranged from 0 to 6,011 days (mean, 143.8; median [interquartile range], 32 [9.5–75.5]; n = 159) (Fig. 2).

Correlation between the duration of disease before presentation and the days from presentation to surgery was not statistically significant (correlation coefficient, 0.109; 95% confidence interval, -0.0478 to 0.261).

Time from symptom onset to surgery ranged from 0 to 336.9 months (mean, 32.6; median [interquartile range], 6.6 [2–34.8]; n = 158) (Fig. 3).

Neurological function before surgery, classified in mMS, was grade I in 14, grade II in 67, grade III in 39, grade IV in 30, and grade V in 10 patients. Patients with severe preoperative neurological dysfunction (mMS grades IV and V) had spent shorter
Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>All cases</th>
<th>Preoperative modified McCormick scale</th>
<th>p-value(^\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 14)</td>
<td>2 (n = 67)</td>
<td>3 (n = 39)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52 (7–85)</td>
<td>40.5 (23–77)</td>
<td>53 (14–85)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>Female</td>
<td>70</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>73</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Thoracic</td>
<td>87</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Types of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>11</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>142</td>
<td>14</td>
<td>62</td>
</tr>
<tr>
<td>Recurrence</td>
<td>7</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Duration of disease before</td>
<td>4 (0–336)</td>
<td>6 (0–336)</td>
<td>6 (0–240)</td>
</tr>
<tr>
<td>presentation (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between presentation and</td>
<td>32 (0–6011)</td>
<td>27.5 (1–697)</td>
<td>47 (2–6011)</td>
</tr>
<tr>
<td>surgery (day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between symptom onset and</td>
<td>6.6 (0–336.9)</td>
<td>8.1 (0.03–336.9)</td>
<td>13.8 (0.7–269.5)</td>
</tr>
<tr>
<td>surgery (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number.

\(\dagger\) Fisher exact test for age, sex, types of surgery, and recurrence and by Kruskal-Wallis rank-sum test for age and time.

Fig. 1. Disease duration before presentation to the hospital, stratified by preoperative modified McCormick scale (mMS).
Surgical procedures performed were biopsy in 1 patient, partial or subtotal resection in 17 patients, and total resection in 142 patients. Four patients underwent surgery via anterior approach and 156 via posterior approach.

Patients were followed up for an average of 45.5 months (median, 39; range, 0–142) after surgery. At the last follow-up evaluation, mMS was grade I in 33, grade II in 71, grade III in 32, grade IV in 17, and grade V in 7 patients (Table 2). Difference in the distribution of mMS grades before surgery and at last follow-up was statistically significant ($p = 0.013$, Fisher exact test). Patients whose preoperative mMS was grade V were more likely to improve at the follow-up if they were operated on within 3 months from symptom onset compared with after 3 months ($p = 0.048$, Table 2).

<table>
<thead>
<tr>
<th>Preoperative mMS</th>
<th>Final follow-up mMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Sum</td>
<td>33</td>
</tr>
</tbody>
</table>

Note the decrease in number of patients with mMS grade 4 and 5 at the follow-up in comparison with preoperative state. Boxes in shades represent cases with mMS at the follow-up worse than before surgery.
Fisher exact test) (Table 3). Such difference was not found in patients with preoperative mMS grades I to IV.

The mMS grades at follow-up worsened in 18 out of 160 patients (11.3%). The risk of neurological worsening was not significantly different for those who underwent surgery within 3 months from onset (5 of 46, 10.9%) and after 3 months (13 of 112, 11.6%). There was no statistically significant difference in the distribution of patients with each mMS at the follow-up between patients with cervical and thoracic lesions. Similarly, there was no significant difference in the proportion of patients whose mMS worsened at the follow-up compared to their preoperative level between these 2 groups.

Recurrences occurred in 7 patients: 3 after partial or subtotal resection (17.6%, 3 of 17) and 4 after total resection (2.8%, 4 of 142). The recurrence rate was significantly lower after total resection (p = 0.027, Fisher exact test). All 7 patients with recurrences underwent surgery within 60 days after presentation. But there was no statistically significant difference in rate of recurrence between patients who underwent surgery within 60 days from presentation and those whose surgeries were more than 60 days after presentation (7 of 107 vs. 0 of 52, p = 0.095, Fisher exact test).

There were 53 patients who presented to the hospital within 1 month after symptom onset. Fifteen of them (28.3%, 15 of 53) underwent surgery within 7 days after presentation, which may have been emergency surgery, and 38 had surgery more than 7 days after presentation (range, 8–534 days). In the 15 patients who underwent emergency surgery, preoperative neurological dysfunction in mMS were grade I in 2 patients, grade II in one, grade III in one, grade IV in 9, and grade V in 2. At the last follow-up, mMS were grade I in 3 patients, grade II in 3, grade III in 4, grade IV in 3, and grade V in 2. In the 38 patients who underwent delayed surgery, patients with preoperative mMS grades I to V were 0, 12, 15, 8, and 3, respectively, and at the last follow-up, 9, 17, 8, 4, and 0, respectively. The difference between preoperative and last follow-up mMS grade distribution was not statistically significant in emergency surgery group but was significant in delayed surgery group (p = 0.213 and p = 0.001, respectively, Fisher exact test).

**DISCUSSION**

This is the first multicenter survey that showed a contemporary practice pattern in Japan regarding the timing of surgery for spinal cord CM. This study revealed that patients with spinal cord CM had a wide variation in duration of disease before presentation to the hospital, from 0 to 336 months. These patients were operated on after a wide range of waiting periods, from 0 to 6,011 days after presentation with a median of 32 days. In total, patients underwent surgery from 0 to 336.9 months after symptom onset, with 50% undergoing surgery within 6.6 months. We found that patients with preoperative mMS grade V neurological dysfunction were more likely to improve if they had surgery within 3 months from symptom onset. Favorable neurological outcome of patients who underwent surgery within 3 months of symptoms was also noted in a previous systematic review.15

Overall rate of functional deterioration at the final follow-up was 11.3% (18 of 160). Seventeen of these worsening had one-level change from the baseline. This retrospective study did not contain the details of symptomatic response from patients, and any symptomatic changes that occurred within the borders of each mMS scales are not recognizable. There is always a risk of functional deterioration after surgery of spinal cord CM. In case

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**Table 3. Preoperative and final follow-up neurological function graded using modified McCormick scale (mMS) in patients who underwent surgery within 3 months (n = 46) and more than 3 months (n = 112) after symptom onset**

<table>
<thead>
<tr>
<th>Preoperative mMS</th>
<th>Final follow-up mMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery within 3 months from onset</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Sum</td>
<td>12</td>
</tr>
</tbody>
</table>

Boxes in shades represent cases with mMS at the follow-up worse than before surgery. Note the number of patients with mMS grade 5 decreased in patients who underwent surgery within 3 months, while it was unchanged in those who had surgery more than 3 months after onset.
series studies from high-volume centers, neurological worsening occurred in approximately 10% of patients immediately after surgery and remained in 3%-7% of patients at the follow-up. Reasons for somewhat higher rate of worsening in our series is unclear, but one of the reasons may be short follow-up in some patients.

Spinal cord CM may manifest with slowly progressive symptoms or acute neurologic deterioration. Acute episodes may be followed by spontaneous recovery or deterioration over hours to months. There is no known prognostic factor to distinguish patients who will spontaneously recover from those who will deteriorate. One study reported that patients at risk of not recovering stable gait were those with large lesions and those with lesion in the thoracic spinal cord. Our study did not find statistically significant difference in outcome with lesion involving different levels, but we think it is reasonable that a lesion in the thoracic spinal cord is more detrimental than that in the cervical cord because the thoracic spinal cord has smaller cross-section area with a circular contour compared with the cervical cord. It is commonly known in geometry that for the same perimeter, a circle, not ellipses, has the greatest area. Therefore, when a spinal cord lined by a rigid pia mater becomes swollen, an elliptical cervical cord can increase cross-section area without stretching the pia, while in a circular thoracic cord a small increase in the cross-section area would stretch the pia and result in increased parenchymal pressure. Additionally, a certain amount of bleeding within the cord would damage larger portion of the cross-section area in the smaller thoracic cord. Because the pia mater is a rigid material, increased spinal cord parenchymal pressure results in shifting of the spinal cord parenchyma cranially and caudally. This shift of parenchyma would obstruct the arterioles supplying the spinal cord, because they are fixed to the rigid pia at the penetration point. With a concomitant decrease in perfusion pressure (difference between the blood pressure and the parenchymal pressure), ischemia and infarction would develop in the adjacent segments of the spinal cord, which in turn, result in edema and further longitudinal progression of necrosis, a phenomenon called pencil-shaped softening of the spinal cord. This progressive expansion of the lesion may be more pronounced in the conus medullaris, where the cross-section area is small and circular, and the pial tube is closed distally. We think that progressive neurological deteriorations in patients with spinal cord CM are caused by repeated hemorrhage and/or pencil-shaped softening of the spinal cord. Emergency surgery theoretically would relieve spinal cord parenchymal pressure and prevent secondary neural injury. However, our data did not show benefits of emergency surgery due to lack of statistical power.

Emergency surgery should not be employed in all patients presenting with acute neurological decline because many of them will spontaneously recover. Many authors recommend several weeks of waiting period to facilitate resection. We agree that resection of CM is difficult in the acute phase because the lesion is often collapsed due to compression by hematoma, gliotic plane is absent between the lesion and the spinal cord, and the spinal cord tissue is edematous and fragile. However, we have seen patients who rapidly deteriorated to complete spinal cord injury and did not recover after rehabilitation and lost the opportunity to have surgery. These patients could have benefitted from emergency surgery.

This study was a retrospective analysis of patients who were surgically treated. There is a selection bias because it lacks information on patients who did not have surgery after recovering normal function or deteriorating to complete paraplegia or quadriplegia. In our database, the neurologic dysfunction graded in mMS are recorded before operation, not at the times of onset and presentation. This limits our ability to tell whether the surgery was performed at acute stage or as an elective case. A data of a patient with preoperative neurological dysfunction of mMS grade V who underwent surgery 60 days after onset could mean that the patient had only a mild sensory disturbance for 59 days and suddenly deteriorated to paraplegia on the 60th day and had an emergency surgery, but it also could mean that the patient initially presented with paraplegia and did not improve after 60 days of rehabilitation and had an elective surgery. Another limitation of our study is a lack of data on detailed anatomical location of the lesions within the spinal cord, such as anterior, posterior, subpial, or deeply embedded. Such anatomical feature is important in surgical decision making and should be included in future studies of spinal cord CM.

**CONCLUSION**

In Japanese neurosurgical spine centers, patients with spinal cord CM underwent surgery generally in early phase. Half of patients underwent surgery within 32 days after presentation to hospital, and 75% of patients within 75.5 days. Emergency surgery within 7 days were applied to approximately 28% of patients who presented within 1 months of onset.

Patients with paraplegia were more likely to improve at the last follow-up if they underwent surgery within 3 months from symptom onset. Although this retrospective study did not seek
to determine the optimal timing of surgery, it may be acceptable that patients with severe neurological symptoms or progressive worsening should be operated on early to prevent secondary neural injury from increased intraparenchymal pressure. Whether emergency surgery is beneficial cannot be determined in this retrospective study. Future studies should investigate details of clinical course to identify risk factors for progressive neurological deterioration. Such studies would enable us to correctly select patients for emergency surgery or initial rehabilitation.

NOTES

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Author Contribution: Conceptualization: RK, TE; Data curation: RK, TE, TT; Formal analysis: RK, TE, TT; Methodology: RK, TE; Project administration: RK; Visualization: RK; Writing - original draft: RK; Writing - review & editing: RK, TE, TT.

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REFERENCES


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Early Surgery for Spinal Cord Cavernous Malformation

Kurokawa R, et al.


Spinal cord cavernous malformations (SCCMs) are relatively common intramedullary lesions characterized by thin, sinusoidal vascular channels without intervening neural tissue. Recent multicenter study from Japan has reported surgical removal of SCCMs was performed in 15.4% of total intramedullary tumor surgeries. The incidence of initial hemorrhagic event is not high, which is estimated about 2.1% per year by meta-analysis, however, the risk of rebleeding will increase up to 66%. From the recent analysis of 305 symptomatic patients (83% of patients presented with hemorrhage), an annual hemorrhage rate was calculated to be 8.5% per person-year with 35.1% of 5-year cumulative hemorrhage risk. In this study, prior hemorrhage was independent predictors of subsequent hemorrhage and subsequent hemorrhage events were independent risk factors for worsening of neurological function. Moreover, even in conservative management for SCCMs, 11.3% of cases presented exacerbation of neurological function suggesting the natural history of SCCMs totally seems to be progressive deterioration over time.

Therefore, it become a reasonable consensus on surgical removal in symptomatic patients of SCCMs in spite of exiting the potential risk of operative neurological complication. However, the optimal timing for SCCMs is still controversial. Early surgery is generally recommended for symptomatic SCCMs and Li et al. have indicated the surgical timing within 3 months provides a higher improved outcome. On the other hand, emergent operation includes some problems because conditions of the spinal cord are not ordinarily suitable for intramedullary perilesional dissection especially in acute phase after hemorrhage. Zevgari-dis et al. recommended that 4–6 weeks after a hemorrhage seems to be the optimal timing if lesion is in critical areas. In this phase, lesion removal become easier by a glial scar formation and hematomas in resolution with minimal damage to the spinal cord. Imagama et al. also suggested SCCMs resection after hemorrhage should be conducted after primary and secondary damage to the spinal cord are reduced as much as possible. They concluded surgery may be postponed after maximum motor recovery if patients have preoperative paresis. In addition, surgical outcome is highly influenced by spinal cord level and location pre-
Surgical Treatment of Spinal Cord Cavernous Malformation

Takahashi T, et al.

The potential of neurological recovery is also controversial in accordance with preoperative neurological severality. The reality of benefit in surgical removal of SCCMs is also unclear, if patients had tetraplegia or paraplegia without any sign of recovery.

Kurokawa et al. demonstrated the results of surgical timing and outcome for symptomatic SCCMs from multicenter survey. This article has provided contemporary practice pattern in surgical treatment among neurosurgical spine centers in Japan. Kurokawa et al. have found that neurological function was more likely to improve in patients with preoperative modified McCormick scale grade V if they had surgery within 3 months from symptom onset. Although no relationship was found between surgical timing and outcome except for this neurological grade, this result supports early surgery can be beneficial even in patients with critical neurological deficit. And more advanced surgical techniques including neuromonitoring which assist complete and safe operation can provide more aggressive surgical indication and urgent surgical timing.

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

**REFERENCES**

Efficacy of Transforaminal Endoscopic Lumbar Discectomy in Elderly Patients Over 65 Years of Age Compared to Young Adults

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²Gachon University Graduate School of Medicine, Incheon, Korea

Objective: Spine surgery rates are increasing in the elderly population due to social aging, and it is known that prognoses related to surgery are worse for the elderly compared to younger individuals. However, minimally invasive surgery, such as full endoscopic surgery, is considered safe with low complication rates due to minimal damage to surrounding tissues. In this study, we compared outcomes of transforaminal endoscopic lumbar discectomy (TELD) in elderly and younger patients with disc herniation in the lumbosacral region.

Methods: We retrospectively analyzed the data of 249 patients who underwent TELD at a single center between January 2016 to December 2019, with a minimum follow-up of 3 years. Patients were allocated to 2 groups: a young group aged ≤ 65 years (n = 202) or an elderly group aged > 65 years (n = 47). We evaluated baseline characteristics, clinical outcomes, surgery-related outcomes, radiological outcomes, perioperative complications, and adverse events during the 3-year follow-up period.

Results: Baseline characteristics, including age, general condition based on American Society of Anesthesiologist physical status classification grade, age-Charlson Comorbidity Index, and disc degeneration, were worse in elderly group (p < 0.001). However, except for leg pain at 4 weeks after surgery, overall outcomes, including pain improvement, radiological change, operation time, blood loss, and hospital stay, were not different between the 2 groups. Furthermore, the rates of perioperative complications (9 patients [4.46%] in the young group and 3 patients [6.38%] in the elderly group, p = 0.578) and adverse events over the 3-year follow-up period (32 patients [15.84%] in the young group and 9 patients [19.15%] in the elderly group, p = 0.582) were comparable in the 2 groups.

Conclusion: Our findings suggest that TELD produces similar outcomes in both elderly and younger patients with a herniated disc in the lumbosacral region. TELD can be considered a safe option for appropriately selected elderly patients.

Keywords: Aged, Disc herniation, Lumbosacral region, Percutaneous discectomy, Treatment outcome

INTRODUCTION

As the population ages, there is an increasing number of patients with spinal diseases and a corresponding need for spinal surgery.¹ In particular, degenerative lumbar spine diseases are on the rise, leading to a significant increase in the economic burden.²³ This trend is the inevitable result of a growing elderly population and the gradual accumulation of age-related degenerative changes in the spine.

In elderly patients, biological age, frailty, and other risk factors identified by prognostic prediction models negatively impact the outcome after surgery.⁴⁵ The incidence of complications, which exceed 30% in some studies, and recovery time after spinal surgery are worse in the elderly compared to younger
individuals. Therefore, physicians should prudently consider the risks and benefits before performing spinal surgery in elderly patients.

The comparative clinical outcomes after full endoscopic spine surgery in elderly and younger patients are controversial. Several recent studies have suggested that minimally invasive spine surgery (MISS) reduces postoperative complications and hospital stays compared to conventional surgery, and that MISS may be particularly effective in the elderly. In particular, full endoscopic spine surgery, which is performed under local anesthesia or epidural anesthesia, is considered relatively safe as it minimizes damage to surrounding tissues. However, there are few direct comparative studies that have examined the efficacy and safety of full endoscopic spine surgery in the elderly and younger adults.

To address this controversy, we compared the outcomes of transfominal endoscopic lumbar discectomy (TELD), a water-based uniporal endoscopic procedure, between elderly and young patients with herniated disc in the lumbosacral region, focusing on complications and adverse events. The criteria used to define the elderly range from 60 to 80 years of age, but 65 is commonly used based on socioeconomic and physical activity considerations. In this study, we used 65 years as the age criterion because it is socially acceptable and in line with recent literature.

**MATERIALS AND METHODS**

1. **Surgical Indication**

The study was approved by the Institutional Review Board of Gachon University Gil Medical Center (GBIRB2023-028), which waived the requirement for informed consent due to the retrospective design of the study and the anonymized nature of the data used.

All patients who underwent surgery were diagnosed with lumbar disc herniation causing leg pain by lumbar magnetic resonance imaging (MRI). The indications for TELD were as follows: (1) persistent back pain and leg pain despite conservative treatment, including medication and/or nerve block, for a minimum of 6 weeks; or (2) extreme pain, making daily life impossible or (3) motor weakness of grade ≤ 3 regardless of conservative treatment duration.

2. **Patient Selection**

The data of patients that underwent TELD by one of 2 surgeons (SS, AY) at a single institute between January 2016 and December 2019. One surgeon had more than 15 years of experience (>1,000 cases), and the other surgeon had 3 years of experience (>100 cases).

The study exclusion criteria used were as follows: (1) transfominal endoscopic lumbar foraminotomy or extraforaminal endoscopic lumbar discectomy cases for foraminal stenosis or far lateral disc rupture, (2) history of previous surgery at the same level, (3) insufficient follow-up during the prescribed 3-year period, or (4) inadequate medical or imaging records.

During the study period, 345 patients underwent TELD by the 2 surgeons, and after excluding 96 patients, the remaining 249 were enrolled. These patients were then allocated to a young group (≤ 65 years of age, n = 202) or an elderly group (> 65 years of age, n = 47) (Fig. 1).

3. **Operative Technique**

All surgical procedures were carried out in the prone position on a Jackson spine table to reduce abdominal pressure. All patients were lightly sedated by an intravenous injection of midazolam, with dosage varying case to case, while vital signs were monitored. After local anesthesia with lidocaine, a skin incision of 0.5 to 0.7 cm in length was made at the surgical level, which was 10 to 15 cm from the midline. The entry points were determined based on anatomical variations and surgical targets.

A discogram was obtained using indigo carmine after insert-
ing a discogram needle into the surgical level under fluoroscopic guidance. The discogram needle was then replaced with a guide wire, and a dilator, an obturator, and a working cannula were sequentially inserted. A Vertebris system (Richard Wolf, Knittlingen, Germany) or a Joimax system (Joimax, Irvine, CA, USA) was used. Foraminoplasty to facilitate cannula approach, removal of ruptured disc, evacuation of the disc space, and annuloplasty/coagulation using radiofrequency were performed on a case-by-case basis under water-based endoscopic view. Finally, the wound was closed with 1–2 stitches of subcutaneous suture and skin tape without drainage.\textsuperscript{11,22}

4. Outcome Evaluation

1) Baseline characteristics

Demographic data and baseline characteristics, such as age, sex, body mass index, occupation, smoking status, alcohol intake, surgical level, dominant symptom side, preoperative symptom duration, previous history of nerve block, trauma history, and presence of motor weakness, were analyzed. In addition, general patient conditions were assessed using American Society of Anesthesiologist (ASA) physical status (PS) classification grades and age-Charlson Comorbidity Index (age-CCI).\textsuperscript{23,24}

2) Clinical outcome

Clinical outcomes were assessed using visual analogue scale (VAS) scores for low back pain and leg pain. Clinical data were collected preoperatively and at each follow-up visit (4 weeks ± 1 week, 1 year ± 1 month, and 3 years ± 3 months after surgery). Patient satisfaction was estimated using Odom criteria at each follow-up visit.\textsuperscript{25}

3) Radiological outcome

Radiological outcomes were obtained from MRI and simple radiography. Lumbar MRI was performed before and immediately after surgery in all patients to confirm nerve root decompression and determine remnant ruptured disc volumes. Plain and dynamic radiographs were performed preoperatively and at 3 years postoperatively to evaluate changes in disc height and lumbar alignment.

Baseline Pfirrmann grade, which represents disc degeneration, and the type of disc rupture (migrated or subligamentous) were evaluated using preoperative MRI.\textsuperscript{26} The estimated extruded disc volume was determined using the formula \( \frac{\text{transverse diameter} \times \text{depth} \times \text{height of herniated disc}}{2} \) at the section of greatest nerve compression on preoperative and postoperative MRIs.\textsuperscript{11}

Calibrated disc height was measured by averaging the anterior, middle, and posterior disc heights. Then, the disc height ratio to anteroposterior diameter of the L5 vertebral body was determined, considering variations in x-ray magnification, using the formula \( \frac{\text{anteroposterior diameter of L5 body}}{\text{anteroposterior diameter of L5 body} \times 100\%} \).\textsuperscript{27} Segmental angle and range of motion at the surgical level and whole lumbar spine were measured using Cobb method.

4) Surgery-related outcome

Surgery-related outcomes were evaluated using the total operation time, blood loss during surgery as assessed by changes in hemoglobin levels post-surgery, and recovery time based on hospital stays. The total operation time was calculated by adding preparation time (time for positioning the patient and preparing the surgical site) and operation time from skin incision to wound closure. Hemoglobin levels were checked prior to the surgery and on the day after to assess changes.

5) Complications and adverse events

Perioperative complications and adverse events during the 3-year study period were thoroughly investigated. Perioperative complications included surgery-related complications (e.g., exiting root irritation/injury, durotomy, nerve damage, and surgical site infection), non–surgery-related complications (e.g., cardiopulmonary complications, deep vein thrombosis, and urinary retention), and surgical failure and conversion to another surgical method. Adverse events during follow-up included additional admission for care, additional nerve block for pain control, remnant lesion detected postoperative MRI requiring additional treatment, recurrence in the same lesion site, revision surgery for the same lesion, and revision surgery for another lesion.

5. Statistical Analysis

Data management and statistical analysis were conducted using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA). Pearson chi-square test, Fisher exact test, the nonparametric Mann-Whitney U-test, the nonparametric Friedman test, the independent t-test, the paired t-test, or Kaplan-Meier survival analysis were used according to the characteristic of the values. Results are presented as means ± standard deviations, means with 95% confidence intervals (CIs), or medians and interquartile ranges (IQR) depending on whether data were normally distributed. Statistical significance was determined at a p-value of less than 0.05.
RESULTS

1. Demographic Data and Baseline Characteristics

The mean age of overall population was 51.72 ± 15.87 years with normal distribution. The median ages in the young and elderly groups were 49 (IQR, 37.00–58.00) and 72.00 (IQR, 67.25–79.75), respectively (p < 0.001, nonparametric Mann-Whitney U-test) (Fig. 2).

The ASA PS classification grade and age-CCI were significantly higher in the elderly group (p < 0.001, by Pearson chi-square test and the nonparametric Mann-Whitney U-test, respectively). The occupational distribution among the patients revealed a significant proportion of retired individuals in the elderly group, which was different from the distribution in the young group (p < 0.001, Pearson chi-square test). Notably, the elderly group had a relatively high proportion of patients above the L4–5 level of surgery, which was also significantly different from the young group (p < 0.001, Pearson chi-square test).

Other factors, including sex ratio, smoking, alcohol intake, duration of symptoms, dominant symptom side, trauma history, and presence of paresis, were not different between the 2 groups. Additionally, body mass index was not significantly different between the 2 groups, although height and weight were greater in the young group (Table 1).

2. Clinical Outcome

Longitudinal analysis of both groups showed that the VAS scores for back and leg pain significantly improved after surgery, and that pain reduced progressively during the 3-year follow-up (p < 0.001, nonparametric Friedman test) (Fig. 3).

Comparative analysis revealed that median VAS scores for back pain were similar in the 2 groups across all survey periods, and that median VAS scores for leg pain were not different between the 2 groups before surgery and at 1- and 3-year follow-up visits. However, at 4 weeks after surgery, the young group showed greater improvement in VAS scores for leg pain than the elderly group (median [IQR]: 2.0 [2.0–3.0] vs. 3.0 [2.0–4.0], p = 0.012, nonparametric Mann-Whitney U-test) (Table 2).

---

**Fig. 2.** Diagram showing the age distribution for the entire populations and each group.
### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Young (n = 202)</th>
<th>Elderly (n = 47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.00 (37.00–58.00)</td>
<td>72.00 (67.25–79.75)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>107:95</td>
<td>25:22</td>
<td>0.978‡</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.62 ± 9.38</td>
<td>161.01 ± 9.76</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.00 (59.55–75.00)</td>
<td>60.70 (53.15–70.25)</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.57 (21.63–26.00)</td>
<td>23.34 (21.46–26.25)</td>
<td>0.504‡</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White collar:blue collar:others</td>
<td>86:46:70</td>
<td>10:6:31</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Smoking</td>
<td>28:174</td>
<td>4:43</td>
<td>0.324‡</td>
</tr>
<tr>
<td>Alcohol</td>
<td>71:131</td>
<td>17:30</td>
<td>0.895‡</td>
</tr>
<tr>
<td>Surgery level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2–3:L3–4:L4–5:L5–S1</td>
<td>0:10:147:45</td>
<td>1:13:26:7</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Dominant symptom side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right:left:equivocal</td>
<td>89:107:6</td>
<td>17:30:0</td>
<td>0.241†</td>
</tr>
<tr>
<td>Symptom duration (wk)</td>
<td>8.57 (3.00–25.71)</td>
<td>12.86 (3.32–51.43)</td>
<td>0.428§</td>
</tr>
<tr>
<td>Previous nerve block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes:No</td>
<td>128 (63.4):74</td>
<td>28 (59.6):19</td>
<td>0.663‡</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes:No</td>
<td>15 (7.4):187</td>
<td>2 (4.3):45</td>
<td>0.433‡</td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes:No</td>
<td>31 (15.4):171</td>
<td>8 (17.0):39</td>
<td>0.776§</td>
</tr>
<tr>
<td>ASA PS classification grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I:II:III:IV</td>
<td>102:82:18:0</td>
<td>2:30:15:0</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Age-CCI</td>
<td>1.0 (0.0–3.0)</td>
<td>4.0 (3.0–5.0)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A:B</td>
<td>140:62</td>
<td>38:9</td>
<td>0.114†</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range), mean ± standard deviation, or number (%).
ASA PS, American Society of Anesthesiologist physical status; CCI, Charlson Comorbidity Index.
† Nonparametric Mann-Whitney U-test. ‡ Pearson chi-square test. § Independent t-test.

### Fig. 3. Visual analogue scale (VAS) scores for back and leg pain in the 2 study groups.

https://doi.org/10.14245/ns.2346192.096
According to Odom criteria, both groups showed favorable satisfaction, with success rates above 90%, and no intergroup difference was evident at any follow-up visit (Table 2).

### 4. Surgery-Related Outcome

In terms of the surgical procedure, there was no difference in the rate of performing bone work, such as foraminoplasty, partial pediculectomy, or partial endplate drilling, between the 2 groups. In addition, the total operation time, including preparation and operation time, was not different between the 2 groups (median [IQR], 75.0 minutes [65.0–80.0 minutes] in the young group and median 75.0 minutes [65.0–80.0 minutes] in the elderly group, p = 0.301, nonparametric Mann-Whitney U-test) (Table 4).

The reduction in hemoglobin level, indicating intraoperative blood loss, was not different between the 2 groups (median [IQR], 0.60 [0.30–1.00] in the young group and median 0.70 [0.30–0.90] in the elderly group, p = 0.596, nonparametric Mann-Whitney U-test), although pre- and postoperative hemoglobin levels were significantly lower in the elderly group (Table 4).

Hospital stay was also not significantly different between the 2 groups (median [IQR], 4.0 days [3.0–6.0 days] in both groups, p = 0.927, nonparametric Mann-Whitney U-test) (Table 4).

### 5. Perioperative Complication and Adverse Event

The incidence of perioperative complications was not significantly different between the 2 groups (9 patients [4.46%] in young group versus 3 patients [6.38%] in elderly group, p = 0.578, Pearson chi-square test). In the young group, 8 patients (3.96%) experienced surgery-related complications, including 4 cases of...
Table 3. Radiological outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n = 202)</th>
<th>Elderly (n = 47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfirrmann grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III:IV:V</td>
<td>70:126:6</td>
<td>5:41:1</td>
<td>0.013†</td>
</tr>
<tr>
<td>Type of ruptured disc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migrated;subligamentous</td>
<td>146:56</td>
<td>35:12</td>
<td>0.875†</td>
</tr>
<tr>
<td>Ruptured disc volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative (mm³)</td>
<td>1,595.58 (926.49–2,476.69)</td>
<td>1,278.43 (882.20–2,125.31)</td>
<td>0.135‡</td>
</tr>
<tr>
<td>Postoperative (mm³)</td>
<td>361.73 (227.72–526.68)</td>
<td>439.50 (192.82–548.56)</td>
<td>0.504§</td>
</tr>
<tr>
<td>Reduction ratio (%)</td>
<td>73.92 (56.72–86.69)</td>
<td>69.34 (58.39–80.18)</td>
<td>0.301†</td>
</tr>
<tr>
<td>Disc height ratio to vertebral body (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>27.46 ± 8.93</td>
<td>27.22 ± 6.15</td>
<td>0.891†</td>
</tr>
<tr>
<td>3 Years</td>
<td>26.84 ± 9.91</td>
<td>26.07 ± 6.08</td>
<td>0.431†</td>
</tr>
<tr>
<td>Segmental angle of surgery level (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>13.61 ± 7.75</td>
<td>14.83 ± 6.55</td>
<td>0.417§</td>
</tr>
<tr>
<td>3 Years</td>
<td>14.70 ± 6.26</td>
<td>16.14 ± 6.53</td>
<td>0.273§</td>
</tr>
<tr>
<td>Range of motion of surgery level (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>3.82 ± 1.67</td>
<td>4.49 ± 1.91</td>
<td>0.473§</td>
</tr>
<tr>
<td>3 Years</td>
<td>3.99 ± 1.57</td>
<td>3.58 ± 1.74</td>
<td>0.664§</td>
</tr>
<tr>
<td>Lumbar lordosis (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>38.91 ± 14.65</td>
<td>40.00 ± 12.53</td>
<td>0.704§</td>
</tr>
<tr>
<td>3 Years</td>
<td>43.20 ± 11.05</td>
<td>43.70 ± 12.16</td>
<td>0.833§</td>
</tr>
<tr>
<td>Range of motion of lumbar spine (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>19.63 ± 5.66</td>
<td>21.75 ± 5.79</td>
<td>0.382§</td>
</tr>
<tr>
<td>3 Years</td>
<td>21.27 ± 5.91</td>
<td>22.10 ± 6.03</td>
<td>0.125§</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or mean ± standard deviation.
†Pearson chi-square test. ‡Nonparametric Mann-Whitney U-test. §Independent t-test.

Table 4. Surgery-related outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n = 202)</th>
<th>Elderly (n = 47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone work during surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td>36 (17.8):166</td>
<td>7 (14.9):40</td>
<td>0.632†</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation time</td>
<td>20.0 (15.0–25.0)</td>
<td>20.0 (15.0–20.0)</td>
<td>0.651†</td>
</tr>
<tr>
<td>Operation time</td>
<td>55.0 (45.0–60.0)</td>
<td>55.0 (50.0–60.0)</td>
<td>0.352‡</td>
</tr>
<tr>
<td>Total operation time</td>
<td>75.0 (65.0–85.0)</td>
<td>75.0 (65.0–80.0)</td>
<td>0.738‡</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative hemoglobin</td>
<td>14.22 ± 1.58</td>
<td>13.27 ± 1.60</td>
<td>&lt; 0.001§</td>
</tr>
<tr>
<td>Postoperative hemoglobin</td>
<td>13.52 ± 1.55</td>
<td>12.63 ± 1.56</td>
<td>&lt; 0.001§</td>
</tr>
<tr>
<td>Decrease of hemoglobin</td>
<td>0.60 (0.30–1.00)</td>
<td>0.70 (0.30–0.90)</td>
<td>0.596‡</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>4.0 (3.0–6.0)</td>
<td>4.0 (3.0–6.0)</td>
<td>0.927‡</td>
</tr>
</tbody>
</table>

Values are presented as number (%), median (interquartile range), or mean ± standard deviation.
†Pearson chi-square test. ‡Nonparametric Mann-Whitney U-test. §Independent t-test.
transient exiting root irritation, 2 cases of iatrogenic durotomy, 1 case of surgical site infection with discitis, and 1 case of new disc herniation in the foramen along the endoscope trajectory. In the elderly group, 2 patients (4.26%) experienced surgery-related complications, including 1 case of iatrogenic durotomy and 1 case of surgical site infection with discitis. In terms of nonsurgery-related complications, there was one patient in the elderly group who was newly diagnosed with arterial insufficiency after surgery. Additionally, there was one case of conversion to open surgery in the young group because of intradural disc rupture (Table 5).

The number of patients who experienced an adverse event during follow-up was similar between the 2 groups (32 patients [15.84%] in the young group vs. 9 patients [19.15%] in the elderly group, \( p = 0.582 \), Pearson chi-square test). Significant residual extruded discs requiring further treatment occurred in 2 patients (1.00%) in the young group and 1 patient (2.13%) in the elderly group (\( p = 0.468 \), Fisher exact test). Recurrent disc herniation with symptom aggravation occurred in 14 patients (6.93%) in the young group and 5 patients (10.64%) in the elderly group (\( p = 0.394 \), Pearson chi-square test). Revision surgery for the previously treated lesion was performed in 17 patients (8.42%) in the young group (5 cases of revisional TELD for recurrence, 4 cases of revisional microscopic discectomy for recurrence, 3 cases of fusion surgery for recurrence, 3 cases of microscopic discectomy for remnant lesion, 1 case of fusion for iatrogenic durotomy, and 1 case of revisional TELD for discitis) and 7 patients (14.89%) in the elderly group (3 cases of revisional microscopic discectomy for recurrence, 1 case of revisional TELD for recurrence, 1 case of revisional TELD for remnant lesion, 1 case of fusion surgery for recurrence, and 1 case of fusion surgery for discitis) (\( p = 0.175 \), Pearson chi-square test). In addition, surgery for another lesion was performed in 3 patients (1.49%) in the young group (1 case of disc herniation in the contralateral side at 1 month after surgery, and 2 cases of disc herniation at an adjacent cranial level at 2 and 3 months after surgery, whereas no surgery for another lesion was performed in the elderly group) (\( p = 1.000 \), Fisher exact test) (Table 5).

No overall significant intergroup difference was observed for any complication or adverse event (37 patients [18.32%] in the young group versus 10 patients [21.28%] in the elderly group, \( p = 0.640 \), Pearson chi-square test). According to Kaplan-Meier survival analysis of all perioperative complications and adverse events during the 3-year follow-up period, the mean time to occurrence of an event was similar between the 2 groups (908.3 days [95% CI, 853.1−963.4] in the young group and 911.7 days [95% CI, 800.2−1,023.3] in the elderly group, \( p = 0.682 \), log-rank test) (Fig. 4).

On the other hand, regarding age as a risk factor for recurrence after TELD, the mean age of the recurrence group (\( n = 19 \)) was higher compared to the nonrecurrence group (\( n = 230 \)), but the difference was not statistically significant (mean age of 51.30

### Table 5. Perioperative complication and adverse event during follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n = 202)</th>
<th>Elderly (n = 47)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery-related</td>
<td>8 (3.96)</td>
<td>2 (4.26)</td>
<td>0.926†</td>
</tr>
<tr>
<td>Nonsurgery-related</td>
<td>0 (0)</td>
<td>1 (2.13)</td>
<td>0.189‡</td>
</tr>
<tr>
<td>Conversion to open surgery</td>
<td>1 (0.50)</td>
<td>0 (0)</td>
<td>1.000†</td>
</tr>
<tr>
<td>No. of patients who experienced any complication</td>
<td>9 (4.46)</td>
<td>3 (6.38)</td>
<td>0.578‡</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional admission and conservative treatment</td>
<td>3 (1.49)</td>
<td>1 (2.13)</td>
<td>0.569‡</td>
</tr>
<tr>
<td>Additional nerve block</td>
<td>10 (4.95)</td>
<td>2 (4.26)</td>
<td>0.841†</td>
</tr>
<tr>
<td>Remnant lesion</td>
<td>3 (1.49)</td>
<td>1 (2.13)</td>
<td>0.468‡</td>
</tr>
<tr>
<td>Recurrence</td>
<td>14 (6.93)</td>
<td>5 (10.64)</td>
<td>0.394†</td>
</tr>
<tr>
<td>Revision surgery of previous lesion</td>
<td>17 (8.42)</td>
<td>7 (14.89)</td>
<td>0.175†</td>
</tr>
<tr>
<td>Revision surgery of another lesion</td>
<td>3 (1.49)</td>
<td>0 (0)</td>
<td>1.000‡</td>
</tr>
<tr>
<td>No. of patients who experienced any adverse event</td>
<td>32 (15.84)</td>
<td>9 (19.15)</td>
<td>0.582‡</td>
</tr>
<tr>
<td>Sum of patients with any complication or adverse event</td>
<td>37 (18.32)</td>
<td>10 (21.28)</td>
<td>0.640†</td>
</tr>
</tbody>
</table>

Values are presented as number (%). †Pearson chi-square test. ‡Fisher exact test.
Efficacy of TELD in Elderly

Son S, et al.

In addition, others have suggested that and disc degenera

Nevertheless, based on our findings, there was no differ

Based on this concept,

The in

However,

Several authors have reported that TELD is superior to

DISCUSSION

According to the results of this study, overall outcomes, including clinical and radiological outcomes, perioperative complications, and adverse events, were comparable in both the elderly group (age > 65 years) and the young group. As expected, several baseline characteristics, such as baseline general condition (based on ASA PS classification grade and age-CCI), basic physique (based on height and weight), hemoglobin level, and degenerative disc changes, were significantly worse in the elderly group. Baseline general condition and age are known to be associated with postoperative prognosis, and disc degeneration has known to be associated with recurrence. However, clinical and radiological outcomes were not significantly different between the 2 groups, except for VAS leg pain at 4 weeks after surgery. Additionally, both groups showed similar outcomes in terms of recovery rates, based on the length of hospital stay and incidences of perioperative complications and adverse events during the 3-year follow-up period.

These findings of the present study are not consistent with previous suggestions that the elderly have a higher probability of experiencing adverse events after undergoing full endoscopic surgery. A previous study based on a nationwide database suggested that the cutoff age for endoscopic surgery was 57 years because the risk of reoperation after this age increased more than that of open surgery. In addition, others have suggested that patients with a mean age between 52.1 to 68.5 years have higher rates of recurrence, reoperation, or readmission after endoscopic surgery compared to younger patients.

We postulate several hypotheses for the discrepancy of results between this study and previous reports. First, the difference of statistical methods can affect the conclusion. We directly compared the young and elderly groups, whereas previous studies compared the event-occurred group and non–event-occurred group. However, in this study, comparison between the recurrence group and the nonrecurrence group also showed no statistical difference in terms of age, although there was a trend that the recurrence group had an older age compared to the nonrecurrence group. Secondly, fundamental difference in collected data, such as surgical approach or follow-up period, can affect the overall results of the analysis. To validate our results, large-scaled studies or prospective studies are necessary.

Full endoscopic surgery has several advantages over conventional spine surgery, which includes local anesthesia, a smaller incision, less blood loss, and a shorter recovery time. MISS techniques have rapidly improved over the past 2 decades, and one of the most advanced MISS techniques for patients with lumbar disc herniation is TELD. TELD minimizes damage to surrounding structures and does not require general anesthesia. Several authors have reported that TELD is superior to conventional surgery, including microscopic discectomy, in terms of outcomes and complication rates. Based on this concept, many authors have suggested that MISS might be more beneficial than conventional surgery in the elderly, and full endoscopic surgery could be applied safely in elderly patients. Previous studies have shown that the overall results of full endoscopic surgery in patients aged over 70 were favorable.

Despite the several advantages of TELD, its application in the elderly has several limitations. For example, the surgical approach is more challenging in elderly patients, and greater surgical proficiency is often required because of degenerative changes such as facet joint hypertrophy or reduced disc height. The indications for TELD in elderly patients are also more restrictive because of advanced pathologic conditions, such as severe central stenosis, calcified discs, spondylolisthesis, or sagittal imbalance. Nevertheless, based on our findings, there was no difference in baseline disc height, although the preoperative disc de-

https://doi.org/10.14245/ns.2346192.096
generation was different. This phenomenon could be caused by the patient selection process for TELD. As a result, TELD could be an excellent option in elderly patients, given sufficient surgical proficiency and proper patient selection.

The present study has several limitations that need to be considered. Firstly, the retrospective design of the study did not allow for objective comparisons between the 2 study groups. However, the study included a relatively large number of patients with a minimum 3-year follow-up period, which provided statistical reliability. Secondly, surgeries were performed by different surgeons, and the analysis was not controlled for confounders. However, we attempted to minimize selection bias by adopting strict exclusion criteria. Nonetheless, this study is the first to compare the outcomes of TELD for young and elderly patients to the best of our knowledge.

CONCLUSION

The overall outcomes, including occurrence of complication/adverse events, were not significantly different between young and elderly groups. These findings indicate that the clinical efficacy and safety of TELD in elderly patients (>65 years) are comparable to younger patients. Additionally, full endoscopic spine surgery has relatively good risk-benefits compared to conventional surgeries requiring general anesthesia. We hope that this study will serve as a reference for surgeons considering TELD in the elderly population.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: SS; Data curation: SS, HJK, SKS; Formal analysis: SS, BRY, SKS; Funding acquisition: SS; Methodology: SS; Project administration: SS; Visualization: SS; Writing - original draft: SS, BRY, YA. Writing - review & editing: SS, BRY, YA.

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REFERENCES

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The Role and Clinical Outcomes of Endoscopic Spine Surgery of Treating Spinal Metastases; Outcomes of 29 Cases From 8 Countries

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Objective: We aim to report the outcomes and feasibility of endoscopic spine surgery used to treat symptomatic spinal metastases patients. This is the most extensive series of spinal metastases patients who underwent endoscopic spine surgery.

Methods: A worldwide collaborative network group of endoscopic spine surgeons, named ‘ESSSORG,’ was established. Patients diagnosed with spinal metastases who underwent endoscopic spine surgery from 2012 to 2022 were retrospectively reviewed. All related patient data and clinical outcomes were gathered and analyzed before the surgery and the follow-up period of 2 weeks, 1 month, 3 months, and 6 months.

Results: A total of 29 patients from South Korea, Thailand, Taiwan, Mexico, Brazil, Argentina, Chile, and India, were included. The mean age was 59.59 years, and 11 of them were female. The total number of decompressed levels was 40. The technique was relatively equal (15 uniportal; 14 biportal). The average length of admission was 4.41 days. Of all patients with an American Spinal Injury Association Impairment Scale of D or lower before surgery, 62.06% reported having at least one recovery grade after the surgery. Almost all
INTRODUCTION

Spinal metastasis is considered one of the significant challenges in spine care worldwide. Although most are asymptomatic, symptomatic spinal metastases can severely affect the patient’s quality of life by causing excruciating pain, neurological deficit, and deteriorating ambulation status. The mainstay of treatment consists of palliative radiation and spine surgery in appropriately selected patients. However, considering the natural history of cancer disease and the patient’s deteriorating frailty status, higher complication rates and more surgical stress is suspected in this population compared to other spinal disorders. Recently, minimally invasive spine surgery (MISS) has been implemented. It can reduce the collateral damage to the surrounding structure, yield better results in reducing blood loss and the length of stay (LOS), and consequently enhance patient recovery. It also provides a comparable efficacy in reducing pain and recovering neurological functions compared to traditional surgery.

Endoscopic spine surgery is one of the recently developed MISS techniques. During the last decade, it has proven its efficacy and safety in treating various spinal pathologies, such as disc herniation, spinal degeneration, and spinal canal stenosis. However, report for its use in spinal metastases patients is still rare; most are case reports or case series. Therefore, in this study, we aim to report the outcomes and efficacy of endoscopic spine surgery when treating symptomatic spinal metastases patients from our extensive collaborative network worldwide. To our knowledge, this is considered the most large-scale cohort ever to be reported.

MATERIALS AND METHODS

This is a multinational, multicenter, retrospective cohort study. After Institutional Review Board approval (Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea; KC22RISI0968), a collaborative network group of experienced endoscopic spine surgeons, named ‘Endoscopic Spine Surgery for Spinal Oncology Research Group’ or ‘ESSSORG,’ was created. They were assigned to collect related data from their respective institutes. The group included 14 spine surgeons from 12 healthcare centers in 8 countries, including South Korea, Thailand, Taiwan, Mexico, Brazil, Argentina, Chile, and India. All patients older than 18 years diagnosed with spinal metastases and underwent endoscopic spine surgery as a palliative treatment from 2012 to 2022 were included in the study.

The patient’s preoperative demographic data, including gender, age, primary tumor of origin, involved vertebrae, age-adjusted Charlson Comorbidity Index (ACCI), American Society of Anesthesiologists (ASA) physical status classification grade, history of previous systemic therapy, history of prior radiotherapy, the revised Tokuhashi Score, the Spinal Instability Neoplastic Score (SINS), and the Metastatic Epidural Spinal Cord Compression Scale (MESCC) were all gathered. The MESCC is a 6-point grading system to describe the severity of epidural spinal cord compression by the tumor. Grades 0, 1a, and 1b are defined as low grades, while grades 2 and 3 are defined as high grades of compression. According to the neurologic, oncologic, mechanical, and systemic or NOMS framework, the use of low and high grades MESCC could help guide the decision of treatment. However, the role of radiation options or surgery is still controversial in grade 1c. Therefore, the collected radiographic images of MESCC were accordingly interpreted into low (grades 0, 1a, or 1b), intermediate (grade 1c), and high grades (grades 2, 3), respectively. At the time of data collection, we also asked all the collaborated surgeons to confirm the dead or alive status of their included patients. One’s status that could not be retrieved was categorized as not known or loss follow-up.

The surgical-related data, including the total number of decompressed levels for each patient, the technique used, the approach used, the use of additional spinal stabilization or augmentation procedure, operative time, and intraoperative blood...
loss, were also collected. The technique used consists of uniporal (full-endoscopic) surgery or biportal (unilateral biportal endoscopic; UBE) surgery, respectively. The approach used consists of interlaminar and transformaminal techniques. The main surgery goal is to palliatively decompress the spinal canal or the foramen and remove the tumor. So, these approaches would aim to decompress those sites, not disectomy as used to perform in the traditional endoscopic spine surgery procedure. All the techniques and approaches were performed under general anesthesia. To corporate the concept of separation surgery, ventral side decompression was also performed in every case if it was feasible and not limited by anatomical hindrance (e.g., in the cervical spine).

Indication and the decision-making to perform the surgery in spinal metastases patients are based on many factors, such as the patient’s performance status, the systemic burden of disease, life expectancy, the controlling status of systemic disease, and the systemic treatment options available, according to an integrated multidisciplinary algorithm from the report of International Spine Oncology Consortium, which should be made in a case-by-case basis. Then, the definite options to include for the surgery will be decided based on NOMS decision framework, or the mechanical, neurological, oncological, preferred treatment, or the MNOP algorithm. Posterior instrumentation, especially via the percutaneous technique, can be added if indicated (e.g., mechanical back pain or SINS of equal or more than 7 points, according to the aforementioned algorithm). However, because metastatic cancer disease cannot be cured and has a short life expectancy, the aggressiveness and costly definite surgical options should be balanced. Therefore, sometimes, not all the indicated procedures can be performed for the patients. All these decision-making processes should also be consensus from a multidisciplinary care team and also aligned with the expectation of patients and their respective families. Nevertheless, according to the above, endoscopic spine surgery would be performed as an alternative to the traditional open, mini-open, or tubular surgery, aiming to decompress the spine as indicated in spinal metastases patients.

Several parameters and patient-reported outcomes were used to evaluate the procedure’s results, including the Eastern Cooperative Oncology Group (ECOG) status, the American Spinal Injury Association (ASIA) Impairment Scale, the pain Numeric Rating Scale (NRS), Oswestry Disability Index (ODI), Neck Disability Index (NDI; in cases with cervical region involvement), and the EuroQol 5-Dimension 5-Levels Utility (EQ5D5L-U) and visual analogue scale (EQ5D5L-VAS), were all collected at the preoperative period and postoperative period of 2 weeks, 1 month, 3 months, and 6 months, respectively. The total LOS in the hospital, follow-up time, and the latest known patient status (whether the patient is alive or has already passed away) were also gathered. Surgical-related complications that occurred during the perioperative or postoperative period, such as neurological progression, wound infection or dehiscence, cerebrospinal fluid leakage, instrumentation failure, local recurrence, the incidence of revision surgery, and intraoperative mortality, were reported together with the occurred time and its related treatment.

In order to compare the preoperative and postoperative data at different time points (months), we employed 2 statistical tests depending on the distribution of the data: the paired t-test and the paired samples Wilcoxon test. The choice of the statistical test was based on the normality of the data distribution. Before conducting the tests, we checked the normality of the data using the Shapiro-Wilk test. If the data met the assumptions of normality, we performed a paired t-test. In cases where the data violated the assumption of normality, we used the non-parametric paired samples Wilcoxon test as an alternative. For each test, we calculated the test statistic and corresponding p-value. We considered a p-value of less than 0.05 as statistically significant. The Stata 17 (Stata Corp., College Station, TX, USA) software was used for all statistical analyses.

RESULTS

A total of 29 patients were included, and 11 (37.93%) were female. The mean age was 59.59 ± 12.61 years. The total number of metastatic involved vertebrae from the patients was 47 levels; most came from the lumbar region (23 levels, 48.9%), followed by the thoracic (17 levels, 36.2%), cervical (4 levels, 8.5%), and sacral region (3 levels, 6.4%), respectively. The mean ACCI was 9.29 ± 2.32. Most patients had a high MESCC grade before the surgery (25 patients, 53.2%). SINS were interpreted as stable and potentially unstable for 6 (20.7%) and 14 (48.3%), respectively. The mean revised Tokuhashi Score was also low (< 6 months) in most of the patients (21 patients, 72.4%), while the mean follow-up time was 8.52 ± 8.1 months. All the details of the demographic data of the included patients are shown in Table 1.

The total number of levels decompressed is 40. For a single operation, 1-, 2-, and 3-level of decompression were performed in 21 cases (70%), 8 cases (26.67%), and 1 case (3.33%), respectively. Because 1 patient received 2 surgeries at different locations of pathology during a single admission, the total number
The number of patients stratified by their preoperative and postoperative neurological status according to the ASIA Impairment Scale is shown in Table 3. Of these, 27 patients (93.1%) had an ASIA Impairment Scale of D or lowered before the surgery, and up to 18 patients (66.67%) had at least one recovery grade after the surgery. Before the surgery, the pain NRS (8.41 ± 1.8)
Role of Endoscopic Spine Surgery in Spinal Metastases

Suvithayasiri S, et al.

Table 3. The number of patients stratified by their neurological status according to the American Spinal Injury Association (ASIA) Impairment Scale compared before and after the endoscopic decompression spine surgery

<table>
<thead>
<tr>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>-</td>
</tr>
</tbody>
</table>

and the ODI or NDI (77.27 ± 17.96) decreased significantly at 2 weeks (pain NRS = 3.3 ± 1.81, p < 0.001; ODI or NDI = 54.13 ± 22.46, p < 0.0001), and able to maintain throughout the follow-up period of 1 month (pain NRS = 2.91 ± 2.02, p < 0.0001; ODI or NDI = 45.62 ± 24.13, p < 0.0001), 3 months (pain NRS = 2.77 ± 1.93, p < 0.0001; ODI or NDI = 49.7 ± 29.67, p < 0.0001), and 6 months (pain NRS = 2.42 ± 1.93, p < 0.0001; ODI or NDI = 49.7 ± 29.67, p < 0.005). Other parameters, such as ECOG, EQ5D5L-U, and EQ5D5L-VAS, followed the same trend with the improvement achieved rapidly 2 weeks after the surgery and could be maintained up to at least 3 months after the surgery; all statistically significant differences from before the surgery (Fig. 1). All the details of the patient's clinical outcomes before and after the surgery at each follow-up time are shown in Table 4. The survival analysis revealed an overall mean survival of 9.15 months. The Kaplan-Meier graph is displayed in Fig. 2.

From our cohort, complications occurred in 4 patients (13.79%). One patient had a superficial wound problem 1 week after the surgery, which could resolve with regular wound dressing and
empirical oral antibiotics. No organism was found. One patient had a postoperative hematoma with severe progressive back and leg pain symptoms 2 weeks after the surgery. Revision surgery for exploration and hematoma removal was carried out, and the patient's symptoms were resolved without further complications. Another patient had neurological progression immediately after the surgery, and urgent revision surgery for wide decompression was carried out. The final patient had a local tumor recurrence 4 months after the surgery. He had a new onset of back pain, and the computed tomography scans revealed a progressive pathologic fracture of the previously involved and operating level of the vertebrae. Percutaneous vertebroplasty was carried out, and the patient's symptoms improved without further complications. A summary of surgical-related complications is displayed in Supplementary Table 1.

**DISCUSSION**

Treatment in spinal metastases requires multidisciplinary approaches and primarily consists of palliative surgery followed by subsequent conventional external beam radiation or stereotactic radiosurgery (SRS), depending on the tumor type of origin radioresistance. With the patient's frailty combined with multiple comorbidities, traditional open surgery is usually associated with higher blood loss, prolonged LOS, and delayed recovery time. This could also cause the postponement of other subsequent treatment processes, such as radiotherapy or other systemic therapy. Thus, MISS has recently been preferable in treating symptomatic spinal metastases patients. It can limit the unnecessary surrounding soft tissue damage, provide less blood loss, less LOS, and enhance the recovery time with comparable outcomes and rate of complications to the traditional open surgery.

Endoscopic spine surgery is considered one of the recent advancements of MISS, especially in degenerative spine disease. Using the recent AOSpine Nomenclature in endoscopic spine surgery, we summarized these advancements and their expanding indications in Table 5. With the larger working cannula and

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**Table 4. Comparisons of patient's clinical outcomes before and after surgery at each interested follow-up period**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before surgery (n = 29)</th>
<th>PO 2 weeks (n = 26)</th>
<th>p-value</th>
<th>PO 1 month (n = 23)</th>
<th>p-value</th>
<th>PO 3 months (n = 21)</th>
<th>p-value</th>
<th>PO 6 months (n = 12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG</td>
<td>2.59 ± 0.75</td>
<td>2.16 ± 0.8</td>
<td>&lt; 0.05*</td>
<td>1.92 ± 0.81</td>
<td>&lt; 0.05*</td>
<td>1.89 ± 0.81</td>
<td>&lt; 0.05*</td>
<td>2 ± 1.04</td>
<td>&lt; 0.05*</td>
</tr>
<tr>
<td>Pain NRS</td>
<td>8.41 ± 1.8</td>
<td>3.3 ± 1.8</td>
<td>&lt; 0.05*</td>
<td>2.91 ± 2.02</td>
<td>&lt; 0.05*</td>
<td>2.77 ± 1.93</td>
<td>&lt; 0.05*</td>
<td>2.42 ± 1.93</td>
<td>&lt; 0.05*</td>
</tr>
<tr>
<td>ODI or NDI</td>
<td>77.27 ± 17.96</td>
<td>54.13 ± 22.46</td>
<td>&lt; 0.05*</td>
<td>45.62 ± 24.13</td>
<td>&lt; 0.05*</td>
<td>49.39 ± 25.13</td>
<td>&lt; 0.05*</td>
<td>49.7 ± 29.67</td>
<td>&lt; 0.05*</td>
</tr>
<tr>
<td>EQ5D5L-U</td>
<td>0.12 ± 0.42</td>
<td>0.38 ± 0.36</td>
<td>&lt; 0.05*</td>
<td>0.52 ± 0.33</td>
<td>&lt; 0.05*</td>
<td>0.4 ± 0.44</td>
<td>&lt; 0.05*</td>
<td>0.34 ± 0.48</td>
<td>0.3833</td>
</tr>
<tr>
<td>EQ5D5L VAS</td>
<td>21.27 ± 20.78</td>
<td>50.46 ± 12.76</td>
<td>&lt; 0.05*</td>
<td>59.58 ± 18.15</td>
<td>&lt; 0.05*</td>
<td>59.62 ± 16.39</td>
<td>&lt; 0.05*</td>
<td>59.25 ± 19.23</td>
<td>&lt; 0.05*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. PO, postoperative; ECOG, Eastern Cooperative Oncology Group; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; NDI, Neck Disability Index; EQ5D5L, EuroQol 5-Dimension 5-Levels; EQ5D5L-U, EQ5D5L Utility; VAS, visual analogue scale.

*Statistically significant (p < 0.05).

**Table 5. Summary of the recent evolution in lumbar endoscopic spine surgery according to the targeted pathology**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Targeted</th>
<th>AOSpine Nomenclature&lt;sup&gt;21&lt;/sup&gt;</th>
<th>Level of skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discectomy</td>
<td>Herniated disc</td>
<td>TELD</td>
<td>Basic</td>
</tr>
<tr>
<td>Discectomy</td>
<td>Herniated disc</td>
<td>IELD</td>
<td>Basic</td>
</tr>
<tr>
<td>Foraminoplasty</td>
<td>Herniated disc</td>
<td>TELD with foraminoplasty</td>
<td>Basic</td>
</tr>
<tr>
<td>Foraminotomy</td>
<td>SAP</td>
<td>TELF</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Foraminotomy</td>
<td>Contralateral SAP</td>
<td>ICRLF</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Decompression</td>
<td>Central canal+lateral recess</td>
<td>LE-ULBD</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ventrer facetectomy</td>
<td>SAP+lateral recess</td>
<td>TELF with TE-LRD</td>
<td>Master</td>
</tr>
<tr>
<td>Fusion</td>
<td>Instability</td>
<td>Endoscopic TLIF</td>
<td>Master</td>
</tr>
</tbody>
</table>

TELD, transforaminal endoscopic lumbar discectomy; IELD, interlaminar endoscopic lumbar discectomy; TELF, transforaminal endoscopic lumbar foraminotomy; ICRLF, interlaminar contralateral endoscopic lumbar foraminotomy; LE-ULBD, lumbar endoscopic unilateral laminotomy for bilateral decompression; TE-LRD, transforaminal endoscopic lateral recess decompression; SAP, superior articular process; TLIF, transforaminal lumbar interbody fusion.
specialized armamentarium, it has been able to expand the surgical indications from simple decompression reaching up to lumbar interbody fusion, and more complicated spine surgery (e.g., infection), with noninferiority to better results compared to the traditional MISS procedures. However, because the support of these technical evolutions is very recent, report of its use in spinal metastases is still scarce. To the best of our knowledge, there are only 11 cases from 7 studies in previous literature. Although all have revealed good results of rapid pain relief, neurological recovery, less blood loss, and the reduction of LOS, the level of evidence is considered low as they are all case reports or series with an insufficient number of patients (Supplementary Table 2). This could also be from the lower incidence of symptomatic spinal metastases undergone surgery compared to other general spinal diseases. Therefore, less number of cases and fewer adoption of endoscopic spine surgery used in spinal metastases is expected. To overcome this, a worldwide collaboration of spine surgeons is established by our senior author (KJS). As a result of the last 10 years from 14 surgeons in 8 countries, there was a total of 29 cases enrolled in our study, which is considered the most extensive cohort to date.

From our study, good to excellent outcomes were achieved as all clinical outcomes related to the patient's quality of life were improved significantly and could be maintained up to 6 months after the surgery. Among 27 patients with an ASIA Impairment Scale of D or lower, up to 66.67% achieved at least one recovery grade. Moreover, the mean length of admission from our study was also low (4.41 ± 3.38 days). These results were comparable or even better to previous reports of spinal metastases patients treated with MISS. Miscusi et al. compared the outcomes of MISS with traditional open surgery for thoracic spinal metastases patients with acute myelopathy. Although no apparent significant differences regarding neurological status improvement were found, significant improvements in decreasing blood loss (mean, 240 mL), operative time (mean, 2.2 hours), and LOS (mean, 7.2 days) were achieved from the MISS group. This can also indirectly indicate that this enhanced recovery time, as revealed by the shortened LOS, could also allow patients to receive other adjunct cancer-related treatment faster than traditional procedures. Thus, it can potentially enhance the overall survival of metastatic cancer patients. Complication rates were also comparable to previous studies. Vargas et al. retrospectively reviewed the records of 205 patients regarding wound complications in spinal metastases patients and reported rates of wound complications between 10.8%–14.3%. Another review by Igoumenou et al. has also demonstrated relatively comparable rates of various complication types to our study, including wound infection and dehiscence (1.5% to 30%), hemorrhage and hematomas (5.9% to 12%), and neurological complications (0.6% to 14.5%).

One of the potential limitations of the ESS for patients with spinal metastases lies in the learning curve itself. Adopting this technique for this specific type of patient would be more challenging than disc herniation or degenerative diseases. Initially, almost all techniques used in the previous study were full-endoscopic with a transfornaminal approach (Supplementary Table 2). This means that the endoscopic spine surgery from those studies was able to do the role of the local decompression around the intervertebral foramen, primarily only for pain reduction. This differs from our study, as 30 out of 40 operated levels (75%) used the interlaminar approach. Because this approach is as feasible for central and bilateral decompression as traditional microsurgery, it allowed surgeons to achieve better spinal canal decompression. Another reason could be that the adoption of endoscopic spine surgery is relatively new in spinal metastases treatment. The interlaminar approach is more familiar to many surgeons as it shares the same features as the traditional posteri approach and could also shorten the overall learning curve process.

The number of full-endoscopic and UBE surgeries that surgeons used in our cohort is relatively the same. The UBE technique uses the 2 independent portals to work and has a more flexible working angle. This could ease the learning curve and be adopted more readily by many surgeons familiar with arthroscopy or tubular spine surgery. Nevertheless, both techniques provided better intraoperative visualization than tubular-based microsurgery. The concept of separation surgery is to allow the safe delivery of the SRS after surgery to achieve better local tumor control by adequately separating the neural element from the tumor to a certain margin (usually 2–5 mm). Therefore, using an interlaminar approach with either full-endoscopic or UBE, the optimal visualization provided by both techniques is another potential advantage, especially when doing the ventral side decompression into the vertebral body, to ultimately achieve the goal of separation surgery (Figs. 3, 4).

Intraoperative hemostasis is one of the major concerns during surgery in spinal metastases patients. More excessive bleeding may negatively affect the visualization during endoscopic spinal procedures. Similar to other surgeries, several options are available for us to use for achieving better hemostasis control during endoscopic spinal surgery, including radiofrequency ablation probes or various types of hemostatic agents, such as
bone wax, gelatin foam, or human gelatine-thrombin matrix sealant. The manual control pressure of the saline irrigation for a brief period is also an advantage in full-endoscopic spine surgery. Furthermore, UBE could also provide some unique benefits for hemostasis. Optimizing the irrigation flow control during the UBE procedure or creating a new channel to allow more irrigation flow can provide better visualization (Fig. 4). As to our studies, the mean estimated blood loss is 94.63 mL (range, 5–300 mL), which is considered comparable or less bleeding to other MISS in the literature. Lastly, although we do not have the data regarding the preoperative endovascular embolization used in our series, it is also one of the good options for spinal metastases patients to enhance bleeding control, as proven in previous literature. However, controversy regarding its effectiveness still exists, especially in patients with nonhypervascular tumors of origin.

Theoretically, saline irrigation during endoscopic spine surgery in spinal metastases patients might have a negative impact as the tumor cell could be spread, causing more contamination. However, there is still no clear evidence that endoscopic spine surgery will cause more contamination than traditional or MISS when treating spinal metastases. Moreover, our study found only 1 case (3.45%) of local tumor recurrence. Park and Jeon conducted a retrospective study of 102 symptomatic spinal metastases patients who underwent spinal surgery. Primary tumors mainly consisted of gastrointestinal, breast, and lung in origin, and they reported a symptomatic tumor recurrence rate of 2.94%. Another prospective nonrandomized MISS study by Tancioni et al. also found a symptomatic local recurrence rate of 8% among the spinal metastases patients in their cohort. Further studies focusing on the extent of tumor cell contamination or the recurrence rate after the surgery in these populations that underwent endoscopic spine surgery with a larger population will be beneficial to confirm this finding.

Patient selection is also challenging in surgically treated spinal metastases patients. Following the algorithms, all have recommended many systemic factors to consider, including the patient’s performance status, the systemic burden of disease, life expectancy, and the controlling status of systemic disease, to name a few. However, with the nature of the ultraminimally invasiveness of ESS, it is possible that more frailty of patients with those systemic burdens could benefit from the decompression.

Fig. 3. A patient with acute onset of both sides of paraplegia underwent full-endoscopic decompression surgery. (A, B) Preoperative magnetic resonance imaging (MRI) images reveal T10–12 epidural metastases and severe spinal cord compression. (C, D) Intraoperative fluoroscopic images show the optimal position for the interlaminar approach used in this case. (E, F) Postoperative MRI images demonstrate the tumor has been removed and the neural element was free. (G) Postoperative computed tomography scan showed the postlaminectomy site, where wide decompression was achieved.
sion surgery, ultimately enhancing their quality of life throughout their remaining survival time. This was also demonstrated well in our study. Although from our series, the preoperative mean ACCI was high (9.29 ± 2.32), the patients still benefited from the surgery by having a better quality of life, and the complication rates were also comparable with previous studies, as previously mentioned.

Several limitations exist in our studies. With the nature of the retrospective study, it will unavoidably be subject to bias. In the future, a control group, such as open surgery or other MISS techniques, to compare with the ESS technique will be very helpful in demonstrating its efficacy in these patients. Endoscopic spine surgery is a relatively new technique, mainly when used to treat spinal metastases patients. Therefore, various factors regarding differences in practice, equipment settings, or learning curves between surgeons could not be fully controlled and might affect the overall results. Moreover, with the complexity of the procedure, it is possible that we may not cover some patients with multiple levels of involvement of spinal metastases that need to be decompressed, and this could lead to selective bias. Lastly, with the nature of the oncologic study, the poor prognosis of these patients could impact our study’s drop-out rate. However, from our research, the overall mean survival time was 9.15 months which is similar to the spinal metastases studies from previous literature.

**CONCLUSION**

As a result of the most extensive number of cases to date from the collaboration of 12 healthcare centers in 8 countries world-
wide, endoscopic spinal surgery is a valid option in the palliative treatment of spinal metastases. It can achieve the same goal of decompression while providing comparable to excellent outcomes to the other MISS technique. The enhanced recovery time could also allow patients to go on other cancer-related treatments more rapidly.

NOTES

Supplementary Material: Supplementary Tables 1 and 2 can be found via https://doi.org/10.14245/ns.2346274.137.

Conflict of Interest: The corresponding author (JSK) is a consultant of Richard Wolf, GmbH, and Elliquence, LLC. The other authors have no conflicts of interest to declare.

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Role of Endoscopic Spine Surgery in Spinal Metastases

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Supplementary Table 1. Summary of surgical-related complications and its detail

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Time occurred after surgery</th>
<th>Treatment given?</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of complications (%)</td>
<td>4 (13.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection/dehiscence</td>
<td>1</td>
<td>1 Week</td>
<td>Yes</td>
<td>Regular wound dressing and empirical oral antibiotics</td>
</tr>
<tr>
<td>Postoperative hematoma</td>
<td>1</td>
<td>2 Weeks</td>
<td>Yes</td>
<td>Revision surgery for exploration and hematoma removal</td>
</tr>
<tr>
<td>Neurological progression</td>
<td>1</td>
<td>Immediate</td>
<td>Yes</td>
<td>Revision surgery for exploration and wide decompression</td>
</tr>
<tr>
<td>Cerebrospinal fluid leakage</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Instrumentation Failure</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Local Tumor Recurrence</td>
<td>1</td>
<td>4 Months</td>
<td>Yes</td>
<td>Percutaneous vertebroplasty</td>
</tr>
<tr>
<td>Intraoperative mortality</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
## Supplementary Table 2. Summary of the previous reports of endoscopic surgery in spinal metastases patients

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Sex/age (yr)</th>
<th>Primary tumor</th>
<th>Level</th>
<th>Techniques</th>
<th>Results</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joo et al., 2012</td>
<td>1</td>
<td>M/82</td>
<td>Colon</td>
<td>T11</td>
<td>Transforaminal</td>
<td>The pain disappeared immediately after surgery.</td>
<td>None</td>
</tr>
<tr>
<td>Tsai et al., 2018</td>
<td>1</td>
<td>M/80</td>
<td>Liver</td>
<td>S1</td>
<td>Interlaminar</td>
<td>VAS arm pain decreased from 8 to 2 at 3 months after the surgery</td>
<td>None</td>
</tr>
<tr>
<td>Gao et al., 2012</td>
<td>1</td>
<td>F/71</td>
<td>Colon</td>
<td>L3</td>
<td>Transforaminal (both sides)</td>
<td>Prompt and permanent pain relief until the patient died 6 months later</td>
<td>None</td>
</tr>
<tr>
<td>Senturk and Unsal, 2020</td>
<td>1</td>
<td>F/72</td>
<td>Lung</td>
<td>L3</td>
<td>Interlaminar</td>
<td>Rapid pain relief after surgery</td>
<td>NR</td>
</tr>
<tr>
<td>Henderson et al., 2020</td>
<td>2</td>
<td>F/61</td>
<td>Ovary</td>
<td>L2</td>
<td>Transforaminal</td>
<td>Complete pain relief and resolution of weakness</td>
<td>None</td>
</tr>
<tr>
<td>Henderson et al., 2020</td>
<td></td>
<td>F/75</td>
<td>Lung</td>
<td>L5</td>
<td>Transforaminal</td>
<td>Partial pain relief</td>
<td>None</td>
</tr>
<tr>
<td>Telfeian et al., 2020</td>
<td>4</td>
<td>F/16</td>
<td>Ewings-like tumor</td>
<td>T6</td>
<td>Transforaminal</td>
<td>Immediate pain relief</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F/75</td>
<td>Lung</td>
<td>L5</td>
<td>Transforaminal</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M/76</td>
<td>Prostate</td>
<td>L4</td>
<td>Transforaminal</td>
<td>Significant improvement of pain and motor recovery; remained symptom free at 1 year follow-up</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M/85</td>
<td>Prostate</td>
<td>L3</td>
<td>Transforaminal</td>
<td>Significant pain relief after surgery; remained symptom free at 1-year follow-up</td>
<td>None</td>
</tr>
<tr>
<td>Kotheeranurak et al., 2022</td>
<td>1</td>
<td>M/54</td>
<td>Liver</td>
<td>C4–5</td>
<td>Interlaminar</td>
<td>VAS arm pain decreased from 7 to 1 after the surgery</td>
<td>None</td>
</tr>
</tbody>
</table>

L, lumbar; T, thoracic; VAS, visual analogue scale; NR, not reported.
Spinal metastasis is a serious issue in spine care that can have a negative impact on a patient's quality of life by causing pain, neurological deficits, and ambulation issues. It affects approximately 20%–50% of cancer patients, with a higher prevalence in lung and breast cancer.1,2 The risk of spine metastases increases with age, time since diagnosis, and the number of comorbidities. Patients with spine metastases usually present with pain, spinal instability, and nerve function deficit, which can impact their quality of life.1,3 Spine metastases can be detected using various diagnostic methods, including computed tomography (CT), magnetic resonance imaging, bone scintigraphy, and positron emission tomography.2,3 The progression of spine metastases involves transportation from the primary tumor, arrest within the spine, and growth of cancer cells.3 Metastasis occurs more frequently in the thoracic and lumbar spine compared to the cervical spine, making the spine the third most common site for metastasis of malignant neoplasm.4 Spinal cord compression, which may affect up to 15% of individuals with metastatic neoplastic malignancies,3 can lead to myelopathy or radiculopathy, and in severe cases, debilitating and potentially fatal myelopathy. Early diagnosis and treatment are crucial in such cases.4 A modified Tomita score of 6 to 8 points indicates the need for radiation therapy or palliative surgery, and can also help predict a patient's survival and response to treatment.5

The widely accepted treatment protocol for spine metastases involves a multidisciplinary approach, including surgery, radiotherapy, bone cement, bisphosphonates, and chemotherapy. Radiotherapy is an efficient therapeutic approach for symptomatic spine metastases patients, while surgery remains the standard treatment for patients with rapidly progressive spinal cord compression or a high risk of fracture.2,6 The primary goal of surgical management is to decompress the neural elements by tumor mass, thereby improving the patient's neurological symptoms. However, in cases where the metastatic tumor compromises spinal stability, stabilization is needed.7 Open surgical procedures for spinal metastases carry a higher risk of complications, making minimally invasive procedures preferable as they can re-
lieve neural systems without compromising spinal stability. Minimally invasive surgery has shown promising outcomes, minimizing the damage to soft tissue and resulting in less blood loss.\textsuperscript{7-9} However, it is important to note that not all treatment methods are suitable for every patient, and each approach has its own advantages and limitations.\textsuperscript{4} A recent procedure, called endoscopic spine surgery, has emerged as a potential alternative. It minimizes collateral damage, blood loss, and duration of hospital stay, while being as effective as open surgery in alleviating pain and restoring neurological function.\textsuperscript{7,8,10,11} Despite being supported primarily by case reports or case series, endoscopic spine surgery remains underutilized in patients with spinal metastases.

This study\textsuperscript{12} represents the first investigation using a worldwide collaborative network of endoscopic spine surgeons, known as 'ESSSORG', comprising 12 centers across 8 countries (South Korea, Thailand, Taiwan, Mexico, Brazil, Argentina, Chile, and India). The study evaluates the effectiveness and viability of endoscopic spine surgery as a symptomatic palliative surgery for patients with symptomatic spinal metastases. In this retrospective investigation, 29 patients who underwent endoscopic spine surgery between 2012 and 2022 were included. Consistent with previous minimally invasive spine surgery methods, the study concluded that endoscopic spine surgery is a viable alternative for treating people with spinal metastases. The average age of participants in the study was approximately 60 years, and 11 of them were female with the total number of 61 decompressed levels. The technique was similar to the unportal and biportal full-endoscopic spine surgery techniques. The research reported statistically significant improvements in almost all clinical outcome measures, which sustained from 2 weeks to 6 months following the surgery. The procedure proved valuable in palliative oncologic spine surgery, aiming to enhance patients’ quality of life. Only 4 surgical-related complications were reported.

Uniportal or biportal full-endoscopic spine surgery techniques are the most rapidly increasing techniques in contemporary spine surgery.\textsuperscript{10,11,13,14} The increasing acceptance of these techniques can be attributed to improved intraoperative visualization of pathological structures, lower complication rates, shorter recovery times, reduced postoperative discomfort, better symptom management, and earlier return to daily activities. With improved patient outcomes and cost-effectiveness, these techniques are likely to become more acceptable, relevant, and popular in the coming years.\textsuperscript{3,13,15-18}

In conclusion, we agree with the authors regarding the inherent limitations of retrospective study and the potential for biases. Including patients who underwent open surgery or other minimally invasive techniques would strengthen the illustration of the efficacy of the endoscopic surgery technique. We strongly believe that endoscopic spine surgery will emerge as one of the preferred palliative surgeries for patients with spinal metastases, in the near future.

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

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https://doi.org/10.14245/ns.2346598.299

www.e-neurospine.org 621
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METTL3 Affects Spinal Cord Neuronal Apoptosis by Regulating Bcl-2 m6A Modifications After Spinal Cord Injury


Department of Orthopedics, Fujian Medical University Union Hospital, Fuzhou, China

Objective: Spinal cord injury (SCI) is a severe type of neurological trauma. N6-methyladenosine (m6A) modification is one of the most common internal modifications of RNA. The role of METTL3, the predominant methylation enzyme of m6A modification, in SCI remains unclear. This study aimed to investigate the role of methyltransferase METTL3 in SCI.

Methods: After establishing the oxygen-glucose deprivation (OGD) model of PC12 cells and rat spinal cord hemisection model, we found that the expression of METTL3 and the overall m6A modification level were significantly increased in neurons. The m6A modification was identified on B-cell lymphoma 2 (Bcl-2) messenger RNA (mRNA) by bioinformatics analysis, and m6A-RNA immunoprecipitation and RNA immunoprecipitation. In addition, METTL3 was blocked by the specific inhibitor STM2457 and gene knockdown, and then apoptosis levels were measured.

Results: In different models, we found that the expression of METTL3 and the overall m6A modification level were significantly increased in neurons. After inducing OGD, inhibition of METTL3 activity or expression increased the mRNA and protein levels of Bcl-2, inhibited neuronal apoptosis, and improved neuronal viability in the spinal cord.

Conclusion: Inhibition of METTL3 activity or expression can inhibit the apoptosis of spinal cord neurons after SCI through the m6A/Bcl-2 signaling pathway.

Keywords: m6A, METTL3, Spinal cord injury, Oxygen-glucose deprivation, Bcl-2, STM2457

INTRODUCTION

Spinal cord injury (SCI) is a common type of neurological trauma that leads to motor and sensory deficits below the injured segment. Severe SCI can even cause death or physical, emotional, and economic consequences for the patient, the family, and society.1,2 SCI can be traumatic or nontraumatic.3 Traumatic SCI is caused by direct mechanical injuries such as contusion and compression, while infection and impaired circulation are the etiologies of nontraumatic SCI.4,5 The local edema, ischemia, and hypoxia caused by the injury in the spinal cord and surrounding tissues, are the main causes of neuronal apoptosis and irreversible spinal cord dysfunction.6,7 Therefore, it is crucial to hinder the progression of SCI to neuronal apoptosis.

Recently, scientists have found that RNA modifications can be an important target for treating cancer. Particularly, they unfolded that changes in N6-methyladenosine (m6A) modification levels can modulate cancer progression.8,9 m6A modifications are highly enriched on RNA, especially near the stop codon region. They are catalyzed by methyltransferase and removed by demethylase. Reader proteins recognize the m6A methylation site of RNA.10-12 m6A modifications have important roles in RNA stability and processing in both physiological and pathological statuses such as immune regulation and cancer.13,14 m6A
methyltransferases mainly consist of METTL3 and METTL14 heterodimers and bind to other regulatory factors such as Wilms’ tumor-associated protein (WTAP) to form the methyltransferase complex. In most cases, METTL3 is an oncogene that promotes the development and progression of several types of cancer. For example, a study by Lin et al. found that METTL3 knockdown in human gastric cancer cell lines, AGS and MKN45, activated apoptosis. Sang et al. showed that METTL3 can promote the development of acute myeloid leukemia through the mdm2/p53 signaling pathway. METTL3 plays a major role in neuronal development, and also in the proliferation and differentiation of stem cells. Wang et al. found that METTL3 can control messenger RNA (mRNA) stability and splicing of cerebellar development-related genes. Chen et al. found that METTL3 deletion inhibited neuronal development and shifted adult neural stem cells differentiation toward neuroglia. METTL3 deletion also affected the morphological maturation of newborn neurons in the adult brain. However, there are fewer studies on the role of METTL3 on neuronal apoptosis in SCI. It has been previously reported that Bcl-2, a target gene of METTL3, regulates proliferation and inhibits apoptosis in breast cancer cells. In addition, Zhang et al. indicated that METTL3 increased the expression of Bcl-2 through m6A modification, thereby enhancing the viability and migration of non-small cell lung cancer cells. As a major antiapoptotic protein, Bcl-2 is a crucial factor affecting neuronal apoptosis after injury. Based on these findings, Bcl-2 may be a key molecule in inhibiting neuronal apoptosis after SCI. However, it is not clear whether METTL3 can mediate m6A methylation of Bcl-2 in SCI. Therefore, we measured the relationship between m6A, METTL3, and Bcl-2 in SCI models to explore the mechanisms by which METTL3 participates in neuronal apoptosis after SCI. Our findings can provide new insights for treating SCI.

**MATERIALS AND METHODS**

1. **Cell Culture, Differentiation, and Establishment of OGD Model**

Rat adrenal pheochromocytoma cell line (PC12 cells) was purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). PC12 cell line belongs to a class of neurons that have been widely used in in vitro studies of SCI. PC12 cells were cultured in Roswell Park Memorial Institute 1640 medium (RPMI; Gibco, Carlsbad, CA, USA) containing 10% horse serum (Gibco, New Zealand origin), 5% fetal bovine serum (FBS; Gibco, Brazil origin), and 1% penicillin/streptomycin (P/S; Gibco) in a complete culture incubator with CO₂, 37°C temperature, and 5% humidity. PC12 cells were inoculated on 6-cm dishes coated with poly-L-lysine and cultured for 24 hours. Cell differentiation was promoted with RPMI 1640 medium containing 10% FBS, 50-ng/mL nerve growth factor (NGF) (Sangon Biotech, Shanghai, China), and 1% P/S. The culture was changed every 2 days and oxygen-glucose deprivation (OGD) was induced for day 5. PC12 cells differentiated by NGF were incubated with serum-free Hanks’ balanced salt solution (Gibco) in 1% O₂, 5% CO₂, and 95% N₂ to establish an OGD model and induce ischemia, early cell injury, and apoptosis. 

2. **Cell Treatment and Establishment of Stable Cell Lines**

OGD model was established using a novel METTL3 inhibitor, STM2457 (HY-134836, MedChemExpress, Monmouth Junction, NJ, USA) in RPMI 1640 medium containing 10% FBS, 50-ng/mL NGF, and 1% P/S in PC12 cells for 24 hours. After METTL3 inhibition, incubation continued for 12 hours under glucose-free hypoxic conditions. Stable cell lines were constructed with a lentiviral system. The plasmid used to construct the stable knockout cell lines was based on short hairpin (sh)RNA-METTL3. To construct the Lent-METTL3 shRNA vector, METTL3 shRNA oligonucleotides were ligated to the LV2N (U6/Puro) vector. PC12 cells were infected with lenti-METTL3 shRNA in RPMI 1640 complete medium containing 5 μg/mL of polybrene (Gene-Pharma, Shanghai, China) for 24 hours and then screened with 4 μg/mL of puromycin for ≥ 5 days. PC12 cells were collected for reverse transcription quantitative polymerase chain reaction (RT-qPCR) and immunoblotting to detect METTL3 knockdown efficiency. The target sequence of METTL3 shRNA was as follows: shMETTL3, GCTACCGTATGGGACGTTAAC.

3. **Animal Model**

Forty male Sprague-Dawley rats with 8 weeks of age and 200 ± 20-g body weight were purchased from Fujian Medical University Experimental Animal Center, China. The rats were kept in a temperature-controlled room (22°C–24°C), with 45%–55% humidity and 12-hour light-dark cycles. They had free access to autoclaved food and water. Animal care and experimental procedures were approved by the Animal Ethics Committee of Fujian Medical University (No. IACUC FJMU 2022–0473) and were performed according to the National Institute of Health Guide for the Care and Use of Laboratory Animals. Rats were
anesthetized with intraperitoneal injection of 1% sodium pentobarbital (20 mg/kg). For constructing a rat spinal cord hemisection model, the spinal colon was marked on the T9 spinous process and the skin was incised until exposing the T9–10 spinous process. The spinal cord was completely exposed by biting the vertebral plate with biting forceps. The spinal cord was cut on one side with ophthalmic scissors centered on the central canal of the spinal cord. The rats were expected to show a transient lower limb retraction response, indicating the successful establishment of the model. In the sham-operated group, the spinal cord was only exposed.39 The wound was sutured, and penicillin 8 (U/kg/day for 3 days) was given intraperitoneally to prevent infection.

4. Assessment of Locomotor Capacity

The locomotor function of rats with SCI was assessed using the Basso, Beattie, and Bresnanah (BBB) locomotor rating scale, with scores ranging from 0 to 21. A score of 0 represented no significant movement of the hind limb, and a score of 21 represented full movement. The rats were evaluated on days 0, 1, 3, 7, and 14, postoperatively. The rats moved in the field for 5 minutes, and 2 blinded investigators assessed each rat. The hind limb movement score was recorded, and the mean value was obtained.40

In the inclined plane test (IPT), the rats were placed on a smooth inclined plane. The slope of the plane started from the horizontal position (0°) and increased by 5° each time. The maximum slope at which the rat remained on the plane for 10 seconds was recorded. The measurement was repeated 5 times for each rat and the mean value was calculated.41

5. Quantitative Real-Time PCR

Total cellular and tissue RNA was extracted using Trizol (15596018, Invitrogen, Thermo Fisher Science, Waltham, MA, USA). Then, 1 μg of RNA was reverse transcribed using a 5X All-In-One RT MasterMix (G490, Applied Biological Materials, Vancouver, Canada) with reaction conditions of 10 minutes at 155°C, 15 minutes at 37°C, and 5 minutes at 85°C for 5 minutes. The expression levels of mRNAs were determined using the PrimerTastic software. Total protein was extracted and protein concentration was quantified using a BCA assay kit (Boster Biotech, Wuhan, China). The proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to a polyvinylidene difluoride membrane. The membrane was blocked with 5% skim milk powder for 3 hours at room temperature, and incubated with the following primary antibodies: METTL3 (ab195352, 1:1,000, Abcam, Cambridge, England), Bcl-2 (ab196495, 1:1,000, Abcam), BAx (#14796, 1:1,000, Cell Signaling Technology, Danvers, MA, USA), cleaved-caspase3 (#9664, 1:1,000, Cell Signal Technology), caspase3 (#9662, 1:1,000, Cell Signal Technology), and β-actin (AF0003, 1:1,000, Beyotime). The membrane was incubated with primary antibodies for 15 hours at 4°C and then incubated with horseradish peroxidase-labeled secondary antibodies (A0208, A0216, 1:5,000, Beyotime) for 3 hours at room temperature. The protein bands were detected using chemiluminescence reagents (Beyotime). Quantification was performed using ImageJ software.

6. Quantification of m6A RNA Methylation Assay

Total RNA was extracted from tissues and cells using the EpiQuik method. The overall level of m6A in RNA was detected by EpiQuik m6A RNA Methylation Quantification Kit (P-9005, Colorimetric, Epigentek, Farmingdale, NY, USA). Briefly, 200 ng of RNA was added to each well. Thereafter, capture and detection antibodies were separately added. Detection was performed at 450 nm and the relative m6A levels were calculated for each sample.

7. Western Blotting

Cells and tissues were lysed with RIPA lysis buffer (Beyotime, Shanghai, China) containing protease inhibitors. Total protein was extracted and protein concentration was quantified using a BCA assay kit (Boster Biotech, Wuhan, China). The proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to a polyvinylidene difluoride membrane. The membrane was blocked with 5% skim milk powder for 3 hours at room temperature, and incubated with the following primary antibodies: METTL3 (ab195352, 1:1,000, Abcam, Cambridge, England), Bcl-2 (ab196495, 1:1,000, Abcam), BAx (#14796, 1:1,000, Cell Signaling Technology, Danvers, MA, USA), cleaved-caspase3 (#9664, 1:1,000, Cell Signal Technology), caspase3 (#9662, 1:1,000, Cell Signal Technology), and β-actin (AF0003, 1:1,000, Beyotime). The membrane was incubated with primary antibodies for 15 hours at 4°C and then incubated with horseradish peroxidase-labeled secondary antibodies (A0208, A0216, 1:5,000, Beyotime) for 3 hours at room temperature. The protein bands were detected using chemiluminescence reagents (Beyotime). Quantification was performed using ImageJ software.

8. Bioinformatics Analysis

METTL3 expression was analyzed using data from the control and SCI 3-, 7-, and 14-day groups from the GSE45006 dataset (https://www.ncbi.nlm.nih.gov/). m6A modified motif distribution and secondary structure of Bcl-2 mRNA were analyzed using the SRAMP database (http://www.cuilab.cn/sramp). RMBase v2.0 (https://rna.sysu.edu.cn/rmbase/index.php) was used to identify METTL3 binding to its target. The main m6A motifs of METTL3 after binding to the target genes were identified. The binding region of Bcl-2 mRNA to METTL3 was pre-
and analyzed by Flow Jo software (BD, Ashland, OR, USA).

13. Statistical Analysis
All data were analyzed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Data are presented as mean ± standard deviation in this article. Dataset was assessed for normal distribution and homoscedasticity. Comparisons between the 2 groups were performed by t-test, and comparisons between more than 2 groups were performed by 1-way analysis of variance and Tukey test. A p-value of < 0.05 was considered statistically significant. Data from at least 3 independent experiments were collected for each group.

RESULTS

1. OGD Damage Can Increase METTL3 Expression and m6A Modification Levels
As the most prevalent methylation modification on messenger RNA and noncoding RNAs, m6A is involved in RNA stabilization, degradation, and processing, thereby regulating gene expression. Previous studies found that silencing METTL3 reduced m6A methylation levels in OGD/R-induced LNC-D63785 and decreased neuronal apoptosis. However, the role of METTL3 in SCI has not been fully elucidated. Therefore, we aimed to investigate whether METTL3 can influence the outcome of SCI by regulating m6A. We first constructed an OGD model using PC12 cell line and measured METTL3 transcription levels and overall m6A modification levels at different time points of OGD (3, 6, and 12 hours). The results showed that the transcription level of METTL3 and the overall m6A modification level gradually increased after inducing OGD (Fig. 1A, B). Western blotting also indicated the same results. RT-qPCR was performed to detect the enrichment level of Bcl-2 RNA.

2. SCI Increases METTL3 Expression and m6A Modification in Rats
Recent studies have shown that SCI can change m6A methylation in rats, which is closely related to its prognosis. We measured METTL3 expression and overall m6A modification level in a rat model of spinal cord right hemisection to further explore the role of METTL3 in SCI. First, we assessed rat movement after SCI using the BBB score and the IPT. After 3, 7, and 14 days...
of surgery, the BBB score and tilt angle gradually increased, and the mobility of rats gradually recovered from the 3rd day. After 14 days, the right lower limb regained most of its mobility, but all indicators were at a lower level compared with the sham group (Fig. 2A, B). Using the GSE45006 dataset in the National Center for Biotechnology Information database, we selected the

Fig. 1. Changes in METTL3 expression and m6A modification in PC12 cells after OGD. (A) Reverse transcription quantitative polymerase chain reaction detected the transcript levels of METTL3 at different time points. (B) m6A modification measurement by m6A colorimetric assay at different time points after OGD. (C) Western blotting analysis for METTL3 expression at time points after OGD. m6A, N6-methyladenosine; OGD, oxygen-glucose deprivation. The significance levels are shown as follows: ns, not significant; versus 0-hour group: *p < 0.05, **p < 0.01, ***p < 0.001.

Fig. 2. Changes in METTL3 expression and m6A modification after spinal cord hemisection in rats. (A) BBB locomotor rating scale to assess hindlimb motor function. (B) Inclined plane test to observe the changes in tilt angle at different time points after spinal cord injury (SCI). (C) Analysis of METTL3 expression at different time points using the GSE45006 dataset. (D) Reverse transcription quantitative polymerase chain reaction to detect changes at different time points by m6A colorimetry. (F) Western blotting for measuring the protein expression of METTL3. BBB, Basso, Beattie, and Bresnahan; m6A, N6-methyladenosine. The significance levels are shown as follows: ns, not significant; versus sham group: *p < 0.05, **p < 0.01, ***p < 0.001.
METTL3 expression values of the control group and 3 other SCI samples (3, 7, and 14 days) and found that METTL3 expression level was highest on the 3rd day and then gradually decreased (Fig. 2C). The transcription levels and overall m6A modification levels of METTL3 were detected by RT-qPCR and m6A colorimetric assay at different time points (3, 7, and 14 days) after spinal cord hemisection. Similar to the overall m6A modification level, the transcription level of METTL3 was highest on the 3rd day and then gradually decreased (Fig. 2C).

**Fig. 3.** m6A modification sites and common motifs and the interaction between METTL3 with Bcl-2 mRNA. (A) The distribution of m6A modification on Bcl-2 mRNA. (B) The secondary structure of Bcl-2 mRNA. (C) Distribution of m6A modification in Bcl-2 target genes and common motifs (GGACA). (D) The binding site of METTL3 on Bcl-2 mRNA. (E) meRIP shows the presence of m6A modification of Bcl-2 mRNA. (F) RIP shows that METTL3 interacts with Bcl-2 mRNA. Bcl-2, B-cell lymphoma 2; mRNA, messenger RNA; m6A, N6-methyladenosine; meRIP, m6A-RNA immunoprecipitation; RIP, RNA immunoprecipitation; M6A-IP, N6-methyladenosine-immunoprecipitation; METTL3-IP, methyltransferases like 3-immunoprecipitation; 5’UTR, 5’-untranslated region; CDS, coding sequence; 3’UTR, 3’-untranslated region. The significance levels are shown as follows: versus IgG group: ***p < 0.001.
day, then gradually decreased (Fig. 2D, E). Western blotting showed that the protein level of METTL3 was also highest on the 3 days and gradually decreased afterward (Fig. 2F). The results demonstrated that decreased METTL3 expression was inversely associated with the recovery of spinal cord function in rats. Therefore, METTL3 expression is closely related to the overall m6A modification level, which reflects the severity of SCI.

3. Predicting the m6A Site of Bcl-2 mRNA and Its Interaction With METTL3

Previously, it has been shown that Bcl-2 mRNA has m6A modifications, which can influence its expression with METTL3. Therefore, we used the SRAMP database to predict the possible presence of m6A methylation modifications in Bcl-2 mRNA and the most likely secondary structure of mRNA (Fig. 3A, B). It has been shown that after completing m6A modification in the nucleus, METTL3 can remain bound to the transcript. After translocation into the cytoplasm, METTL3 can bind to eIF3, which may cause a link between METTL3 at the 3’ UTR of the mRNA and the 5’ mRNA cap to create an mRNA loop. The mRNA loop can enable the ribosome on the termination codon to reload into the transcript and directly activate translation.

Understanding this secondary structure can help us to explore other functions of METTL3. We also used the RMBase v2.0 database to predict the m6A motif of Bcl-2 mRNA in the GSE2460366 dataset and found that the m6A modification was mainly enriched between the coding sequence and 3’-untranslated region, mainly near the termination codon (Fig. 3C). Meanwhile, the interaction of Bcl-2 mRNA with METTL3 was analyzed using the catRAPID database. The results showed a strong binding between the 300th and 600th nucleotides (Fig. 3D). This was different from the m6A-rich position, suggesting that METTL3 itself may have 2 structural domains: a catalytic domain, mainly responsible for m6A modifications, and a binding domain, to anchor on RNA and facilitate m6A modifications. Previous studies have shown that METTL3 consists of a zinc finger domain (ZFD) and a methyltransferase domain, and ZFD is critical for target recognition. However, it has been reported that METTL3 and METTL14 can form a complex and that METTL14 mainly helps METTL3 bind to RNA. Therefore, the binding domain of METTL3 may assist the catalytic domain to complete m6A modification in specific regions by anchoring on specific sites. On the other hand, we used RIP and meRIP to verify the relationship between Bcl-2 mRNA and m6A modification. The results of meRIP showed that the m6A-immuno-precipitation group had higher enrichment levels of Bcl-2 mRNA compared with the IgG group. In contrast, the METTL3-IP group possessed a higher Bcl-2 mRNA enrichment level than the IgG group (Fig. 3E, F). In summary, METTL3 interacts with m6A modification on Bcl-2 mRNA, indicating that the m6A modification on Bcl-2 mRNA is catalyzed by METTL3.

4. STM2457 Inhibits METTL3 Activity, Alters Bcl-2 Expression, and Regulates Neuronal Apoptosis

STM2457 has excellent inhibitory activity against METTL3. We used the CCK8 method and m6A colorimetric assay to detect the cellular activity and overall m6A modification degree with different drug concentrations (5, 10, 15, 20, 25 μM). The results showed that the cell activity was not affected between 0–25 μM. The overall m6A modification degree gradually decreased with increasing concentrations between 0 μM and 10 μM, while remaining constant between 10 μM and 25 μM (Fig. 4A, B). Therefore, we chose 10 μM as the effective inhibitory concentration for the OGD model. As the major antiapoptotic protein, Bcl-2 can stop programmed cell death. Therefore, we used RT-qPCR to detect the transcription levels of Bcl-2 after OGD. There was no difference between the control group and the control+STM2457 group, indicating that the expression level of Bcl-2 mRNA was not affected by 10 μM of STM2457, while it decreased in the OGD group. Compared with the OGD group, the expression level of Bcl-2 mRNA significantly increased in the OGD+STM2457 group, indicating the close link between METTL3 function and Bcl-2 transcription after OGD (Fig. 4C). Then, we used western blotting to detect the expression level of apoptosis-related proteins. The results showed that there was no significant difference between the control group and the control+STM2457 group, but Bax/Bcl-2 and cleaved-caspase3/caspase3 ratios were higher in the OGD group compared with the control group. Furthermore, these ratios were significantly lower in the OGD+STM2457 group compared with the OGD group (Fig. 4D). Next, TUNEL staining was used to measure the apoptosis rate in each group. The number of TUNEL-positive cells significantly increased in the OGD group compared with the control group. The number of TUNEL-positive cells was significantly lower in the OGD+STM2457 group compared with the OGD group (Fig. 4E). We also performed Annexin V-FITC/PI flow cytometry to measure apoptosis rate. We found that the total apoptosis rate was significantly higher in the OGD group compared with the control group. In addition, Annexin V-FITC/PI flow cytometry revealed that the apoptosis rate was significantly lower in the OGD+STM2457 group than in the control group.
Fig. 4. STM2457 regulates neuronal apoptosis by inhibiting METTL3 activity. (A) Cellular activity was not affected at drug concentrations of 0–25 μM. (B) STM2457 decreased the overall m6A modification level. (C) STM2457 enhanced Bcl-2 transcription under OGD. (D) Western blotting of Bax, Bcl-2, cleaved-caspase3, and caspase3 in the presence of STM2457. (E) TUNEL assay of PC12 cells for assessing apoptosis. (F) Flow cytometry for PC12 cell apoptosis. m6A, N6-methyladenosine; Bcl-2, B-cell lymphoma 2; mRNA, messenger RNA; OGD, oxygen-glucose deprivation; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; V-FITC, V-fluorescein isothiocyanate. The significance levels are shown as follows: ns, not significant; versus control group: *p < 0.05, **p < 0.01, ***p < 0.001; versus OGD+STM2457 group: #p < 0.05, ##p < 0.01, ###p < 0.001.
METTL3 Affects Spinal Cord Neuronal Apoptosis

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Fig. 5. METTL3 Knockdown promotes survival and inhibits apoptosis of PC12 cells after OGD. (A) Reverse transcription quantitative polymerase chain reaction measuring METTL3 transcription after its knockdown. (B) m6A colorimetric assay measuring m6A modification after METTL3 knockdown. (C) Reduced protein expression of METTL3 measured by western blotting after METTL3 knockdown. (D) METTL3 Knockdown increased Bcl-2 transcription under OGD. (E) Western blotting of apoptosis-related protein after METTL3 knockdown. (F) CCK8 assay for measuring cell activity. (G) TUNEL assay for assessing apoptosis. (H) Flow cytometry assay of PC12 cells for apoptosis. WT, wild type; NC, negative control; sh-METTTL3, short hairpin METTTL3; m6A, N6-methyladenosine; OGD, oxygen-glucose deprivation; Bcl-2, B-cell lymphoma 2; mRNA, messenger RNA; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; V-FITC, V-fluorescein isothiocyanate. The significance levels are shown as follows: ns, not significant; versus control group: *p < 0.05, **p < 0.01, ***p < 0.001.
OGD group (Fig. 4F). This shows that METTL3 inhibition can enhance Bcl-2 transcription, increase its protein expression, and inhibit neuronal apoptosis.

5. METTL3 Knockdown Increases Bcl-2 Expression and Attenuates OGD-Induced Neuronal Apoptosis

We knocked down METTL3 by lentiviral infection of PC12 cells to investigate whether METTL3 inhibition can inhibit apoptosis by upregulating Bcl-2. After 24 hours, we detected the changes in METTL3 expression level and overall m6A modification. RT-qPCR, western blotting, and m6A colorimetric analysis demonstrated that the mRNA and protein levels of METTL3 and overall m6A modification were significantly lower in the sh-METTL3 group compared with the wild type (WT) and negative control (NC) groups (Fig. 5A-C). RT-qPCR was used to detect the transcription level of Bcl-2 after OGD injury. There was no significant difference between the OGD+WT group and the OGD+NC group, while the transcription level of the OGD+sh-METTL3 group increased (Fig. 5D). Next, we used western blotting to detect the expression levels of apoptosis-related proteins. Compared with other groups, the Bax/Bcl-2 and cleaved-caspase3/caspase3 ratios decreased after METTL3 knockdown (Fig. 5E). Meanwhile, cell activity was detected using the CCK8 method. After OGD, the cell activity was significantly higher in the OGD+sh-METTL3 group than in the other groups (Fig. 5F). The apoptosis rate was detected using TUNEL staining, and it was observed that the number of TUNEL-positive cells significantly reduced in the OGD+sh-METTL3 group and was lower than the number of TUNEL-positive cells in the OGD+WT and OGD+NC groups (Fig. 5G). The apoptosis rate was also measured by Annexin V-FITC/PI flow cytometry. We found that the total apoptosis rate was significantly higher in the OGD+WT group and OGD+NC groups and there was not a significant difference between them. The total apoptosis rate was significantly lower in the OGD+sh-METTL3 group than in other groups (Fig. 5H). These results suggest that METTL3 knockdown can decrease m6A levels, increase the mRNA and protein levels of Bcl-2, and inhibit neuronal apoptosis after OGD.

DISCUSSION

SCI is associated with increased social costs and a reduced life expectancy.54,55 SCI can be primary and secondary.56 Recently, accumulating evidence has shown that secondary neuronal injury plays an important but preventable role in the late stages of SCI.57,58 m6A modification, the most common mRNA modification, and its recognized methylation enzyme, METTL3, play critical roles in various diseases.59 m6A modification and METTL3 are essential for neuronal physiological functions such as learning and memory.60,61 METTL3 and m6A levels are up-regulated in lung and breast cancer cells.30,31 However, the role of METTL3 in SCI has not been entirely elucidated.

In the present study, the overall m6A level and METTL3 expression levels gradually increased in PC12 cells after OGD. However, in the rat spinal cord hemisection model, the overall m6A modification levels and METTL3 expression levels reached the maximum on the third day of injury, indicating that SCI is associated with overall m6A modification levels and METTL3 expression levels. Apoptosis induced by SCI exacerbates the extent of injury due to neuronal loss and dysfunction.62 In previous studies, altered m6A modification and increased METTL3 expression have been observed in SCI, and gene transcription levels increased by hypomethylation.63 In a mouse model of chronic inflammatory pain, the levels of m6A modifications and METTL3 significantly increased in the spinal cord.64 These studies suggest that METTL3 may play an important role in SCI. Based on changes in METTL3 and m6A in the spinal cord, we hypothesized that METTL3 inhibition can regulate m6A modifications and modulate SCI.

Bcl-2 regulates apoptosis by controlling intracellular signaling pathways.52 By binding to Bax, Bcl-2 reduces Bax-mediated caspase3 activation and apoptosis; Therefore, Bcl-2 downregulation can enhance apoptosis.64,65 METTL3 has been reported to catalyze m6A modifications of Bcl-2 in chondrocytes.45 Bcl-2 has also been indicated as a target gene of METTL3 in lung and breast cancers.30,31 Similarly, Bcl-2 inhibits neuronal apoptosis.32,66,67 In our study, bioinformatics revealed the m6A methylation modification sites and common motifs of Bcl-2 mRNA. It has been shown that METTL3 can bind to transcripts in the cytoplasm to form a loop structure, resulting in repeated translation of the protein.46 Therefore, we suggested that the secondary structure of RNA may have an impact on METTL3 function; therefore, we predicted the secondary structure of Bcl-2 mRNA using the SRAMP database. METTL3 has 580 amino acids and consists of a ZFD domain, which ZFD plays a role in RNA recognition, and a methyltransferase domain.18,47 Therefore, we analyzed the interaction between Bcl-2 mRNA and METTL3 using the catRAPID database. We found that there are interactions between Bcl-2 mRNA and METTL3 and the binding region of METTL3 is not in the same site as its catalytic region. We used meRIP to confirm the presence of m6A modification on Bcl-2 mRNA, and RIP analysis to show that Bcl-2 mRNA is a downstream target.
gene of METTL3. There was a significant difference in the enrichment level of Bcl-2 mRNA between the 2 experiments, indicating that Bcl-2 mRNA can be formed by METTL3, but the possible role of other methyltransferases cannot be excluded. Therefore, we hypothesize that the m6A modification of Bcl-2 in SCI is mediated by METTL3 and can affect neuronal apoptosis.

It has been reported in the literature that METTL14, another methylation enzyme, exacerbates the severity of SCI, and m6A modification reduces the expression of genes that inhibit neuronal apoptosis.68,69 Han et al.70 revealed a higher m6A methylation of many genes and METTL3 upregulation in Alzheimer disease. Therefore, we further explored the role of METTL3 in neuronal apoptosis in SCI. STM2457, a novel METTL3-specific inhibitor, can bind to the SAM binding site and effectively inhibit METTL3.71 We measured the inhibitory effect of STM2457 on METTL3 in PC12 cells. *In vitro* experiments revealed that the inhibitory effect of STM2457 on METTL3 started from 5 μM, and stabilized after 10 μM, but the cellular activity was fixed between 0 μM and 25 μM. Therefore, we set the effective inhibitory concentration to 10 μM. The results showed that the mRNA and protein levels of Bcl-2 significantly increased in the presence of STM2457, while the expression of other apoptosis-related proteins showed different degrees of decrease. After adding STM2457, the TUNEL-positive PC12 cells were reduced, the neuronal survival rate significantly increased, and the total apoptosis rate was significantly lower in the OGD+STM2457 group than in the OGD group on Annexin V-FITC/PI flow cytometry. These results suggest that STM2457 has an important role in inhibiting PC12 cells apoptosis. Previous studies have also shown that METTL3, m6A methylation, and neuronal apoptosis are closely related.72,73 Xu et al.43 found that silencing METTL3 can decrease the m6A methylation level of LNC-D63785, upregulate its expression, and reduce neuronal apoptosis. Therefore, we constructed stable knockdown METTL3 cell lines to investigate the effect of METTL3 on Bcl-2 and PC12 cells apoptosis. After METTL3 knockdown, a 12-hour OGD model was established, and it was found that the transcription and protein expression of Bcl-2 increased in the OGD+sh-METTL3 group, while other apoptosis-related proteins were downregulated. In addition, lower TUNEL-positive cells and apoptosis rates were observed in the OGD+sh-METTL3 group.

In summary, we demonstrated that inhibition of METTL3 activity and expression reduces OGD-induced apoptosis of PC12 cells. Specifically, METTL3 modulates Bcl-2 transcription in an m6A-dependent manner, thereby altering the protein level of Bcl-2, and neuronal apoptosis (Fig. 6). The METTL3/m6A/Bcl-2 axis is a new target for treating SCI. This study did not validate the downstream targets of METTL3 and other possible pathways in *vivo*, and there are some limitations. Based on the results of this study, we continue our in-depth analysis in our future studies.

### NOTES

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

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**Fig. 6.** METTL3 forms an m6A modification near the 3′-untranslated region of the Bcl-2 gene, thereby inhibiting Bcl-2 expression and promoting neuronal apoptosis after OGD. Therefore, METTL3 inhibition can upregulate Bcl-2 expression and inhibit neuronal apoptosis. The METTL3/m6A/Bcl-2 axis may provide new insights for targeted therapy in spinal cord injury. m6A, N6-methyladenosine; Bcl-2, B-cell lymphoma 2; mRNA, messenger RNA; OGD, oxygen-glucose deprivation.
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REFERENCES
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METTL3 Affects Spinal Cord Neuronal Apoptosis

Guo S, et al.

Original Article

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Moderate to Severe Multifidus Fatty Atrophy is the Risk Factor for Recurrence After Microdiscectomy of Lumbar Disc Herniation

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Objective: We attempted to investigate the potential risk factors of recurrent lumbar disc herniation (rLDH) after tubular microdiscectomy.

Methods: We retrospectively analyzed the data of patients who underwent tubular microdiscectomy. The clinical and radiological factors were compared between the patients with and without rLDH.

Results: This study included 350 patients with lumbar disc herniation (LDH) who underwent tubular microdiscectomy. The overall recurrence rate was 5.7% (20 of 350). The visual analogue scale (VAS) score and Oswestry Disability Index (ODI) at the final follow-up significantly improved compared with those preoperatively. There was no significant difference in the preoperative VAS score and ODI between the rLDH and non-rLDH groups, while the leg pain VAS score and ODI of the rLDH group were significantly higher than those of the non-rLDH group at final follow-up. This suggested that rLDH patients had a worse prognosis than non-rLDH patients even after reoperation. There were no significant differences in sex, age, body mass index, diabetes, current smoking and drinking, disc height index, sagittal range of motion, facet orientation, facet tropism, Pfirrmann grade, Modic changes, interdisc kyphosis, and large LDH between the 2 groups. Univariate logistic regression analysis revealed that rLDH was associated with hypertension, multilevel microdiscectomy, and moderate-severe multifidus fatty atrophy (MFA). A multivariate logistic regression analysis indicated that MFA was the sole and strongest risk factor for rLDH after tubular microdiscectomy.

Conclusion: Moderate-severe MFA was a risk factor for rLDH after tubular microdiscectomy, which can serve as an important reference for surgeons in formulating surgical strategies and the assessment of prognosis.

Keywords: Lumbar disc herniation, Recurrence, Risk factor, Microdiscectomy, Multifidus fatty atrophy, Logistic regression

INTRODUCTION

Lumbar disc herniation (LDH) is a very common lumbar degenerative disease and imposes a significant burden on patients worldwide.1 The lifetime incidence of LDH is estimated to be between 13% and 40%, with major socioeconomic implications.2 LDH is rare before the age of 20, and its incidence reaches a peak around the age of 50 and then declines gradually.3 The incidence of LDH did not differ between the sexes.2 However, different professions or sports may influence incidence of LDH. For example, the machine operators and carpenters are more likely to suffer from LDH than sedentary office workers.4
ing postures, such as bending or twisting the torso for a long time, or frequent exposure to strenuous physical activity can increase the incidence of LDH. Additionally, except jogging and walking, overall physical exercise and most physical activities will not increase the incidence rate of LDH.

Conservative treatment is usually recommended at the onset of disease. Surgical treatment such as microdiscectomy is usually recommended when conservative treatment fails. However, its complications, especially recurrent LDH (rLDH), have been reported to occur in 5%–15% of patients after primary surgery. Patients undergoing reoperation tend to have longer operative times or hospital stays, more difficult procedures, and a poorer prognosis or quality of life than do patients undergoing primary surgery. Therefore, it is necessary to identify patients with LDH at risk for surgical revision prior to the initial surgery.

Current clinical studies have identified some possible related or risk factors for the recurrence of LDH. In terms of clinical factors, studies have found that age, obesity, smoking, and diabetes may be risk factors for rLDH. In terms of radiological factors, it was found that the degree of disc degeneration, Modic changes, disc height, facet direction, and sagittal range of motion (sROM) are related to rLDH. Nevertheless, the current reality is that whether these clinical or radiological variables do affect rLDH remains controversial. For example, the sex of female was found to be a risk factor for rLDH, while some studies have found the opposite outcomes. There are also different conclusions about the relationship between age and rLDH. Furthermore, in addition to some variables that have been extensively studied previously, we hypothesize that some common but not studied variables such as interdisc kyphosis, large LDH, and multifidus fatty atrophy (MFA) may be related to rLDH in this study.

rLDH is a complex process involving biomechanics and social behavior. A single consideration may be inadequate for this complex process. Thus, a comprehensive analysis of clinical and radiological variables for rLDH was developed for better surgical planning and assessment of the prognosis in this study.

MATERIALS AND METHODS

We retrospectively analyzed the data from patients who underwent microdiscectomy in a single spine center by one qualified surgeon from December 2016 to December 2020. This study was approved by the Ethics Committee of Xinqiao Hospital of the Army Medical University (2022-499-01).

The inclusion criteria were as follows: (1) microdiscectomy for LDH and (2) follow-up duration of > 1 year. The exclusion criteria were as follows: (1) extreme lateral disc herniation or calcified disc herniation and (2) follow-up duration of < 1 year. The extreme lateral disc herniation was defined as a herniated disc located outside the intervertebral foramen.

1. Collection of Basic Information and Clinical Outcomes

We collected data on the basic information and clinical outcomes of the patients, including sex, age, body mass index (BMI), diabetes, hypertension, current smoking and drinking, and multilevel microdiscectomy (≥2 levels). Additionally, we collected the low back pain and leg pain visual analogue scale (VAS) scores and Oswestry Disability Index (ODI) scores of the patients preoperatively and at the final follow-up. All clinical data were recorded by qualified clinical follow-up staff. The follow-up methods included outpatient clinic visits and telephone interviews. For the patients who were followed up through outpatient clinic visits, we completed the ODI questionnaire face-to-face. For those who were followed up through telephone interviews, we completed the ODI questionnaire by asking them question-by-question.

In addition, the postoperative low back pain and leg pain VAS scores were evaluated. For the patients with recurrent symptoms, we re-examined their lumbar magnetic resonance imaging (MRI) scans to determine whether they had rLDH. rLDH was defined as reherniation in the same segment and the same side on repeated MRI consistent with this symptom after at least 1 month of symptom relief after surgery. In the previous studies, the pain-free interval is inconsistent, ranging from 2 weeks to 6 months. We took one month as the minimum pain-free interval after prior surgery in this study. The “recurrent symptoms” which we defined must be similar to or more serious than those before the primary surgery, especially lower limb symptoms. Mild back pain or remnant paresthesia will not be defined as a recurrence.

2. Radiological Assessment

All included patients underwent lumbar radiography, computed tomography, and MRI before surgery. The radiological variables assessed included the herniated disc Pfirrmann grade, Modic changes, disc height index (DHI), sROM, facet orientation (FO), facet tropism (FT), interdisc kyphosis, large LDH, and degree of MFA (Fig. 2C). Pfirrmann grades I, II, and III are defined as low grades and Pfirrmann grades IV and V as senior grades. Modic change is divided into 3 types based on different intervertebral signals on MRI. Type I: hypoin-
tense signal in T1-weighted imaging (T1WI) and hyperintense signal in T2-weighted imaging (T2WI). Type II: hyperintense signal in T1WI and hyperintense signal in T2WI. Type III: hypointense signal in T1WI and hypointense signal in T2WI. DHI was defined as the ratio of the disc height to the lower vertebral body height on the lumbar lateral x-ray of the herniated disc segment (Fig. 3A, B). sROM was defined as the value of the hyperextension intervertebral angle minus the hyperflexion intervertebral angle on the lumbar lateral x-ray of the herniated disc segment (Fig. 3C, D). FO was defined as the mean value of the right and left facet joint angle degrees (Fig. 1). FT was defined as the absolute value of the difference between the right and left facet joint angle degrees (Fig. 1). Large LDH was defined as the herniated disc account for over 50% of the spinal canal area on axial MRI (Fig. 2A, B). Interdisc kyphosis was defined as lordosis angle of the intervertebral space at the surgical segment in the lateral x-ray is less than 0°. If it is greater than or equal to 0°, it does not belong to interdisc kyphosis (Fig. 3E, F). MFA is divided into 4 grades based on the multifidus muscle's cross-sectional area on herniated disc level (Fig. 2D, G). That is, 0%–10% fatty infiltration (normal), 10%–30% fatty infiltration (mild), 30%–50% fatty infiltration (moderate), and more than 50% fatty infiltration (severe). All radiological factors were measured and assessed by 2 qualified radiologists blinded to the research design. All numerical results were expressed as the mean values.
of the radiological variables measured by the 2 radiologists. All radiological variables that need to be measured were completed through Surgimap software (Nemaris, New York, NY, USA). For the degree of MFA, we originally preformed the quantitative measurements of muscle fatty atrophy based on the quantification. The mean value of the measurements by the 2 radiologists was adopt. Then, we performed the qualitative analysis according to the quantitative values. These cases were classified as normal, mild, moderate, and severe MFA according to the fatty infiltration ratio.

3. Surgery

All patients underwent standardized tubular microdiscectomy according to our previously reported method performed by one qualified surgeon (HB) in a single spine center. Patients were placed in prone position after general anesthesia. After positioning of the surgical segment, an incision was made approximately 1 cm lateral to the midline on the symptomatic side of the identified surgical segment. A surgical pathway to the lumbar spine was created by inserting the sequential dilators through the multifidus. We usually implanted a tapered retractor with a diameter of 20–22 mm on the upper end and a diameter of 16–18 mm on the opposite end (Bosscom Technology, Chongqing, China) (Fig. 4A). In this procedure, we removed the inferior edge of the lower lamina and the inner edge of the inferior articular process. The overlying ligamentum flavum was then excised and the nerve root was exposed. Then, the herniated disc was exposed and removed under a microscope (Carl Zeiss, Inc., Oberkochen, Germany) (Fig. 4B). We do not destroy the disc of origin in the process of removing the herniation. The surgical philosophy is to remove a herniated disc with minimal disruption of the normal disc under a microscope (limited discectomy).

4. Statistical Methods

The Kolmogorov-Smirnov test was used to test the distribution of the data. Normally distributed data were analyzed using the t-test and nonnormally distributed data using the Wilcoxon
Mann-Whitney U-test. Initially, we compared the differences in the clinical and radiological outcomes between the non-rLDH and rLDH groups using a univariate analysis. Student t-test or the Wilcoxon Mann-Whitney test was used to examine the differences in age, BMI, DHI, sROM, FO, and FT. The chi-square or Fisher exact test was used to examine the differences in sex, diabetes, hypertension, current smoking and drinking, disc degeneration, Modic changes, multilevel microdiscectomy, MFA, interdisc kyphosis, and large LDH.

Thereafter, we performed univariate and multivariate logistic regression analyses to assess the relationship between rLDH and the independent variables with a p-value of < 0.2. The Omnibus tests of model coefficients were used to test the effectiveness of this multivariate logistic regression analysis model. The Hosmer-Lemeshow test was used to evaluate whether the model makes full use of the existing information, fits the model to the greatest extent, and explains the variation of the model. The statistical significance level was set at a p-value of < 0.05. Statistical analysis was performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). The forest plot of the multivariable analysis was drawn by the Graphpad Prism 6.0 (Graphpad Software Inc., San Diego, CA, USA).

RESULTS

1. Patient’s Demographics

A total of 506 patients were initially enrolled. Among them, 104 patients with lack of clinical or radiological data, 34 patients with calcified disc herniation, and 18 patients with extreme lateral disc herniation were excluded. Finally, 350 patients who met the inclusion criteria from December 2016 to December 2020 were included in this study. Among them, 330 patients were classified into the non-rLDH group and 20 patients (5.7%) into the rLDH group. In 20 patients with rLDH, the time from primary surgery to recurrence is 2 to 54 months (mean, 26.5 months). The follow-up time after recurrence was 6–58 months (mean, 24.2 months).

A total of 208 patients were men, and 142 were women. The mean age, BMI, and follow-up time were 48.5 ± 14.4 years, 24.5 ± 3.4 kg/m², and 37 ± 12.5 months, respectively. The mean lower back and leg VAS scores and ODI at the final follow-up significantly improved compared with those preoperatively. Among the rLDH patients, 9 patients underwent tubular microdiscectomy again, 6 patients cases underwent minimally invasive transforminal lumbar interbody fusion (Mis-TLIF), 4 patients under went TLIF, and 1 patient underwent conservative treatment. Although the preoperative VAS score and ODI in the rLDH group were not significantly different from those in the non-rLDH group, the leg VAS score (p = 0.01) and ODI (p = 0.002) at the final follow-up in the rLDH group (get additional treatment after recurrence) were significantly higher than those in the non-rLDH group. This suggested that despite reoperation in the majority of rLDH patients, they had a worse prognosis than non-rLDH patients.

2. Univariate Analysis of rLDH

The outcomes of the univariate analysis are shown in Tables 1 and 2. In terms of the clinical factors, we did not find signifi-
Table 1. Comparison of clinical variables between the 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>rLDH group (N = 20)</th>
<th>Non-rLDH group (N = 330)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td>Male</td>
<td>8 (40.0)</td>
<td>200 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (60.0)</td>
<td>130 (39.4)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54.5 ± 12.4</td>
<td>48.1 ± 14.5</td>
<td>0.054</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 3.2</td>
<td>24.5 ± 3.5</td>
<td>0.612</td>
</tr>
<tr>
<td>Follow-up time (mo)</td>
<td>48.2 ± 19.7</td>
<td>36.9 ± 15.3</td>
<td>0.020</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (10.0)</td>
<td>19 (5.8)</td>
<td>0.771</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (30.0)</td>
<td>41 (12.4)</td>
<td>0.025</td>
</tr>
<tr>
<td>Current drinking</td>
<td>1 (5.0)</td>
<td>34 (10.3)</td>
<td>0.443</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3 (15.0)</td>
<td>79 (23.3)</td>
<td>0.519</td>
</tr>
<tr>
<td>Pre ODI</td>
<td>52.2 ± 25.1</td>
<td>56.3 ± 18.6</td>
<td>0.354</td>
</tr>
<tr>
<td>Pre VAS of low back pain</td>
<td>3.4 ± 2.3</td>
<td>3.0 ± 2.7</td>
<td>0.479</td>
</tr>
<tr>
<td>Pre VAS of leg pain</td>
<td>6.1 ± 2.0</td>
<td>6.1 ± 2.2</td>
<td>0.962</td>
</tr>
<tr>
<td>Final ODI</td>
<td>18.1 ± 12.4</td>
<td>9.1 ± 12.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Final VAS of low back pain</td>
<td>1.4 ± 2.0</td>
<td>0.7 ± 1.0</td>
<td>0.198</td>
</tr>
<tr>
<td>Final VAS of leg pain</td>
<td>1.9 ± 2.2</td>
<td>0.5 ± 0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Multilevel surgery</td>
<td>5 (25.0)</td>
<td>28 (8.5)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

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

Table 2. Comparison of radiological variables between the 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>rLDH group (N = 20)</th>
<th>Non-rLDH group (N = 330)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHI</td>
<td>0.41 ± 0.08</td>
<td>0.42 ± 0.49</td>
<td>0.945</td>
</tr>
<tr>
<td>sROM</td>
<td>8.84 ± 4.54</td>
<td>8.01 ± 4.07</td>
<td>0.377</td>
</tr>
<tr>
<td>FO</td>
<td>47.0 ± 11.3</td>
<td>48.1 ± 9.4</td>
<td>0.648</td>
</tr>
<tr>
<td>FT</td>
<td>5.96 ± 5.19</td>
<td>6.49 ± 5.20</td>
<td>0.656</td>
</tr>
<tr>
<td>Pfirrmann’s grade</td>
<td></td>
<td></td>
<td>0.586</td>
</tr>
<tr>
<td>Low grade (grade I, II, III)</td>
<td>4 (20.0)</td>
<td>93 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Senior grade (grade IV, V)</td>
<td>16 (80.0)</td>
<td>236 (71.1)</td>
<td></td>
</tr>
<tr>
<td>Modic change</td>
<td>9 (45.0)</td>
<td>95 (28.8)</td>
<td>0.123</td>
</tr>
<tr>
<td>Multifidus fatty atrophy</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade (normal-mild)</td>
<td>11 (55.0)</td>
<td>267 (80.5)</td>
<td></td>
</tr>
<tr>
<td>Senior grade (moderate-severe)</td>
<td>9 (45.0)</td>
<td>63 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Interdisc kyphosis</td>
<td>2 (10.0)</td>
<td>41 (12.4)</td>
<td>0.748</td>
</tr>
<tr>
<td>With large LDH</td>
<td>2 (10.0)</td>
<td>74 (22.4)</td>
<td>0.303</td>
</tr>
</tbody>
</table>

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

Table 3. Interobserver reliability of the radiological variables

<table>
<thead>
<tr>
<th>Interobserver</th>
<th>k (95% CI)</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1 vs. reader 2</td>
<td>0.844</td>
<td>Very good</td>
</tr>
<tr>
<td>(Pfirrmann grade)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1 vs. reader 2</td>
<td>0.938</td>
<td>Very good</td>
</tr>
<tr>
<td>(Modic change)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1 vs. reader 2</td>
<td>0.925</td>
<td>Very good</td>
</tr>
<tr>
<td>(large LDH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1 vs. reader 2</td>
<td>0.819</td>
<td>Very good</td>
</tr>
<tr>
<td>(interdisc kyphosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1 vs. reader 2</td>
<td>0.846</td>
<td>Very good</td>
</tr>
<tr>
<td>(multifidus fatty atrophy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Strength of agreement: k > 0.80 (very good), 0.80 ≥ k > 0.60 (good), 0.60 ≥ k > 0.40 (moderate), 0.40 ≥ k > 0.20 (fair), k ≤ 0.20 (poor).

Table 4. Univariate logistic regression analysis of rLDH

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.075</td>
<td>0.433</td>
<td>0.172–1.089</td>
</tr>
<tr>
<td>Age</td>
<td>0.056</td>
<td>1.063</td>
<td>0.999–1.063</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.032</td>
<td>3.021</td>
<td>1.099–8.300</td>
</tr>
<tr>
<td>Multilevel surgery</td>
<td>0.021</td>
<td>3.595</td>
<td>1.216–10.626</td>
</tr>
<tr>
<td>Modic change</td>
<td>0.130</td>
<td>2.024</td>
<td>0.813–5.041</td>
</tr>
<tr>
<td>Multifidus fatty atrophy</td>
<td>0.008</td>
<td>3.468</td>
<td>1.378–8.725</td>
</tr>
</tbody>
</table>

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

3. Univariate and Multivariate Logistic Regression Analysis of rLDH

We included factors with p-values of < 0.2 (sex, age, hypertension, multilevel microdiscectomy, Modic changes, MFA) and performed univariate and multivariate logistic regression analyses (Tables 4, 5). The univariate logistic regression analysis revealed that rLDH was significantly associated with hypertension,
multilevel microdiscectomy, and moderate-severe MFA. The multivariate logistic regression analysis revealed that moderate-severe MFA was the sole and strongest risk factor for rLDH (p = 0.021; odds ratio, 3.414; 95% confidence interval [CI], 1.190–8.253). In the Omnibus tests of model coefficients, p = 0.01 indicated that this multivariate logistic regression predictive model was valid. In the Hosmer-Lemeshow test, p = 0.306 indicated that the goodness of fit of this model was good. The outcome of this model indicated that after homogenization for other factors, the recurrence probability of LDH combined with moderate-severe MFA was approximately 3.414 times that of LDH combined with normal-mild MFA.

Finally, we compared the sex, age, rates of diabetes hypertension, current smoking, and drinking between the normal-mild MFA group and the moderate-severe MFA group (Table 6). We found that the age and BMI, rates of female, diabetes, hypertension, current smoking of the moderate-severe MFA group were slightly higher than those of the normal-mild MFA group. However, there was no statistical difference in these variables.

### DISCUSSION

The uncertainty of rLDH is unsettling for both surgeons and patients, as reoperation may result in a worse clinical outcome or quality of life than initial surgery. Therefore, it is necessary to establish a predictive model of rLDH for the evaluation of patient prognosis. At present, studies have found some clinical or radiological factors related to rLDH after lumbar decompressive surgery (Table 7). In addition to some previously studied factors, we also included some presumed related but not confirmed variables. In this study, we first explored whether current drinking, multilevel microdiscectomy, degree of MFA, interdisc kyphosis, and large LDH were associated with rLDH.

#### 1. Sex and Age

The relationships between sex, age, and rLDH have been widely studied. Most studies have not found an association between sex and rLDH. However, Oh et al. found that female sex is a risk factor for rLDH, while some studies found men to be more likely to experience recurrence than women. Li et al. and Ziegler et al. found that younger age is a risk factor for rLDH. Yurac et al. also found that an age of < 35 years was a risk factor for requiring revision surgery, whereas Siccoli et al. found that patients aged > 35 years had rLDH earlier. Additionally, Yao et al. and Kienzler et al. both found that an age of < 35 years was a risk factor for requiring revision surgery, whereas Siccoli et al. found that patients aged > 35 years had rLDH earlier. Interestingly, Yao et al. and Kienzler et al. both found that an age of ≥ 50 years was a risk factor for rLDH. Therefore, the correlation between rLDH and sex or age remains controversial. In this study, we found no significant differences in sex (p = 0.068) and age (p = 0.054) between the rLDH and non-rLDH groups. Therefore, the effects of sex and age on rLDH are weak in this study. Therefore, our results do not support the correlation between sex or age and rLDH.

#### 2. Body Mass Index

It seems common to make a subjective link between obesity...
Table 7. A review of risk or related factors of rLDH

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk or related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical study</strong></td>
<td></td>
</tr>
<tr>
<td>Carragee et al.</td>
<td>Annular competence (massive posterior annular loss), type of herniation (extruded fragments)</td>
</tr>
<tr>
<td>Kara et al.</td>
<td>Lack of regular exercise</td>
</tr>
<tr>
<td>McGirt et al.</td>
<td>Larger annular defects, less disc removal</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Smoking, disc degeneration scale, higher DHI and sROM</td>
</tr>
<tr>
<td>Meredith et al.</td>
<td>Obesity</td>
</tr>
<tr>
<td>Molinerno et al.</td>
<td>Surgical methods (open discectomy), lower BMI</td>
</tr>
<tr>
<td>Oh et al.</td>
<td>Female, type of disc herniation (previous extruded and sequestrated disc) and traumatic events</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Surgical procedure (laminectomy)</td>
</tr>
<tr>
<td>Shimia et al.</td>
<td>Male, taller height, heavy works and being smoker</td>
</tr>
<tr>
<td>Matsumoto et al.</td>
<td>Caudally migrated LDH</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Male, a large annular defect, moderate disk degeneration, a large sROM, a small RT, a low iliac crest height index</td>
</tr>
<tr>
<td>Leven et al.</td>
<td>Younger age</td>
</tr>
<tr>
<td>Miwa et al.</td>
<td>Current smoking, occupational lifting</td>
</tr>
<tr>
<td>Chang et al.</td>
<td>Uncorrected scoliosis of young adults (&lt; 40 years)</td>
</tr>
<tr>
<td>Yao et al.</td>
<td>Age (≥ 50 years), obesity (BMI ≥ 25 kg/m²) and Modic change</td>
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<tr>
<td>Yurac et al.</td>
<td>A subligamentous disc herniation and patient's age &lt; 35 years</td>
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<tr>
<td>Yao et al.</td>
<td>Older age (≥ 50 years), obesity (BMI ≥ 25 kg/m²), learning curve of the surgeon (&lt; 200 cases) and central location of herniation</td>
</tr>
<tr>
<td>Willhuber et al.</td>
<td>Higher DHI and percentage of spinal canal, facet joint degeneration</td>
</tr>
<tr>
<td>Yaman et al.</td>
<td>Higher disc height and higher BMI, Modic changes</td>
</tr>
<tr>
<td>Ikuta et al.</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Belykh et al.</td>
<td>Smoking, higher BMI, higher DHI, sROM, lower central angle of lumbarlordosis, Pfirrmann grade 3, Grogan sclerosis grades 3 and 4</td>
</tr>
<tr>
<td>Fotakopoulos et al.</td>
<td>Higher BMI, history of injury</td>
</tr>
<tr>
<td>Li et al.</td>
<td>Male, younger age, current smoking, higher BMI, occupational lifting, trauma, surgical procedures (bilateral laminectomy or total laminectomy), herniation type (transligamentous extrusion), higher DHI, lower FO, larger FT</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>Obesity</td>
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<tr>
<td>Andersen et al.</td>
<td>Smoking</td>
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<tr>
<td>Lee et al.</td>
<td>PLL tear and subarticular herniation</td>
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<tr>
<td>Shin et al.</td>
<td>Lumbosacral transitional vertebrae and a higher sROM</td>
</tr>
<tr>
<td>Ziegler et al.</td>
<td>Younger age and type 2 Modic changes</td>
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<tr>
<td>Park et al.</td>
<td>Smaller-sized herniated discs</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Higher BMI, senior degeneration scale, combined herniated nucleus pulposus, and early ambulation</td>
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<tr>
<td>Li et al.</td>
<td>Decrease of FO and increase of FT</td>
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<tr>
<td>Jalil et al.</td>
<td>Foraminal disc herniation, retrolisthesis</td>
</tr>
<tr>
<td>Ding et al.</td>
<td>Age (older), current smoking, Scheuermann disease</td>
</tr>
<tr>
<td>Zhao et al.</td>
<td>Superior endplate concave angle, sacral slope, Modic changes, sROM, extension intervertebral angle, and lumbar lordosis, DHI, retrolisthesis</td>
</tr>
<tr>
<td>Siccoli et al.</td>
<td>Older patients (&gt; 35 years had rLDH earlier)</td>
</tr>
<tr>
<td>Kienzler et al.</td>
<td>Age ≥ 50 years and moderate disc degeneration</td>
</tr>
<tr>
<td>Jia et al.</td>
<td>The course of disease, Pfirrmann grade, Modic change, and migration grade</td>
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</table>

(Continued)
and rLDH, as a higher BMI generates a greater load on the lumbar discs. Indeed, there are also many studies confirming the association between BMI and rLDH. In most of these studies, a higher BMI was found to be a risk factor for rLDH,\textsuperscript{19,25-30,32-36} although some studies have arrived at the opposite conclusion.\textsuperscript{17} In this study, we did not find differences in the BMI between the 2 groups. This changed our previous notion that patients with obesity are more prone to experiencing recurrence than their counterparts. The relationship between the BMI and rLDH should not be overinterpreted in terms of obesity until sufficient evidence is available. However, for patients with obesity, weight control is recommended to reduce the load on the spine.

3. Diabetes and Hypertension

Although diabetes has been reported as a risk factor for rLDH in previous studies,\textsuperscript{28,37,38} some studies have not found an association between diabetes and rLDH.\textsuperscript{22,31,35} Only 1 previous study by Li et al.\textsuperscript{28} found a correlation between hypertension and rLDH. In this study, we found that hypertension was more common in the rLDH group than in the non-rLDH group (p = 0.025), while diabetes showed no difference between the 2 groups. Nonetheless, whether patients with hypertension or diabetes have a higher recurrence rate remains controversial, as no specific biological mechanism by which hypertension or diabetes affects rLDH has been identified.

4. Current Smoking and Drinking

More than one previous study found smoking to be a risk factor for rLDH.\textsuperscript{19,28,38-41} Unlike some previous studies, we did not find a significant difference in current smoking between the rLDH and non-rLDH groups (p = 0.519). The relationship between current drinking and rLDH has not been previously studied. This study did not find any correlation between current drinking habits and rLDH. The correlation between drinking and rLDH does not seem to be as significant as that with other diseases, such as femoral head necrosis or cirrhosis.

5. Multilevel Microdiscectomy

The relationship between surgical segments and rLDH has not been studied previously. Our study found that the rLDH group had a significantly higher rate of multilevel decompressive surgery than the non-rLDH group, suggesting that multilevel decompressive surgery may be associated with rLDH. A possible explanation is that more spinal stability is removed in multilevel surgery, which leads to a higher recurrence rate than that in single-level surgery.

6. DHI and sROM

Kim et al.\textsuperscript{45} first reported higher DHI and sROM as risk factors for rLDH. Except for some negative reports, most studies found an association between rLDH and a higher DHI or sROM.\textsuperscript{18,28,37,38,44,46,50}

### Table 7. A review of risk or related factors of rLDH (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk or related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al.\textsuperscript{28} (2021)</td>
<td>Hypertension, diabetes, a history of smoking, a history of performing intense physical labor, Pfirrmann grade 3, Modic changes (type 2), herniation in the form of extrusion, a high DHI and rROM</td>
</tr>
<tr>
<td>Shi et al.\textsuperscript{44} (2021)</td>
<td>Lower grade of surgical-level disc degeneration, senior grade of adjacent-level disc degeneration, a high DHI, and a large sROM</td>
</tr>
<tr>
<td>Siccoli et al.\textsuperscript{18} (2022)</td>
<td>Overweight and smoking</td>
</tr>
<tr>
<td>Ono et al.\textsuperscript{39} (2022)</td>
<td>Lower disc height, smoking, diabetes, subligamentous extrusion type, and Modic change</td>
</tr>
<tr>
<td>Review and meta-analysis</td>
<td></td>
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<tr>
<td>McGirt et al.\textsuperscript{54} (2009)</td>
<td>Limited disc removal</td>
</tr>
<tr>
<td>Watters 3rd et al.\textsuperscript{55} (2009)</td>
<td>Conservative discectomy</td>
</tr>
<tr>
<td>Shin\textsuperscript{44} (2014)</td>
<td>Diabetes, family history, history of external injury, duration of illness and BMI</td>
</tr>
<tr>
<td>Huang et al.\textsuperscript{46} (2016)</td>
<td>Smoking, disc protrusion, and diabetes</td>
</tr>
<tr>
<td>Hlubek et al.\textsuperscript{63} (2017)</td>
<td>Younger age, lack of a sensory or motor deficit, and a higher baseline ODI</td>
</tr>
<tr>
<td>Yin et al.\textsuperscript{64} (2018)</td>
<td>Older age (≥ 50 years), obesity (BMI ≥ 25 kg/m\textsuperscript{2}), upper lumbar disc and central disc herniation</td>
</tr>
<tr>
<td>Miller et al.\textsuperscript{65} (2018)</td>
<td>Larger annular defect</td>
</tr>
<tr>
<td>Brooks et al.\textsuperscript{66} (2020)</td>
<td>Higher DHI and sROM, Modic changes</td>
</tr>
</tbody>
</table>

DHI, disc height index; sROM, sagittal range of motion; BMI, body mass index; PLL, posterior longitudinal ligament; LDH, lumbar disc herniation; IHI, iliac crest height index; RT, relative thickness of the transverse process of L5 vertebra; FO, facet orientation; FT, facet tropism; rLDH, recurrent lumbar disc herniation; ODI, Oswestry Disability Index.
One explanation is that a higher DHI indicates more disc materials used, leading to an increased probability of rLDH. Another explanation is that a higher DHI may indicate a larger sROM, which has been found to be associated with rLDH in previous studies. We did not find differences in the DHI or sROM between the 2 groups in this study. One possible reason for this is that we performed primary fusion surgery in some patients with large sROMs who were reluctant to accept any possibility of recurrence. This might have resulted in less patients with large sROM in single decompression group and ultimately lead to the nonsignificant difference in the sROM between the 2 groups.

7. FO and FT

The concepts of FO and FT were first proposed by Noren. A few studies have found a relationship between FO and lumbar degenerative diseases. Some studies have found that an increase in the difference in the angle of the left and right facet joints, that is, an increase in FT, may alter the normal spinal biomechanics, resulting in spinal degeneration or LDH. However, Grogan et al. found that FT is not associated with LDH. Additionally, the relationship between FO, FT, and rLDH has only been mentioned in a few studies. The multicenter retrospective study by Li et al. found that a higher FO and a lower FT were risk factors for rLDH. However, the retrospective matching case-control study by Shi et al. did not find a correlation between rLDH and FO or FT. In this study, we did not find any differences between the rLDH and non-rLDH groups, suggesting that FO, FT, and rLDH were not correlated with each other. Therefore, we do not believe that a smaller FO or a larger FT can predict rLDH.

8. Pfirrmann Grade and Modic Changes

Whether the disc degeneration grade and Modic changes affect rLDH is still widely debated. Some studies have found that moderate disc degeneration is associated with rLDH, while Kim et al. and Jia et al. have found that more severe disc degeneration is a risk factor for rLDH. However, different studies have used the Pfirrmann grade or modified Pfirrmann grade to evaluate disc degeneration, which makes some data comparisons difficult. Many studies have reported a correlation between Modic changes and rLDH. However, although the rLDH group (45%) had a higher rate of Modic changes than the non-rLDH group (28.8%) in our study, the difference was not significant (p = 0.123). The probable cause is that many patients with endplate inflammation undergo primary fusion surgery because of low back pain, which may result in a potential decrease in the rate of patients with rLDH with Modic changes.

9. Interdisc Kyphosis and Large LDH

In addition to the abovementioned clinical and radiological factors, we analyzed some other common radiological factors, including interdisc kyphosis and large LDH. Contrary to our previous predictions, we found no difference in interdisc kyphosis between the 2 groups (p = 0.748). Park et al. found that smaller-sized herniated discs were associated with rLDH. McGirt et al. found that less disc removal was associated with rLDH. Although the rLDH group (10%) had a lower rate of large LDH than the non-rLDH group (22.4%) in this study, the difference was not significant (p = 0.303). This suggests that more discectomies may reduce the probability of rLDH. However, limited discectomy has now become mainstream because aggressive discectomy may lead to intractable low back pain and lower satisfaction.

10. Degree of MFA

Previous studies have found a correlation between multifidus and low back pain, leg pain and even disc degeneration scale. However, the relationship between the degree of MFA and rLDH has not been studied previously. In this study, we found moderate-severe MFA was the sole and strongest risk factor for rLDH. The recurrence probability of LDH combined with moderate-severe MFA was approximately 3.414 times that of LDH combined with normal-mild MFA. The multifidus is an important spinal stabilizing structure. In patients with moderate-severe MFA, a minor surgical procedure may lead to further aggravation of MFA, thereby destabilizing the spine and ultimately leading to an increased probability of recurrence. Although tubular microdiscectomy is a very minimally invasive procedure, it is still unavoidable to perform microdiscectomy through the multifidus muscle. Therefore, although minimally invasive decompressive surgery can significantly improve the pain in patients with moderate-severe MFA, the high potential recurrence probability cannot be ignored. Additionally, we do not recommend open discectomy for LDH patients as this procedure can exacerbate multifidus destruction. For patients with moderate and severe MFA, the preoperative education to the patient will become more targeted. The correct and regular back muscle exercise may be a way to lower the risk of postoperative rLDH although there is no direct evidence presently.
11. Limitations

Although the data for this study were collected prospectively, the retrospective nature of the analysis introduced inevitable bias. The number of positive cases (rLDH) in this study was limited, which might have led to statistical bias. The recurrence of LDH is a complex biomechanical process and may be affected by many social behaviors, clinical and radiological factors, and this study was unable to incorporate all possible factors into the analysis. Additionally, many of the previously studied variables such as sex, age, BMI, diabetes, smoking or sROM, IDH, Pfirrmann's Grade, Modic change are somewhat controversial. We can find positive or negative results for almost all variables in previous studies. Of course, these results may depend on many factors, such as the type of variables included, the type and number of cases, differences in surgical methods, and even statistical methods, etc. In addition, the herniation types, including "protrusion," "subligamentous," "extrusion," and "sequestration" were not included in this study because not all surgical records contained descriptions of the specific location of disc herniation. Furthermore, this study can only provide intraobserver reliability for all radiological variables without providing interobserver reliability, as the 2 radiologists only evaluated all the radiological variables one time. This study included some possible clinical or radiological factors based on our own clinical experiences. The inclusion of factors based on clinical experience is inherently biased, although this is unavoidable in most models for risk factor prediction. Finally, this study lacks short-middle term outcomes of patients to elucidate the recovery process of postoperative low back pain and leg pain.

CONCLUSION

This study investigated the risk factors for recurrence after microdiscectomy in patients with LDH. Although there were significant differences in the rates of hypertension, multilevel microdiscectomy, and the degree of MFA between the rLDH and non-rLDH groups, we found that moderate-severe MFA was the sole and strongest risk factor of rLDH. This finding can serve as an important reference for surgeons in formulating surgical strategies and the assessment of prognosis.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES


Assessment of Cervical Myelopathy Risk in Ossification of the Posterior Longitudinal Ligament Patients With Spinal Cord Compression Based on Segmental Dynamic Versus Static Factors

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Objective: Using segmental dynamic and static factors, we aimed to elucidate the pathogenesis and relationship between ossification of the posterior longitudinal ligament (OPLL) and the severity of cervical myelopathy.

Methods: Retrospective analysis of 163 OPLL patients’ 815 segments. Imaging was used to evaluate each segmental space available for the spinal cord (SAC), OPLL diameter, type, bone space, K-line, the C2–7 Cobb angle, each segmental range of motion (ROM), and total ROM. Magnetic resonance imaging was used to evaluate spinal cord signal intensity. Patients were divided into the myelopathy group (M group) and the without myelopathy group (WM group).

Results: Minimal SAC (p = 0.043), (C2–7) Cobb angle (p = 0.004), total ROM (p = 0.013), and local ROM (p = 0.022) were evaluated as an independent predictor of myelopathy in OPLL. Different from the previous report, the M group had a straighter whole cervical spine (p < 0.001) and poorer cervical mobility (p < 0.001) compared to the WM group. Total ROM was not always a risk factor for myelopathy, as its impact depended on SAC, when SAC > 5 mm, the incidence rate of myelopathy decreased with the increase of total ROM. Lower cervical spine (C5–6, C6–7) showing increased “Bridge-Formation,” along with spinal canal stenosis and segmental instability (C2–3, C3–4) in the upper cervical spine, could cause myelopathy in M group (p < 0.05).

Conclusion: Cervical myelopathy is linked to the OPLL’s narrowest segment and its segmental motion. The hypermobility of the C2–3 and C3–4, contributes significantly to the development of myelopathy in OPLL.

Keywords: Ossification of the posterior longitudinal ligament, Degenerative spondylosis, Segmental compression, Segmental range of motion, Increased signal intensity
INTRODUCTION

Ossification of the posterior longitudinal ligament (OPLL) of the cervical spine is a common cause of spinal cord dysfunction, which is characterized by progressive spinal stenosis and spinal cord compression.\(^1\)\(^-\)\(^4\) In the elderly, OPLL can lead to severe neurological dysfunction, which may manifest as hyperreflexia, clumsy gait, paresthesia, decreased strength, and signs of radiculopathy.\(^5\)\(^,\)\(^6\) Some patients with OPLL-caused degenerative cervical spinal stenosis never had symptoms or signs of myelopathy; in a cadaver study that included both myelopathy and OPLL, 9% of patients over 70 years old had evidence of obvious cervical spinal stenosis after death.\(^7\)\(^-\)\(^9\) Despite the high prevalence rate, clinical experience indicates that only a small number of patients with these findings have symptomatic myelopathy and require surgical decompression. Despite the low degree of ossification, some patients develop myelopathy. OPLL-induced spinal canal stenosis can affect multiple vertebral segments, and the degree of compression in each segment influences the severity of myelopathy.\(^10\)

Myelopathy is caused by several factors, including (1) the formation of the spinal canal and intervertebral foramen, (2) pathological invasion, (3) biomechanical effects, and (4) circulatory dysfunction. Furthermore, inflammation is a mechanism of disc degeneration in patients with cervical spondylosis (CSD).\(^11\)\(^-\)\(^15\) The pathogenesis of OPLL-induced myelopathy cannot be explained solely by static spinal cord compression in OPLL patients; dynamic factors amplify the static effect of spinal canal stenosis caused by ligament ossification.\(^16\)\(^,\)\(^17\) According to Matsumaga et al.,\(^18\) pathological compression of the ossified ligament causes myelopathy above a certain critical point, while dynamic factors cause it below that critical point. Previous research has investigated the effect of OPLL on myelopathy severity, but mainly static factors, or analysis from the whole cervical level, make it difficult to identify the clinical factors that best predict the severity of myelopathy.\(^19\)

In this study, we aimed to examine the relationship between imaging data and clinical symptoms of cervical OPLL patients, as well as to assess the morphology, thickness, stability, and other pathogenic factors of ossification foci at each cervical segment. The association of dynamic and static factors with responsible segments of OPLL-induced myelopathy was investigated. Furthermore, we investigated whether the classification of increased signal intensity (ISI) by magnetic resonance imaging (MRI) in OPLL patients reflects the severity of symptoms.

MATERIALS AND METHODS

1. Patient Demographics

This study reviewed 389 patients with cervical OPLL diagnosed in the clinic from 2012 to 2014. Initially, the findings of radiographs and computed tomography (CT) scans of the cervical spine were used to diagnose all patients at our university hospital. Demographic information, such as gender and age, was obtained from electronic medical records. The exclusion criteria are listed as follows: (1) Patients suffering from stroke or neurological disease, cardiovascular disease, or thromboembolic disease. (2) Patients with a history of spinal and nervous system trauma, spinal deformity, cervical spine surgery, bone fractures, or cancer. (3) The absence of imaging data or clinical data was excluded. Therefore, the study eventually included 163 patients (108 men and 55 women; mean age, 66.5 years; range, 37–90 years). Ossification type: continuous in 26 cases, segmental in 29 cases, mixed in 81 cases, and localized in 27 cases. The Toyama University Hospital’s Ethics Committee reviewed and approved the human-participant studies (R2015003). The patients/participants provided written informed consent to participate in this study.

2. Radiological Measurements and Clinical Results

Based on a lateral plain radiograph of the cervical spine, the K-line and the C2–7 Cobb angle were evaluated as static factors (Fig. 1A). The K-line was characterized as a straight line connecting the midpoints of the spinal canal at C2 and C7 on lateral radiographs.\(^20\) The Cobb angle was calculated by drawing parallel lines from the lowest endplate of the most superior vertebral level (C2) to the lowest endplate of the lowest vertebral level (C7). The parallel lines were then perpendicularly drawn, with the angle of intersection equal to the Cobb angle.\(^21\) We examined the cervical spine’s physiological curvature as well as the relationship between the ossified ligament and the spinal canal.

In the midline section of sagittal CT, we measured OPLL diameter, space available for the spinal cord (SAC), and occupation ratio (OPLL thickness/osseous anteroposterior diameter) of each segment from C2–7.\(^17\) OPLL distribution at each vertebral body and intervertebral disc level was recorded to quantify posterior longitudinal ligament hyperostosis, and the number of levels where OPLL was present was calculated to calculate the ossification index (OP-index). Furthermore, we measured the OPLL angle, which is defined as the angle formed by 2 tangents to the ossification foci (Fig. 1B). The axial ossified pattern
can be divided into 2 types: central and lateral. The central type was defined as having the most occupied portion of the OPLL tip within the middle one-third of the width of the vertebral canal, while the lateral type had the most occupied portion of the OPLL tip outside the middle one-third of the width. Furthermore, we measured the available space in the narrowest axial image, which we defined as the minimum axial bone space (Fig. 1C). Ossification of the intervertebral space was characterized as "Bridge-Formation" and the number and proportion of bridges formed per segment were measured. Furthermore, all patients underwent high-resolution MRI at the same time. In sagittal T2 images, the ISI of the spinal cord at the narrowest level was classified into 3 groups according to Yukawa et al.22: grade 0, none; grade 1, light (obscure); and grade 2, intense ISI was defined to be similar to the signal from the cerebrospinal fluid (Fig. 2).

Based on static factors, we used previous criteria to categorize ossification into the following types: (a) continuous, (b) segmental, (c) mixed, and (d) localized based on cervical spine lateral radiography23 (Fig. 3A). Based on the morphology of different segments in patients, we classified them into 6 types based on whether they were stable or not. The stable form is shown as follows: (a) nonbridge formation, (b) stable plate, (c) stable beak; and unstable forms included (d) unstable upper-plate, (e) unstable lower-plate, (f) unstable-beak (Fig. 3B).

Dynamic factors were assessed using the angle between each segment of the lower edge of C2 to C7 on a plain radiograph, and the differences between the maximum flexion and extension positions were obtained and expressed as negative extension and positive flexion values. The angle between the lower endplates of the vertebrae at the peak of the OPLL in the flexion-extension lateral view was defined as the segmental range of motion (ROM). Then, in the sagittal position, we defined the local angle as the ROM at the narrowest segment (Fig. 4). Finally, the Japanese Orthopaedic Association (JOA) score was used to determine the severity of OPLL-induced myelopathy.24 OPLL patients were divided into 2 groups: those with myelopathy (M) (JOA score < 17) and those without myelopathy (WM) (JOA score = 17) based on the JOA score. Based on the severity of symptoms, the M group was divided into 2 groups: mild myelopathy (12 ≤ JOA score < 17) and moderate myelopathy (JOA score < 12). Two independent raters performed all radiographic and measurement procedures twice in a 1-month interval.
Segmental Factors of Myelopathy Risk in OPLL

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Fig. 3. Cervical OPLL type. (A) Ossification categorization of the posterior longitudinal ligament into continuous (a), segmental (b), mixed (c), and other types (d) based on lateral radiographs of the cervical spine. (B) A classification system for ossification of the cervical spine’s posterior longitudinal ligament based on the morphology of the motor segment’s ossification block. (a) Nonbridge formation. (b) Stable plate. (c) Stable beak. (d) Unstable upper-plate. (e) Unstable lower-plate. (f) Unstable-beak. OPLL, ossification of the posterior longitudinal ligament.

3. Statistical Analysis

Data are presented in the form of the mean (standard deviation [SD]; range) or mean (SD). Continuous data were compared using the unpaired t-test, while categorical data were compared using Fisher exact test. Variables associated with p < 0.05 on univariate analysis were considered candidate risk factors in multivariate analysis. A multivariate logistic regression analysis was used to identify factors associated with OPLL patients’ myelopathy.

RESULTS

1. Patient Demographics and Clinical Characteristics

Patients were divided into the M group (n = 118) and the WM group (n = 45) based on the JOA score. The JOA score in the M group was 12.4 ± 3.0 and 17 in the WM group. Age, sex, and body mass index (BMI) had no significant effect on clinical outcomes. Our findings revealed that the OPLL type (p = 0.153) and morphological type (p = 0.533) were similar in the 2 groups (Table 1). No statistical difference was found between the 2 groups with ossification, the OP-index of the cervical spine was 7.4 ± 2.3 in the M group and 7.8 ± 2.7 in the WM group (p = 0.310). The proportion of lateral types was significantly higher in the M group (41.5%) than in the WM group (24.4%) (p = 0.043). K-line (-) patients were more prevalent in the M group (27.1%) than in the WM group (15.6%), while there was no statistical significance between the 2 groups (p = 0.152). Among the 2 groups, group M had more “Bridge-Formation” of the intervertebral spaces in the lower cervical spine, with C5/6 (57.6% vs. 40.0%) and C6/7 (49.2% vs. 28.9%) segments demonstrating statistical significance (p < 0.05). Furthermore, there were no statistically significant correlations found between other clinical outcome scales and imaging parameters.

2. Comparison of Radiological Measurements of the Cervical Spine Between the M and WM Groups

Table 2 summarized the contrast measured by x-ray and CT images of the 2 groups respectively. The results showed that among the static factors, the M group’s minimum SAC (5.3 ± 1.7 mm) was significantly lower than the WM group’s (6.5 ± 1.9 mm) (p < 0.001), and the M group’s minimum axial bone space (155.3 ± 34.7 mm²) was also lower than the WM group’s (183.7 ± 47.6 mm²) (p < 0.001). Although the maximum occupied ratio was higher in the WM group (p = 0.005), there was no significant difference in the maximum diameter of OPLL or the minimal sagittal angle between the 2 groups (p = 0.085). The C2–7 Cobb angle of the cervical spine in the M group (10.3° ± 8.4°)
was less than that in the WM group (16.8° ± 11.5°), indicating that the effects of ossification straightened the cervical physiological curvature in myelopathy patients (p < 0.001). Among the dynamic factors, the total ROM of patients in the M group (27.0° ± 13.4°) was lower than that of the WM group (35.7° ± 14.6°) (p < 0.001), and the local ROM was lower as well (p = 0.034).

Following the multivariate analysis, minimal SAC (odds ratio [OR], 0.006; 95% confidence interval [CI], 0.000–0.853; p = 0.043), (C2–7) Cobb angle (OR, 0.936; 95% CI, 0.895–0.980; p = 0.004), total ROM (OR, 0.958; 95% CI, 0.926–0.991; p = 0.013), and local ROM (OR, 0.888; 95% CI, 0.802–0.983; p = 0.022) were measured as independent predictors of myelopathy (Table 3).

3. Comparison of Radiological Measurements of Each Segment Between the M and WM Groups

We compared the measurements of the 2 groups of patients at each segment of the cervical spine. The distribution of morphological type differed significantly among the 815 segments (Fig. 3B). In the M group, C2–3 (37.3%) are mostly of the unstable upper-plate type, C3–4 are mostly of the unstable-beak type
(28.8%); C4–5, C5–6, and C6–7 are mostly of the nonbridge formation type, whereas in the WM group, C3–4 is mostly of the nonbridge formation type (32.4%). Interestingly, we discovered that in the M group, the minimum SAC (4.7 ± 1.1 mm) of C3/4 was significantly lower than in the WM group (6.5 ± 1.2 mm) (p < 0.001). Furthermore, the minimum axial bone space of C3 was less than that of the WM group (p = 0.018). The maximum occupation ratio was greater than that of the WM group (p = 0.015), indicating a statistically significant difference. The ROM in the C3/4 segment M group (7.2° ± 4.2°) was greater than that in the WM (5.5° ± 3.6°) group (p = 0.140). In the M group, the minimum SAC of the C2/3 segment is smaller than

Table 4. Comparison of OPLL cervical spine segmental measurements between the M and the WM groups

<table>
<thead>
<tr>
<th>Segment</th>
<th>Minimal SAC (mm)</th>
<th>Maximum occupation ratio (%)</th>
<th>Minimum axial bone space (mm²)</th>
<th>Maximum local ROM (°)</th>
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<tr>
<td></td>
<td>M group</td>
<td>WM group</td>
<td>p-value</td>
<td>M group</td>
</tr>
<tr>
<td>C2</td>
<td>3.0 ± 0.1</td>
<td>-</td>
<td>-</td>
<td>51.8 ± 21.4</td>
</tr>
<tr>
<td>C2/3</td>
<td>5.2 ± 1.2</td>
<td>7.7 ± 1.9</td>
<td>0.024*</td>
<td>48.2 ± 8.7</td>
</tr>
<tr>
<td>C3</td>
<td>5.3 ± 1.8</td>
<td>6.8 ± 2.3</td>
<td>0.282</td>
<td>32.2 ± 7.6</td>
</tr>
<tr>
<td>C3/4</td>
<td>4.7 ± 1.1</td>
<td>6.5 ± 1.2</td>
<td>&lt; 0.001*</td>
<td>58.8 ± 9.6</td>
</tr>
<tr>
<td>C4</td>
<td>5.0 ± 2.3</td>
<td>6.8 ± 3.0</td>
<td>0.271</td>
<td>50.8 ± 14.0</td>
</tr>
<tr>
<td>C4/5</td>
<td>4.8 ± 1.5</td>
<td>5.3 ± 0.7</td>
<td>0.444</td>
<td>55.2 ± 14.2</td>
</tr>
<tr>
<td>C5</td>
<td>6.2 ± 2.5</td>
<td>4.6 ± 0.7</td>
<td>0.411</td>
<td>39.9 ± 16.0</td>
</tr>
<tr>
<td>C5/6</td>
<td>5.4 ± 1.3</td>
<td>5.8 ± 1.6</td>
<td>0.503</td>
<td>53.2 ± 13.4</td>
</tr>
<tr>
<td>C6</td>
<td>6.5 ± 1.6</td>
<td>7.6 ± 2.6</td>
<td>0.564</td>
<td>45.5 ± 17.8</td>
</tr>
<tr>
<td>C6/7</td>
<td>6.4 ± 2.7</td>
<td>-</td>
<td>-</td>
<td>55.3 ± 16.0</td>
</tr>
<tr>
<td>C7</td>
<td>7.8 ± 6.5</td>
<td>-</td>
<td>-</td>
<td>45.6 ± 6.0</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
OPLL, ossification of the posterior longitudinal ligament; M group, myelopathy group; WM group, without myelopathy group; SAC, space available for the spinal cord; ROM, range of motion.
*p < 0.05, statistically significant differences.

Fig. 5. A scatterplot depicting the relationship between SAC and ROM in OPLL patients’ cervical spines. Open circles indicate no myelopathy; blue circles indicate mild myelopathy; and red circles indicate moderate myelopathy. The percentage represents the number of myelopathy patients in each square. SAC, space available for the spinal cord; ROM, range of motion; OPLL, ossification of the posterior longitudinal ligament.
Table 5. Patient demographics and radiographic measurements in each grade of increased signal intensity on sagittal T2-weighted magnetic resonance imaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>M group</td>
<td>45 (54.9)</td>
<td>63 (90.0)</td>
<td>10 (90.1)</td>
<td></td>
</tr>
<tr>
<td>WM group</td>
<td>37 (45.1)</td>
<td>7 (10.0)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.5 ± 11.5</td>
<td>67.3 ± 10.5</td>
<td>65.5 ± 8.7</td>
<td>0.596</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>52 (49.5):30 (51.7)</td>
<td>49 (46.7):21 (36.2)</td>
<td>4 (3.8):7 (12.1)</td>
<td>0.092</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 4.6</td>
<td>24.6 ± 3.9</td>
<td>26.0 ± 5.1</td>
<td>0.283</td>
</tr>
<tr>
<td>JOA score</td>
<td>14.7 ± 2.9</td>
<td>12.8 ± 3.2</td>
<td>10.7 ± 3.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(C2–7) Cobb angle (°)</td>
<td>13.0 ± 10.5</td>
<td>12.4 ± 8.9</td>
<td>10.2 ± 8.8</td>
<td>0.651</td>
</tr>
<tr>
<td>Minimal SAC (mm)</td>
<td>6.3 ± 1.8</td>
<td>5.0 ± 1.5</td>
<td>4.5 ± 2.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Maximum occupation ratio (%)</td>
<td>44.1 ± 12.7</td>
<td>53.8 ± 13.3</td>
<td>58.6 ± 16.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Minimum axial bone space (mm²)</td>
<td>176.3 ± 43.7</td>
<td>150.1 ± 32.5</td>
<td>148.1 ± 33.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total ROM (°)</td>
<td>30.5 ± 14.6</td>
<td>25.9 ± 13.7</td>
<td>32.8 ± 15.7</td>
<td>0.092</td>
</tr>
<tr>
<td>Local ROM (°)</td>
<td>6.4 ± 4.1</td>
<td>5.8 ± 4.7</td>
<td>6.9 ± 4.1</td>
<td>0.560</td>
</tr>
</tbody>
</table>

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

M Group, myelopathy group; WM Group, without myelopathy group; BMI, body mass index; JOA, Japanese Orthopaedic Association; SAC, space available for the spinal cord; ROM, range of motion.

*p < 0.05, statistically significant differences.

that of the WM group (p = 0.024), and the minimum axial bone space of the C4/5 segment in the M group is smaller than that of the WM group (p = 0.007). Furthermore, the C5/6 segmental ROM is smaller than that of the WM group (p = 0.015). It means that in the M group, the upper cervical spine has greater ROM than the WM group, while the lower cervical spine is more stable than the WM group (Table 4).

4. Correlation Between Static and Dynamic Factors of the Cervical Spine and Clinical Outcomes

According to their JOA level, we divided 163 patients into 3 groups: those without myelopathy, those with mild myelopathy, and those with moderate myelopathy. A positive correlation trend was observed between the minimum SAC and total ROM (Fig. 5). The slope of the without myelopathy group was the largest (R² = 0.1650; p = 0.006), followed by patients with mild myelopathy (R² = 0.052; p = 0.054) and patients with moderate myelopathy had the lowest slope (R² = 0.03173; p = 0.236). The incidence of myelopathy increased with increasing ROM at a minimum SAC of less than 5 mm, with 73.4% incidence at 0°–20° compared to 90.9% at 20°–40°, and 100% at 40°–60°. When the SAC was greater than 5 mm, the incidence rate of myelopathy decreased with increasing total ROM, with 81.0% incidence at 0°–20° compared to 72% at 20°–40° and 45.5% at 40°–60°.

5. MRI Signal Intensity Classification in Cervical OPLL

Out of the M group patients, 73 were found to have ISI on the MRI scan, with 63 patients (53.4%) in grade 1 and 10 patients (8.5%) in grade 2. There were 7 patients (15.6%) in grade 1 and 1 patient (2.2%) in grade 2 among the WM group (p < 0.001). The JOA score (grade 0, 14.7 ± 2.9; grade 1, 12.8 ± 3.2; grade 2, 10.7 ± 3.8 points) decreased with increasing ISI grade (p < 0.001). Simultaneously, as ISI increased, the minimal SAC (p < 0.001) and minimum axial bone space (p < 0.001) gradually decreased, while the maximum occupation ratio (p < 0.001) gradually increased. However, age, gender, BMI, (C2–7) Cobb angle, total ROM, and local ROM were not different in patients in the 3 grades (Table 5).

DISCUSSION

A variety of factors, including static compression and dynamic factors, affect OPLL patients who develop myelopathy. Static compression of the spinal cord by the OPLL is the most important factor contributing to the development of myelopathy, and from the sagittal section, the degree of stenosis of the spinal canal determines the severity of the myelopathy. It is also similar in the axial section, the proportion of lateral type in the axial image was found to be negatively correlated with the incidence...
of myelopathy in this study. Therefore, the lateral type may indicate that patients with cervical OPLL are more likely to develop severe myelopathy. Our findings also showed that the amount of available space in the sagittal and transverse sections of the spinal canal (minimum SAC, minimum axial bone space, maximum occupation ratio) was an influential factor affecting the occurrence of myelopathy in OPLL patients.

Although larger ROM may theoretically be more likely to cause myelopathy, numerous factors may influence the patient's flexion and extension activities during a clinical examination, including symptoms, curvature of cervical spine, cervical muscle group, degeneration of cervical small joints, etc. Multivariate factors can result in different manifestations in patients, as our findings show. Matsunaga et al. examined the cervical spines of OPLL patients and discovered that all patients with SAC below 6 mm developed myelopathy, but none with SAC above 14 mm. This suggests that the static compression factor preferentially promotes the development of myelopathy. They also found that when SAC was between 6 mm and 14 mm, ROM was positively related to the development of myelopathy, indicating that this dynamic factor played a role. A national multicenter prospective study with clear inclusion criteria was designed, and they discovered that more than 60% of spinal canal stenosis caused by OPLL was associated with myelopathy. However, in contrast to previous studies, we found that patients with myelopathy had less total and local ROM than patients without myelopathy. This difference was statistically significant after multivariate logistic regression. According to Luo et al., ossification of the spinal intervertebral space will limit the vertebral body's ROM. Furthermore, patients with OPLL will also have reduced cervical flexion and extension activities due to myelopathy. This may result in a reduction in total ROM and local ROM.

Cervical spine mobility does not always increase the risk of myelopathy. Although the spinal canal had been severely invaded, some patients did not exhibit symptoms of myelopathy. Fujiyoshi et al. studied 27 patients with OPLL of the cervical spine but no clinical symptoms of myelopathy; possibly related to severely limited cervical mobility. In contrast to previous findings, there was no clear boundary on the map between the M and WM groups. We examined total ROM about minimal SAC in patients with myelopathy, using linear regression suggesting that the more severe the myelopathy, the lower the slope. Although total ROM was lower in the M group compared to the WM group, the incidence of myelopathy was positively correlated with total ROM when the minimum SAC < 5 mm, while when SAC > 5 mm, the incidence rate of myelopathy decreased, which may be affected by the confounding factors of the overall ossification level of the cervical spine. The cervical spine may gain more from increased mobility when the minimum SAC is > 5 mm in our patients.

Because OPLL is a 3-dimensional (3D) disease rather than a 2-dimensional disease, segmental factors can influence myelopathy development. According to Saito et al., segmental ROM at the site of preoperative OPLL is an independent predictor of adverse outcomes. Therefore, we investigated the relationship between C2–7 myelopathy incidence and the morphology of each segment, the degree of spinal stenosis, and the ROM of each segment. As a result, C3/4 segment patients had more severe spinal canal stenosis and a greater ROM than asymptomatic patients. This suggested that dynamic and static compression at C3/4 could contribute to myelopathy pathogenesis. According to Yi et al., CSD with dizziness is more prevalent among patients with grade C3/4 CSD, instability on C3/4, and Miyazaki grade IV on C3/4. Tomii et al. also considered patients with cervical spondylotic myelopathy (CSM) to be elderly, and dynamic factors (hypermobility) at the C3/4 level contribute more to the main cause of CSM than static factors. In general, the C5–6 level receives the most load during cervical exercise. In older patients, cervical and/or lower cervical spine mobility is already limited, resulting in an overload of the upper cervical spine. The M group had less cervical ROM (C5/6, C6/7) than the WM group and more ranges of motion (C2/3, C3/4) in the high cervical region. This suggests that upper cervical region instability may contribute to the development of OPLL myelopathy.

ISI of the spinal cord on T2-weighted MRI is frequently seen in OPLL patients. The relationship between ISI classification and myelopathy severity is still debatable. Some studies have found that the postoperative prognosis of ISI patients is poor, but others have found no link between these factors. The study's findings show that ISI grading is related to the severity of myelopathy and the static factors of the spinal canal (minimum SAC, maximum occupancy ratio, minimum axial bone space), indicating that ISI is related to long-term spinal cord compression. According to the data, mild ISI is associated with mild neuropathological changes in the spinal cord, indicating a higher recovery potential, whereas severe ISI is associated with severe changes and a lower recovery potential. As the disease progresses, spinal cord signal intensity increases from none to mild ISI and then to severe ISI.

The current study had several limitations. The study was ret-
rospective and cross-sectional, with a small number of patients from a single institute participating. To validate our findings, a prospective study with larger sample size, frequent observation periods, and multiple time points may be required. Secondly, we did not include 3D-CT, dynamic CT, or MRI for retrospective reasons, and we need to use spinal cord-evoked potentials to diagnose and classify the level of responsibility, which will improve our accuracy. Third, the disease course of the patients must be considered in the study, in addition to prospective follow-ups. More research into this topic is planned for the near future. However, the current study may offer a more comprehensive understanding of the segmental factors that contribute to myelopathy caused by cervical OPLL.

CONCLUSION

Our findings show that minimal SAC, maximum OPLL diameter, total ROM, and local ROM are related to the severity of OPLL myelopathy. The development of myelopathy in OPLL is linked to upper cervical instability and stenosis, specifically C2–3, and C3–4. The incidence rate of myelopathy does not always increase with the increase of ROM. It is more profitable when the minimum SAC > 5 mm. To provide better clinical treatment for asymptomatic or minimally symptomatic OPLL patients we must improve our understanding of the risk factors for myelopathy in OPLL patients.

NOTES

Conflict of Interest: The authors have nothing to disclose.
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Author Contribution: Conceptualization: YK; Data curation: ZH, NTCT, YK; Formal analysis: ZH; Funding acquisition: ZH, YK; Methodology: ZH, NTCT, HM, YK; Project administration: YK; Visualization: ZH, NTCT, YK; Writing - original draft: ZH; Writing - review & editing: ZH, NTCT, HM, TY, SS, KS, KW, HF, KK, YK.

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REFERENCES


Complication Rates and Utilization Trends of 3-Level Posterior Column Osteotomy Compared to Single-Level Pedicle Subtraction Osteotomy

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Objective: The objective of this study is to assess differences in complication profiles between 3-level posterior column osteotomy (PCO) and single-level pedicle subtraction osteotomy (PSO) as both are reported to provide similar degrees of sagittal correction.

Methods: The PearlDiver database was queried retrospectively using International Classification of Disease, 9th and 10th edition and Current Procedural Terminology codes to identify patients who underwent PCO or PSO for degenerative spine disease. Patients under age 18 or with history of spinal malignancy, infection, or trauma were excluded. Patients were separated into 2 cohorts, 3-level PCO or single-level PSO, matched at a 1:1 ratio based on age, sex, Elixhauser comorbidity index, and number of fused posterior segments. Thirty-day systemic and procedure-related complications were compared.

Results: Matching resulted in 631 patients for each cohort. PCO patients had decreased odds of respiratory (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.43–0.82; p = 0.001) and renal complications (OR, 0.59; 95% CI, 0.40–0.88; p = 0.009) compared to PSO patients. There was no significant difference in cardiac complications, sepsis, pressure ulcer, dural tear, delirium, neurologic injuries, postoperative hematoma, postoperative anemia, or overall complications.

Conclusion: Patients who undergo 3-level PCO have decreased respiratory and renal complications compared to single-level PSO. No differences were found in the other complications studied. Considering both procedures achieve similar sagittal correction, surgeons should be aware that 3-level PCO offers an improved safety profile compared to single-level PSO.

Keywords: Kyphosis, Osteotomy, Postoperative complications

INTRODUCTION

Adult spinal deformity (ASD) is a complex condition that may be disabling and have a negative impact on quality of life, especially when severe. Spinal deformity may present with pathological curvature in both sagittal and coronal planes, and the thoracolumbar spine is most frequently impacted. Symptoms and treatment goals may vary with patient age, with older patients often presenting with pain and neurologic symptoms and younger patients often presenting with primarily cosmetic concern. The goal of treatment for all patients is to achieve balance in all planes, alleviate pain, and prevent further deformity or recurrence.1,2

Fortunately, when a deformity cannot be treated by standard approaches such as instrumentation and ligament release, osteotomies provide an effective form of surgical intervention. Vertebroplast osteotomies can be performed via anterior approach, combined anterior-posterior approach, or posterior only approach, the latter of which has gained greater popularity in recent years.1,2

Two of the most commonly used posterior approach osteoto-
my techniques are the posterior column osteotomy (PCO) and the pedicle subtraction osteotomy (PSO). The PCO was first described by Smith-Petersen in 1945 as a 1- to 2-level osteotomy treatment for ankylosing spondylitis.5 Ponte et al. and several others then began advocating for the use of multilevel PCO in the treatment of ankylosing spondylitis-induced kyphosis, as well as Scheuermann’s kyphosis.1,4 PCO allows for both sagittal and coronal correction and involves removal of all posterior ligaments as well as facetectomy in order to allow for posterior compression of the osteotomy. For each level of the spinal column an PCO is performed on, a range of 9.3° to 10.7° of correction is achieved, with a ratio of approximately 1° of correction for every 1 mm of bone resected.2,5,6

PSO is a transpedicular wedge osteotomy that may also provide significant sagittal and coronal correction in spinal deformity. The PSO was first described by Thomasen in 1985 for correction of ankylosing spondylitis-induced kyphosis, though Heining et al. described a variant of the PSO in the same year.7,8 In the PSO, after the transpedicular wedge is removed, the posterior spine is shortened using the anterior spine as a hinge to close the osteotomy and correct the deformity. Depending on the level of resection, a single-level of PSO results in 30° to 40° of correction.5,6,8

Comparisons between any level PCO and PSO have had mixed results, with one meta-analysis reporting a similar therapeutic ability for the correction of thoracolumbar deformity, and another meta-analysis reporting a mean of 8.74° greater corrective ability of PSO.10,11 However, considering that single and double level PSO’s were included, this finding is understandable. In terms of complications, PCO is a generally simpler and less labor-intensive procedure with a mean of 806 mL less blood loss than PSO.10 The rate of neurologic and system complications was found to be similar between the procedures.10,11

Given the cited ranges of correction, a 3-level PCO may provide a similar therapeutic effect as a single-level PSO of at least 30° of correction. However, the complication profile between these procedures has not been extensively investigated. Cho et al.9 compared 3-level PCO (n = 30) and single-level PSO (n = 41) in the correction of sagittal imbalance in kyphosis, finding identical degrees of correction and operating time. There was, however, a greater chance of overcorrecting the patient into concavity with PCO, and substantially greater amount of blood loss in PSO. Additionally, Lau et al.12 retrospectively compared PCO and 3-column osteotomy via PSO in the correction of cervicothoracic deformity in 95 patients. There was no significant difference in complication rates in this study, although the procedures were performed for different indications in the separate study groups. Considering the 2 procedures achieve similar sagittal correction, the purpose of the current study is to thoroughly assess the difference in complication profiles between 3-level PCO and single-level PSO and to assess utilization trends between the 2 procedures via retrospective analysis of a national database.

MATERIALS AND METHODS

Patients were identified using the PearlDiver Mariner Database (PearlDiver Technologies, Fort Wayne, IN, USA), which includes records from more than 90 million patients from 2010 to 2020. The database includes inpatient and outpatient records of demographics, diagnoses, and procedures from both private and public insurance. Informed consent was waived due to the retrospective nature of the study and Institutional Review Board approval was not required as the database is deidentified.

Using International Classification of Disease (ICD), 9th (ICD-9) and 10th (ICD-10) edition and Current Procedural Terminology codes, patients with degenerative spinal disease were identified (Supplementary Table 1). Patients were then separated into 2 cohorts based on the index procedure that they received for their degenerative spine disease: (1) 3-level PCO or (2) single-level PSO. The 2 treatment cohorts were then further categorized based on the number of fused posterior segments: (1) 2 segments, (2) 3 to 6 segments, (3) 7 to 12 segments, and (4) 13 or more segments. Patients were excluded if they were under 18 years of age, if they had a history of spinal malignancy, spinal infection or spinal trauma, or if they underwent a posterior fusion of less than 3 segments.

The primary outcomes of this study were systemic and procedure-related complications within 30 days of the index procedure. The following complications were assessed: wound complications, venous thromboembolism (VTE), stroke, respiratory complications (pneumonia, acute respiratory failure), cardiac complications (myocardial infarction, acute heart failure, cardiogenic shock), renal complications (acute renal failure, urinary tract infection, renal infarction), sepsis, pressure ulcer, dural tear, delirium, neurologic injuries (injury to spinal cord or nerve roots, plegias, cauda equina syndrome, radiculopathies), postoperative hematoma, and postoperative anemia. Secondary outcomes included patient age, sex, and year of procedure to assess trends in 3-level PCO compared to single-level PSO.

Data normality was assessed and continuous variables were analyzed using Student t-test or Mann-Whitney U-test for para-
metric and nonparametric distributions respectively. To compare rates of complications between PCO and PSO cohorts, the 2 cohorts were matched at a 1:1 ratio based on age, sex, Elixhauser comorbidity index (ECI) and number of fused posterior segments. The rates of complications in the 2 matched cohorts were then compared using chi-square tests. Odds ratios are reported with 95% confidence intervals with an alpha of 0.05.

RESULTS

Among patients with a diagnosis of degenerative spine disease, a total of 4,582 patients underwent PCO while 675 under-

Table 1. Demographic data for patients who underwent 3-level posterior column osteotomy (PCO) and single-level pedicle subtraction osteotomy (PSO)

<table>
<thead>
<tr>
<th>Variable</th>
<th>3-Level PCO (n)</th>
<th>Single-level PSO (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 4,582)</td>
<td>3 to 6* (n = 2,534)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td>27 (0.6)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>20–24</td>
<td>81 (1.7)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>25–29</td>
<td>65 (1.4)</td>
<td>12 (0.5)</td>
</tr>
<tr>
<td>30–34</td>
<td>80 (1.7)</td>
<td>28 (1.1)</td>
</tr>
<tr>
<td>35–39</td>
<td>99 (2.2)</td>
<td>42 (1.7)</td>
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<tr>
<td>40–44</td>
<td>205 (4.5)</td>
<td>124 (4.9)</td>
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<td>45–49</td>
<td>297 (6.5)</td>
<td>154 (6.1)</td>
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<td>50–54</td>
<td>414 (9.0)</td>
<td>237 (9.4)</td>
</tr>
<tr>
<td>55–59</td>
<td>644 (14.1)</td>
<td>345 (13.6)</td>
</tr>
<tr>
<td>60–64</td>
<td>789 (17.2)</td>
<td>418 (16.5)</td>
</tr>
<tr>
<td>65–69</td>
<td>836 (18.2)</td>
<td>430 (17.0)</td>
</tr>
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<td>878 (19.2)</td>
<td>460 (18.2)</td>
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<td>75–79</td>
<td>447 (9.8)</td>
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</tr>
<tr>
<td>80–84</td>
<td>57 (1.2)</td>
<td>37 (1.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>2,778 (60.6)</td>
<td>1,405 (55.4)</td>
</tr>
<tr>
<td>Male</td>
<td>1,804 (39.4)</td>
<td>1,129 (44.6)</td>
</tr>
<tr>
<td>Year</td>
<td></td>
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<tr>
<td>2010</td>
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<td>2011</td>
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<td>2019</td>
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<tr>
<td>2020</td>
<td>475</td>
<td>256</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or number. Cumulative categories which were comprised of fewer than 10 patients were calculated using a value of 5 as a standardized median value. This was done in adherence with population data reporting standards to uphold patient confidentiality.

*No. of fused posterior segments.
went PSO. The majority of patients in both PCO and PSO cohorts were female (60.6% vs. 63.3%, p = 0.92) and under age 65 (58.9% vs. 60.2%). Age distribution was, however, significantly different between groups, with PCO being utilized more commonly within younger age groups (p < 0.001) (Table 1). Utilization rates for PSO overall increased from 38 in 2010 to 101 in 2017 (+166%), followed by a decline (-59.4%) in procedure volume to 41 cases in 2021. In contrast, PCO utilization maintained a steady increase from 246 cases in 2010 to 665 by end of 2019 (+170% overall); PCO utilization, however, similarly declined in 2020 to 475 procedures (-28.7%), albeit to a lesser degree compared to PSO. Annual utilization trends for PCO and PSO are depicted in Fig. 1 with case numbers further stratified by number of involved segments in Table 1.

In the PCO cohort, 2,534 (55.3%) had 3 to 6 fused segments, 1,470 (32.1%) had 7 to 12 fused segments, and 578 (12.6%) had 13 or more fused segments. In the PSO cohort, 229 (32.6%) had 3 to 6 fused segments, 359 (51.1%) had 7 to 12 fused segments, and 114 (16.2%) had 13 or more fused segments.

1. 30-Day Complications

In the PCO cohort, a total of 2,216 patients (48.4%) experienced a 30-day complication (Table 2). The most prevalent complications were postoperative anemia (1,178; 25.7%) and neurological injury (819, 16.6%). In the PSO cohort, a total of 390 patients (57.8%) experienced a 30-day complication, wherein the most prevalent complications were postoperative anemia (220, 32.6%) and respiratory complications (127, 18.8%).

2. Matched Cohorts

The PCO and PSO cohorts underwent 1:1 nearest neighbor propensity-score matching to account for age, sex, ECI, and number of segments fused as covariates. There were 631 patients in both cohorts (Table 3). In the chi-square analysis, PCO patients had decreased odds of having a respiratory complication (OR, 0.58; 95% CI, 0.43–0.82; p = 0.001) or renal complication (OR, 0.59; 95% CI, 0.40–0.88; p = 0.009) when compared to PSO patients. Notably, there were no significant differences between PCO and PSO with respect to postoperative anemia (28.1% vs. 30.4%, p = 0.353) and neurological injury (16% vs. 14.4%, p = 0.433), which were the most prevalent complications seen with

---

**Table 2.** Postoperative complication rates of patients who underwent 3-level posterior column osteotomy (PCO) and single-level pedicle subtraction osteotomy (PSO) across varying number of posterior segments fused

<table>
<thead>
<tr>
<th>Variable</th>
<th>3-Level PCO (n)</th>
<th>Single-level (PSO) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>3 to 6*</td>
</tr>
<tr>
<td>Wound complications</td>
<td>153</td>
<td>75</td>
</tr>
<tr>
<td>VTE</td>
<td>146</td>
<td>55</td>
</tr>
<tr>
<td>Stroke</td>
<td>30</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Hematoma</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Anemia</td>
<td>1,178</td>
<td>489</td>
</tr>
<tr>
<td>Transfusion</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>429</td>
<td>123</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>98</td>
<td>39</td>
</tr>
<tr>
<td>Renal complications</td>
<td>351</td>
<td>154</td>
</tr>
<tr>
<td>Sepsis</td>
<td>85</td>
<td>35</td>
</tr>
<tr>
<td>All</td>
<td>2,216</td>
<td>1,034</td>
</tr>
</tbody>
</table>

*No. of fused posterior segments.
PCO prior to propensity-matching. No other differences were seen for rates of 30-day wound complications, VTE, cardiac complications, sepsis, delirium (all \( p > 0.05 \)). We were unable to determine differences in stroke, hematoma, pressure ulceration, and dural tear due to insufficient power.

**DISCUSSION**

In the present study, patients who underwent single-level PSO were found to have increased rates of 30-day respiratory and renal complications when compared to those who underwent 3-level PCO when matched based on age, sex, ECI, and segments fused. There was no difference in rate of 30-day wound complications, VTE, anemia, cardiac, sepsis, delirium, and neurologic complications. Overall, there was a 49.9% complication rate in patients undergoing 3-level PCO and a 55.2% complication rate in patients undergoing single-level PSO, which was not significantly different.

While there has been an abundance of published studies discussing the differences in sagittal correction between PCO and PSO, data on complication rates between PCO and PSO is limited.\(^6,9,13-15\) Liu et al.\(^16\) published a meta-analysis of patients with ankylosing spondylitis undergoing either PCO or PSO and compared outcomes, including medical complications. In total, 441 patients were included in the PCO cohort and 512 in the PSO cohort. The majority of patients underwent single-level procedures. They found no significant difference in terms of dural tear, neurologic complication, implant related complications, infection, aortic rupture, death, and total complications. Average blood loss was found to be 2,012 mL in the PSO cohort and 1,307 mL in the PCO cohort. Operative time was also found to be longer for PSO (4.0 hours vs. 3.1 hours).

Hu et al.\(^10\) published a similar meta-analysis comparing 120 patients who underwent PCO to 300 patients who underwent PSO for the treatment of ankylosing spondylitis. The majority of patients underwent single or 2-level PCO and single-level PSO. Similar to Liu et al.\(^16\) they found that PSO had increased blood loss compared to PCO. There was no difference in rates of neurologic, dural, or systemic complications.

The present matched cohorts comparing 3-level PCO to single-level PSO is the largest study to date to assess systemic complications and the safety profile between these 2 procedures. We found the only significant differences in 30-day complications to be decreased respiratory and renal complications in the PCO cohort. There was no difference in postoperative anemia, which differs from previous reports stating that PSO leads to increased blood loss compared to PCO.\(^10,16\) However, these studies largely compared single-level PCO to single-level PSO, whereas the present study directly compared 3-level PCO to single-level PSO. Furthermore, postoperative anemia does not necessarily corre-

### Table 3. Postoperative complication rates of matched cohorts of patients who underwent 3-level posterior column osteotomy (PCO) and single-level pedicle subtraction osteotomy (PSO)

<table>
<thead>
<tr>
<th>Variable</th>
<th>3-Level PCO (n)</th>
<th>Single-level PSO (n)</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound complications</td>
<td>29 (4.6)</td>
<td>25 (4.0)</td>
<td>1.168</td>
<td>0.534–1.714</td>
<td>0.578</td>
</tr>
<tr>
<td>VTE</td>
<td>14 (2.2)</td>
<td>25 (4.0)</td>
<td>0.550</td>
<td>0.384–1.318</td>
<td>0.078</td>
</tr>
<tr>
<td>Stroke</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hematoma</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>177 (28.1)</td>
<td>192 (30.4)</td>
<td>0.891</td>
<td>0.734–1.201</td>
<td>0.353</td>
</tr>
<tr>
<td>Transfusion</td>
<td>12 (1.9)</td>
<td>15 (2.4)</td>
<td>0.891</td>
<td>0.369–1.715</td>
<td>0.353</td>
</tr>
<tr>
<td>Respiratory</td>
<td>74 (11.7)</td>
<td>116 (18.4)</td>
<td>0.590</td>
<td>0.431–0.818</td>
<td>0.001*</td>
</tr>
<tr>
<td>Cardiac</td>
<td>19 (3.0)</td>
<td>20 (3.2)</td>
<td>0.948</td>
<td>0.596–2.045</td>
<td>0.871</td>
</tr>
<tr>
<td>Renal</td>
<td>44 (7.0)</td>
<td>71 (11.3)</td>
<td>0.591</td>
<td>0.399–0.876</td>
<td>0.009*</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15 (2.4)</td>
<td>12 (1.9)</td>
<td>1.256</td>
<td>0.583–2.708</td>
<td>0.560</td>
</tr>
<tr>
<td>Pressure ulcer</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dural tear</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Delirium</td>
<td>37 (5.9)</td>
<td>52 (8.2)</td>
<td>0.694</td>
<td>0.495–1.181</td>
<td>0.101</td>
</tr>
<tr>
<td>Neurologic injury</td>
<td>101 (16.0)</td>
<td>91 (14.4)</td>
<td>1.131</td>
<td>0.792–1.405</td>
<td>0.433</td>
</tr>
<tr>
<td>All</td>
<td>315/631 (49.9)</td>
<td>348/631 (55.2)</td>
<td>0.811</td>
<td>0.649–1.011</td>
<td>0.063</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism.

*\( p < 0.05 \), statistically significant differences.
late with intraoperative blood loss. While our study observed a higher incidence of neurological complications amongst with 3-level PCO (16.6%) than that reported within the literature, this was likely attributed to several contributive factors including our sole inclusion of 3-level procedures compared to single-level procedures in other studies, reporting of transient neuropraxias within the immediate postoperative period, and inherent discrepancies associated with use of ICD coding across institutions. Nonetheless, incidence of neurological injury remained comparable between matched PCO and PSO cohorts, which is concordant with other studies comparing multilevel PCO and PSO for deformity correction. Additionally, we provide data on 30-day cardiac complications, wound complications, VTE rates, sepsis, and delirium, which have not been reported on previously in the literature. We did not find any significant differences between the 2 cohorts in terms of these complications.

Trends of 3-level PCO compared to single-level PSO were also assessed. We found that the rate of 3-level PCO increased from 2010 to 2019, whereas PSO increased from 2010 to 2017 and then saw a steady decline. Both procedures decreased in 2020, likely due to the COVID-19 pandemic. The decline in utilization of PSO starting 2017 and the steady increase in PCOs likely indicates that more surgeons are utilizing PCOs when possible, perhaps due to the decreased blood loss reported in the literature and because PCO is purported to be less labor intensive. While PCOs seemingly offer a technique which place less physiological demands on patients undergoing ASD surgery, it is also important to highlight the advent of minimally invasive techniques such as mini-open PSO, which could further improve clinical outcomes in ASD patients who are appropriately indicated.

There are several limitations to this study. Like all database studies, it is inherently limited by reliance on accurate medical coding. Second, we were unable to assess sagittal correction between the 2 procedures, as radiographic data is not available in the database. Third, we did not report on reoperation or hardware failure as it was outside the scope of this study. While the use of ICD-9 and ICD-10 diagnosis codes precluded our study from accurately evaluating mechanical complication rates, further research incorporating machine-learning based algorithms could substantially improve risk prediction amongst various osteotomy techniques. Doing so would additionally refine indications for patients undergoing ASD surgery and would better individualize operative treatment strategies for this complex patient population. Nonetheless, despite these limitations, our study is the first to assess nationwide PCO and PSO trends in which we are aware of, and presents an important area of further research.

**CONCLUSION**

In conclusion, 3-level PCO utilization increased steadily throughout the study period, whereas single-level PSO utilization peaked in 2017 and has since seen a steady decline. Patients who undergo 3-level PCO are at decreased risk of renal and respiratory complications compared to patients undergoing single-level PSO. There was no difference in rate of 30-day wound, VTE, anemia, cardiac, sepsis, delirium, and neurologic, and overall complications. Considering the 2 procedures achieve similar sagittal correction, it is important for surgeons to be aware that 3-level PCO has an improved safety profile compared to single-level PSO.

**NOTES**

**Supplementary Material:** Supplementary Table 1 can be found via [https://doi.org/10.14245/ns.2346222.111](https://doi.org/10.14245/ns.2346222.111).

**Conflict of Interest:** Emily S. Mills MD, Kevin Mertz BS, Ethan Faye BS, Jennifer A. Bell MD, Andy T. Ton BS have nothing to disclose. Jeffrey C. Wang has received intellectual property royalties from Zimmer Biomet, NovApproach, SeaSpine, and DePuy Synthes. Ram K. Alluri, MD discloses has received grant funding from NIH, consulting fees from HIA Technologies, and payment from Eccentric Robotics for lectures and presentations. Raymond J. Hah MD has received grant funding from SI bone, consulting fees from NuVasive, and support from the North American Spine Society to attend meetings.

**Author Contribution:** Conceptualization: ESM, RJH; Formal analysis: KM; Methodology: ESM, KM; Visualization: ATT; Writing - original draft: ESM, EF, KM; Writing - review & editing: ESM, EF, JAB, ATT, JCW, RKA, RJH.

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REFERENCES


Vertebral Body Sliding Osteotomy as a Surgical Strategy for the Treatment of Cervical Myelopathy: Complications and Pitfalls

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²Department of Orthopedic Surgery, Ilsan Paik Hospital, Inje University, Goyang, Korea

Objective: This retrospective cohort study has been aimed at evaluating the incidence of complications after vertebral body sliding osteotomy (VBSO) and analyzing some cases. Furthermore, the complications of VBSO were compared with those of anterior cervical corpectomy and fusion (ACCF).

Methods: This study included 154 patients who underwent VBSO (n = 109) or ACCF (n = 45) for cervical myelopathy and were followed up for > 2 years. Surgical complications, clinical and radiological outcomes were analyzed.

Results: The most common surgical complications after VBSO were dysphagia (n = 8, 7.3%) and significant subsidence (n = 6, 5.5%). There were 5 cases of C5 palsy (4.6%), followed by dysphonia (n = 4, 3.7%), implant failure (n = 3, 2.8%), pseudoarthrosis (n = 3, 2.8%), dural tears (n = 2, 1.8%), and reoperation (n = 2, 1.8%). C5 palsy and dysphagia did not require additional treatment and spontaneously resolved. The rates of reoperation (VBSO, 1.8%; ACCF, 11.1%; p = 0.02) and subsidence (VBSO, 5.5%; ACCF, 40%; p < 0.01) were significantly lower in VBSO than in ACCF. VBSO restored more C2–7 lordosis (VBSO, 13.9° ± 7.5°; ACCF, 10.1° ± 8.0°; p = 0.02) and segmental lordosis (VBSO, 15.7° ± 7.1°; ACCF, 6.6° ± 10.2°; p < 0.01) than ACCF. The clinical outcomes did not significantly differ between both groups.

Conclusion: VBSO has advantages over ACCF in terms of low rate of surgical complications related to reoperation and significant subsidence. However, dural tears may still occur despite the lessened need for ossified posterior longitudinal ligament lesion manipulation in VBSO; hence, caution is warranted.

Keywords: Cervical vertebrae, Osteotomy, Complications, Spondylosis, Ossification of posterior longitudinal ligament

INTRODUCTION

Vertebral body sliding osteotomy (VBSO) is a surgical technique for treating cervical myelopathy by anteriorly translating the vertebral body with spondylotic or ossified posterior longitudinal ligament (OPLL) lesions.¹ It has been known to have several advantages over other anterior cervical decompression techniques, including anterior cervical corpectomy and fusion (ACCF) or anterior cervical discectomy and fusion (ACDF).²,³ The strengths of VBSO are a faster fusion rate, restoration of cervical lordosis, short operation time, low amount of blood loss, and low risk of dural tears.¹,⁷

While the advantages of VBSO have been reported by previous studies, not much has been reported regarding the complications and pitfalls of VBSO. Despite the theoretical benefits of this technique, VBSO may not be free from complications. Ap-
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Fig. 1. Patient selection process. VBSO, vertebral body sliding osteotomy; ACCF, anterior cervical corpectomy and fusion.

MATERIALS AND METHODS

1. Study Design and Patients

We retrospectively reviewed the data of all 218 patients who underwent VBSO and ACCF between 2006 and 2020. All of the surgeries were performed by 1 surgeon (DHL). Since 2011, VBSO has been conducted and has been given priority over ACCF in cases of OPLL or spondylotic cervical myelopathy requiring corpectomy. And the study only included patients who underwent VBSO procedures after 2012, considering the learning curve with this procedure. This retrospective study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB number: 2022-0840). All procedures were carried out in compliance with the tenets of the Declaration of Helsinki. The inclusion criteria were patients diagnosed with cervical myelopathy and followed up for more than 2 years. Cases that required only 1 or 2 levels of vertebral body sliding were included for VBSO, while cases that necessitated sliding for 3 or more levels underwent posterior or combined surgery and were excluded from this study. Furthermore, in cases where there is a local lesion around the endplate rather than a pathological lesion throughout the vertebral body at the cephalad and caudal levels in VBSO, the problem lesion was removed through discectomy and trumpet osteotomy procedure without sliding. In the case of ACCF, only one vertebral body corpectomy was included. Additionally, the following cases were also excluded from the study: (1) prior cervical spine surgery; (2) diagnosis of a tumor, infection, or fracture at the cervical spine; (3) OPLL or spondylotic lesions at a high level of the cervical spine; and (4) simultaneous posterior cervical fusion (Fig. 1).

2. Variables

Data on age, sex, past medical history, smoking status, body mass index, operating time, length of hospital stay, follow-up period, the number of involved levels of surgery, and complications were collected from medical records. Neck pain visual analogue scale (VAS), Neck Disability Index (NDI), and Japanese Orthopedic Association (JOA) scores for clinical evaluation and C2–7 lordosis, segmental lordosis, C2–7 sagittal vertical axis (SVA), fusion status, and significant subsidence were evaluated for radiological assessment.

Analysis of complications was divided into 2 categories: perioperative and delayed complications. Complications were clas-
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Reoperation was independently analyzed as it was performed perioperatively or delayed depending on specifically related complications.

3. Statistical Analysis

Parametric statistical analyses were performed for normally distributed variables and nonparametric statistical analyses for other variables. Comparisons of the continuous variables of each group were performed using independent sample t-tests. For nominal variables, Fisher exact test or chi-square test was performed. The paired t-test was performed to analyze changes in postoperative values compared with preoperative values. Interobserver and intraobserver agreements were assessed using the intraclass correlation coefficient (ICC) and kappa coefficient. The kappa coefficients for the intraobserver reliability were 0.926 for fusion status and 0.89 for significant subsidence. The ICC for intraobserver reliability for the measurement of subsidence was 0.871. The ICCs for sagittal alignments were 0.968 (C2–7 lordosis), 0.935 (segmental lordosis), and 0.913 (C2–7 SVA).

All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 154 patients followed up for more than 2 years were included in this retrospective study (VBSO, n = 109; ACCF, n = 45). The VBSO group included 73 men and 36 women (mean age, 59.3 ± 9.8 years). There were no significant age and sex differences between the VBSO and ACCF groups.

The number of levels involved in the operation was significantly higher in the VBSO group (2.8 ± 0.4) than in the ACCF group (2.0 ± 0.0) (p < 0.01). The operation time and length of hospital stay of the VBSO group were not significantly different from those of the ACCF group (operation time: 210.2 ± 37.6 minutes vs. 203.9 ± 29.6 minutes; p = 0.21; length of hospital stay: 5.7 ± 3.4 days vs. 6.2 ± 3.4 days; p = 0.26). The patient characteristics are summarized in Table 1.

Among the surgical complications, the incidence of dysphagia (n = 8, 7.3%) was the highest, followed by a significant subsidence.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VBSO (n = 109)</th>
<th>ACCF (n = 45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>73 (67.0)</td>
<td>25 (55.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.3 ± 9.8</td>
<td>62.1 ± 9.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>44.8 ± 23.2</td>
<td>82.8 ± 47.7</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>No. of involved levels</td>
<td>2.8 ± 0.4</td>
<td>2.0 ± 0.0</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>OPLL</td>
<td>85 (78.0)</td>
<td>9 (20.0)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>DM</td>
<td>14 (12.8)</td>
<td>4 (8.9)</td>
<td>0.49</td>
</tr>
<tr>
<td>HTN</td>
<td>22 (20.2)</td>
<td>12 (26.7)</td>
<td>0.38</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2 (1.8)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 3.2</td>
<td>24.5 ± 3.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>16 (14.7)</td>
<td>5 (11.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>210.2 ± 37.6</td>
<td>203.9 ± 29.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>5.7 ± 3.4</td>
<td>6.2 ± 3.4</td>
<td>0.26</td>
</tr>
</tbody>
</table>

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

Student t-test was used to analyze the age, follow-up period, number of involved levels, BMI, operation time, and hospital stay days; chi-square test or Fisher exact test was used to analyze the number of patients, DM, HTN, malignancy, and current smoker.

*p < 0.05, statistically significant differences.

Table 2. Comparison of surgical complication between the 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>VBSO</th>
<th>ACCF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic deterioration</td>
<td>0 (0)</td>
<td>2 (4.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dural tear</td>
<td>2 (1.8)</td>
<td>1 (2.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>8 (7.3)</td>
<td>6 (13.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>4 (3.7)</td>
<td>2 (4.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>C5 palsy</td>
<td>5 (4.6)</td>
<td>0 (0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Delayed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft dislodgement</td>
<td>0 (0)</td>
<td>2 (4.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Infection</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Implant failure</td>
<td>3 (2.8)</td>
<td>4 (8.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Significant subsidence</td>
<td>6 (5.5)</td>
<td>18 (40)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>Pseudarthrosis</td>
<td>3 (2.8)</td>
<td>4 (8.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reoperation</td>
<td>2 (1.8)</td>
<td>5 (11.1)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Student t-test was used to analyze the age, follow-up period, number of involved levels, BMI, operation time, and hospital stay days; chi-square test or Fisher exact test was used to analyze the number of patients, DM, HTN, malignancy, and current smoker.

*p < 0.05, statistically significant differences.
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Table 3. Clinical and radiological outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>VBSO</th>
<th>ACCF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck pain VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>3.1 ± 2.6</td>
<td>3.8 ± 2.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Final</td>
<td>2.2 ± 2.2</td>
<td>2.4 ± 2.6</td>
<td>0.39</td>
</tr>
<tr>
<td>NDI</td>
<td>13.9 ± 8.3</td>
<td>17.7 ± 11.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Final</td>
<td>8.8 ± 6.8</td>
<td>9.6 ± 6.4</td>
<td>0.33</td>
</tr>
<tr>
<td>JOA</td>
<td>13.4 ± 2.3</td>
<td>14.7 ± 1.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Preoperative</td>
<td>15.2 ± 1.9</td>
<td>15.9 ± 1.1</td>
<td>0.08</td>
</tr>
<tr>
<td>JOA recovery rate</td>
<td>49.9 ± 40.8</td>
<td>48.4 ± 43.9</td>
<td>0.46</td>
</tr>
<tr>
<td>Preoperative alignment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2–7 lordosis (°)</td>
<td>8.5 ± 6.7</td>
<td>7.5 ± 8.5</td>
<td>0.26</td>
</tr>
<tr>
<td>Segmental lordosis (°)</td>
<td>2.2 ± 12.1</td>
<td>0.4 ± 10.0</td>
<td>0.21</td>
</tr>
<tr>
<td>C2–7 SVA (mm)</td>
<td>20.2 ± 12.1</td>
<td>19.7 ± 12.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Final alignment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2–7 lordosis (°)</td>
<td>13.9 ± 7.5</td>
<td>10.1 ± 8.0</td>
<td>0.02*</td>
</tr>
<tr>
<td>Segmental lordosis (°)</td>
<td>15.7 ± 7.1</td>
<td>6.6 ± 10.2</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>C2–7 SVA (mm)</td>
<td>19.9 ± 9.4</td>
<td>18.9 ± 10.8</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
VBSO, vertebral body sliding osteotomy; ACCF, anterior cervical corpectomy and fusion; VAS, visual analogue scale; NDI, Neck Disability Index; JOA, Japanese Orthopedic Association; seg, segmental; SVA, sagittal vertical axis.
All variables were analyzed using the Student t-test.
*p < 0.05, statistically significant differences.

The clinical and radiological outcomes are summarized in Table 3. There were no significant differences between VBSO and ACCF in terms of neck pain VAS, NDI, and JOA scores. The final radiological alignments showed that C2–7 lordosis (p = 0.02) and segmental lordosis (p < 0.01) were more restored in the VBSO group (C2–7 lordosis, 13.9° ± 7.5°; segmental lordosis, 15.7° ± 7.1°) than in the ACCF group (C2–7 lordosis, 10.1° ± 8.0°; segmental lordosis, 6.6° ± 10.2°).

DISCUSSION

Based on the results of our study, previously unreported complications were noted, including reoperation, C5 palsy, dysphagia, and implant failure. One case of dural tear was reported from this retrospective review in addition to previous reports.3,5 But when VBSO was compared to ACCF, it was found to be a safe surgical technique with significantly lower reoperation and subsidence rates.

1. Reoperation

Even though few studies have compared reoperation rates after anterior cervical fusion surgery for cervical myelopathy, ACCF is known for having a higher reoperation rate than ACDF.9,10 And like the ACDF group in the previous study, the reoperation rate (n = 2, 1.8%) in the VBSO group was significantly lower than that of ACCF (n = 5, 11.1%; p = 0.02). All cases that needed reoperation were of radiculopathy that originated from adjacent segmental disease (ASD) after VBSO. In the systemic review by Carrier et al.,11 the ASD incidence for 1- or 2-level ACDF was reported to be 5.48%, higher than that of our study, for an average follow-up period of 106.5 months. The incidence of reoperation for ASD after VBSO should be further analyzed, as the follow-up period for VBSO was 44.8 months shorter than in the previous study. Contrary to the VBSO group in which ASD was the main cause of reoperation, hematoma evacuation (n = 2) and graft dislodgement (n = 1) were the main reasons for reoperation surgery in the ACCF group. There were no cases of neurological deterioration, graft dislodgement, or infection after VBSO, compared with ACCF. Therefore, VBSO seems to be a safe surgical technique with no life-related complications.

2. Significant Subsidence

Severe subsidence is correlated with poor clinical outcomes after anterior cervical fusion surgery.12,13 Moreover, it may cause instability, neurological deterioration, and mechanical failure.14
Therefore, a lower significant subsidence rate in the VBSO group is a technical advantage of VBSO over ACCF. As the vertebral body was preserved and multiple screw fixations were performed in VBSO, the distribution of load stress was smaller and the lever arm affecting the vertebral body was shorter in the VBSO group, which provided a lower rate of significant subsidence in the VBSO group. Furthermore, as proven in the previous study, VBSO reached a stable construct earlier than in the ACCF group as the intra or extragraft bone bridging appeared faster in VBSO than in ACCF. None of the patients with significant subsidence needed special surgical treatment because they were free of symptoms or they achieved fusion early in VBSO. Compared to the ACCF group, there were no cases of graft dislodging in the VBSO group. This proves that the VBSO group gained stability faster.

3. Dural Tears

A surgical advantage of VBSO is the lack of the need to directly remove spondylotic or OPLL lesions. Therefore, contrary to ACCF, which directly manipulates and removes compressive lesions, VBSO is much more free from extensive dural defects. And only one case of dural tear after VBSO has been reported. However, from the retrospective review of all surgical complications, 2 cases of dural tears occurred during the resection of the posterior longitudinal ligament (PLL) (Fig. 2) and the accompanying unco-foraminotomy. For the anterior translation of the affected vertebral body with pathologic lesions, PLL resection should be performed behind the uppermost and lowermost discs (Fig. 3). During this procedure, a dural tear occurred, and a dural patch was used to seal the torn site. Another case of dural tear occurred during unco-foraminotomy, a routine procedure. Although VBSO was designed to decrease the complication rate of corpectomy, dural tears can still occur; hence, special care is needed when resecting the ligament around an OPLL mass or when performing accompanying procedures. Furthermore, patients with the wide-base type

Fig. 2. Representative case of dural tear during vertebral body sliding osteotomy. (A–C) A preoperative radiograph and computed tomography (CT) images. (D, E) Postoperative images with anteriorly translated C4 and C5. (F) CT images after posterior longitudinal ligament resection at C5-6-disc space. During resection, a dural tear occurred.
or continuous type of OPLL are not good candidates for VBSO.\(^1\) As these types make it difficult to resect PLL and anteriorly translate the vertebral body, dural tears could occur during the procedure. For these patients, other techniques such as posterior decompression surgery or ACCF would be recommended. However, despite the higher proportion of OPLL in the VBSO patient group, there was no significant difference in the proportion of dural tear between the VBSO and ACCF groups. This is considered a clear advantage of VBSO not directly manipulating OPLL.

### 4. C5 Palsy

In the previous study by Lee et al.,\(^2\) more lordosis could be gained after VBSO than after ACCF. However, the rapid increase in cervical lordosis is known as a risk factor for C5 palsy after anterior cervical fusion surgery.\(^15\) Even though there was no significant difference in C5 palsy rates between the 2 groups, the number of C5 palsy cases was not ignorable in the VBSO group (n = 5, 4.6%). While there was no case of C5 palsy in the ACCF group, it was reported as the second most common perioperative surgical complication following dysphagia in the VBSO group. The VBSO level of the patients with C5 palsy included all of C5 vertebra. However, all C5 palsy patients recovered spontaneously within 1 year of follow-up (Table 4). In the cases of severe C5 palsy, the motor grade decreased from grade 4+ to grade 2. However, all patients recovered to a minimum motor grade of 4 or higher. Therefore, close observation with reassurance during the follow-up period is essential as the patients recover from C5 palsy. However, since the number of patients with C5 palsy is still small, further studies may be needed to analyze this issue.

### 5. Dysphagia

Dysphagia frequently occurs following anterior approach-related cervical surgeries, including ACDF and ACCF.\(^16-18\) In the previous study, dysphagia was the most common complication following ACDF, observed in 9.5% of patients.\(^16\) The rate of dysphagia in our study was 7.3% in VBSO and 13.3% in ACCF. Dysphagia was the most frequent VBSO-related complication in this study. However, all cases were mild dysphagia that did not require treatment.

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Table 4. Clinical data of C5 palsy patients after vertebral body sliding osteotomy

<table>
<thead>
<tr>
<th>Age (yr)/sex</th>
<th>Length of hospital stay (day)</th>
<th>Operation time (min)</th>
<th>VBPO level</th>
<th>OPLL/spondylosis</th>
<th>Foraminotomy side</th>
<th>Change in C2–7 lordosis (°)</th>
<th>Palsy side</th>
<th>Motor grade</th>
<th>Duration (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>56/M</td>
<td>8</td>
<td>165</td>
<td>C5</td>
<td>OPLL</td>
<td>x</td>
<td>2</td>
<td>Both</td>
<td>2/4</td>
<td>4</td>
</tr>
<tr>
<td>53/M</td>
<td>4</td>
<td>188</td>
<td>C5, 6</td>
<td>OPLL</td>
<td>Right</td>
<td>4</td>
<td>Right</td>
<td>3/5</td>
<td>3</td>
</tr>
<tr>
<td>66/M</td>
<td>8</td>
<td>480</td>
<td>C5, 6</td>
<td>OPLL</td>
<td>x</td>
<td>15</td>
<td>Both</td>
<td>2/3</td>
<td>12</td>
</tr>
<tr>
<td>54/F</td>
<td>19</td>
<td>235</td>
<td>C4, 5</td>
<td>OPLL</td>
<td>x</td>
<td>5</td>
<td>Right</td>
<td>4/5</td>
<td>1</td>
</tr>
<tr>
<td>76/M</td>
<td>3</td>
<td>210</td>
<td>C5, 6</td>
<td>Spondylosis</td>
<td>Bilateral</td>
<td>0</td>
<td>Right</td>
<td>2/5</td>
<td>11</td>
</tr>
</tbody>
</table>

VBSO, vertebral body sliding osteotomy; OPLL, ossification of the posterior longitudinal ligament; C, cervical vertebra.
not need special treatment. Even though the vertebral body is anteriorly translated in the VBSO procedure, the protruded body is removed for anterior plating. Therefore, it is considered that the incidence of dysphagia was not particularly high compared to ACCF.

6. Other Complications
Implant failures, including screw breakage (n = 1) and pull-out (n = 2), were observed during the follow-up period in the VBSO group. However, none of the cases needed revision surgery (Fig. 4). The acquisition of stabilization with an earlier fusion rate would minimize the possibility of reoperation surgery from implant failure. In addition, dysphonia and pseudoarthrosis were observed in the VBSO group, but the rate of complications was not significantly different from that in the ACCF group. In the case of pseudoarthrosis in VBSO, additional surgical treatment was not performed because there were no related symptoms. Dysphonia could occur during anterior approach-based cervical surgeries, especially when the recurrent laryngeal nerve was damaged.9-22 During the approach, special care would be needed to prevent this complication by avoiding cauterization, retraction, or pressurization.9

This study has some limitations. First, VBSO has been preferentially performed rather than ACCF in cervical myelopathy patients since 2012, which has made the number of patients in the VBSO and ACCF groups inevitably disparate. However, the number of VBSO patients, which was only 20–40 in previous studies, increased significantly up to 109 patients in the current study, and they showed a higher variety of complications than those in previous studies.3-5 Second, the follow-up periods of VBSO and ACDF were significantly different, which possibly affected the delayed complication rates. However, most of the delayed complications, including graft dislodgment, subsidence, implant failure, and pseudoarthrosis, were associated with instability after surgery. Considering that the fusion rates at a minimum of 2 years after surgery were not significantly different between the groups,4 we believe that there would not be much difference in the complication rates with a longer follow-up period in the VBSO group. Finally, the study is not free from potential bias due to the retrospective study design. In the future, a prospective study comparing VBSO and ACCF based on the same pathology will be necessary.

CONCLUSION
In the present study, all surgical complications related to VBSO were reviewed and compared with those related to ACCF, and it showed that VBSO has obvious advantages over ACCF in terms of the low rate of surgical complications related to reoperation and significant subsidence. However, dural tears may still occur despite the lesser need for OPLL lesion manipulation in VBSO; thus, caution is warranted. As C5 palsy and mild dysphagia could occur after VBSO, patients need to be followed up and reassured that most cases spontaneously recover.

NOTES
Conflict of Interest: The authors have nothing to disclose.
Funding/Support: This study received no specific grant from

Fig. 4. Representative case of implant failure after C4–5 vertebral body sliding osteotomy. Preoperative (A) and postoperative day 2 (B) radiographs without implant failure. (C) Pull-out of the inserted screw was first observed at 1-month postoperative follow-up. (D) Final. The pulled-out screw did not show any change with a solid fusion state.
any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments: Portions of this work was presented in abstract form at the Cervical Spine Research Society (CSRS) 50th Annual meeting, in San Diego, California, on November 18, 2022.

Author Contribution: Conceptualization: DHL, STC, SP; Formal Analysis: STC, SP, CJH. Investigation: STC, SP, JHK; Methodology: DHL, STC, SP, CJH, JHC; Project Administration: DHL, STC, SP, CJH, JHC, JHK; Writing – Original Draft: STC, SP; Writing – Review & Editing: DHL, STC, SP, CJH, JHC, JHK.

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REFERENCES

Outcomes of Intramedullary Spinal Cord Tumor Surgery in Older Versus Younger Adults: A Multicenter Subanalysis Study by the Neurospinal Society of Japan

Hiroto Kageyama1,*, Kotaro Tatebayashi1,*, Shinichi Yoshimura1, Toshiki Endo2,3, Kazutoshi Hida4, Masaki Mizuno5; for the Investigators of Intramedullary Spinal Cord Tumors in the Neurospinal Society of Japan†

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5Department of Minimum-Invasive Neurospinal Surgery, Mie University, Mie, Japan

Objective: Intramedullary spinal cord tumors (IMSCTs) are uncommon and difficult to treat. Studies examining the efficacy of rare IMSCT surgery in the elderly are limited. We conducted a subanalysis using multicenter retrospective-historical data provided by the Japan Neurospinal Society to compare surgical outcomes between older and younger adults with IMSCTs.

Methods: We classified patients with IMSCTs into younger (aged 18–64 years) or older (≥ 65 years) groups. The primary outcomes of “improved” or “worsened” from the preoperative period to 6 months after surgery were evaluated using the modified McCormick scale (mMCs). A favorable outcome was defined as an mMCs grade of I/II at 6 months.

Results: Among 841 patients registered, there were 658 younger (78.2%) and 183 older patients (21.8%) evaluated using mMCs at 6 months. Median preoperative mMCs grades were significantly worse in older patients than in younger patients. Neither the “improved” nor “worsened” rate differed significantly between the groups (28.1% vs. 25.1%; crude odds ratio [cOR], 0.86; 95% confidence interval [CI], 0.59–1.25; adjusted OR [aOR], 0.84; 95% CI, 0.55–1.28; 16.9% vs. 23.0%; cOR, 1.47; 95% CI, 0.98–2.20; aOR, 1.28; 95% CI, 0.83–1.97). Favorable outcomes were significantly less common among older adults in the univariate analysis but were not significant in the multivariate analysis (66.4% vs. 53.0%; cOR, 0.57; 95% CI, 0.41–0.80; aOR, 0.77; 95% CI, 0.50–1.19). In both younger and older patients, preoperative mMCs accurately predicted favorable outcomes.

Conclusion: Age alone is not a sufficient reason to prohibit surgery for IMSCTs.

Keywords: Intramedullary spinal cord tumor, Modified McCormick scale, Older patients, Surgical outcome

INTRODUCTION

The elderly population is increasing rapidly worldwide, and a significant percentage of older adults undergo surgical procedures. There is an urgent issue to examine the surgical criteria that sustainably support the extension of healthy life expectancy. According to the World Population Prospects Report 2022, the global population aged ≥ 65 years is projected to rise from...
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10% in 2022 to 16% in 2050. Japan has the most rapidly aging population, with 28.9% Japanese aged >65 years in 2022. Japan is expected to create a role model for the elderly, including healthcare for patients with cancer. Although age is not a primary consideration for surgical risk generally, older patients have higher perioperative complications and mortality compared to younger patients, despite the advances in surgical and anesthetic techniques. All older adults undergoing surgery should undergo an assessment of frailty risk, including comorbidities, mobility, functional status, and nutrition.

Primary intramedullary spinal cord tumors (IMsCTs) represent a small fraction (2%-4%) of central nervous system tumors, with unique challenges posed by the surrounding tissues. IMsCTs can potentially lead to severe neurologic deterioration, decreased living function, poor quality of life, death, and spinal cord injury from thoughtless surgical intervention, which may directly lead to a poor functional prognosis. Studies examining the efficacy of rare IMsCT surgery in the elderly are limited; some papers have suggested patients aged >65 years with McCormick (modified McCormick scale, mMCs) grade IV or V where imaging suggests a high grade lesion may be better served with a biopsy/chemo/radiation. We tried to clarify what should be noted in IMsCT surgical management of the elderly, by comparing the characteristics and prognosis of IMsCTs in younger and older patients. Furthermore, to confirm whether age is an independent factor in determining the indication for IMsCT surgery and to validate the above suggestion, we conducted a subanalysis to compare surgical outcomes between older and younger adults with IMsCTs.

MATERIALS AND METHODS

We used real-world data derived from a multicenter historical cohort study authorized by the Neurospinal Society of Japan. This retrospective, noninvasive study consecutively enrolled patients with IMsCTs at 58 centers in Japan who were surgically treated between 2009 and 2020. The study protocol and demographic, clinical, and outcome data have been described. The institutional review boards of all 58 participating centers approved the study protocol. The requirement for written informed consent was waived because of the retrospective nature of the study. Instead, a public notice that provided information on this study was given to individual center websites.

1. Patients and Measurements

We excluded nonsurgical cases, spinal lipomas and myxopapillary ependymomas, cases that underwent external decompression only, and those that underwent surgery before 2008. Cavernous malformations are classified as vascular malformations and thus not assigned the World Health Organization classification. However, these IMsCTs may require surgical intervention, so they were included. We classified pediatric patients (<18 years), younger patients (aged 18–64 years), and older patients (≥65 years) based on the definition used by many countries, including Japan. Pediatric cases were excluded. We measured the level of disability using the mMCs and Karnofsky Performance Scale (KPS) and recorded death. For functional and performance status changes, when a patient remained at the same grade, we termed the pattern “stable” by using mMCs and mortality data. Changes in at least one mMCs grade or death, when compared to the preoperative status, were evaluated as “improved” or “worsened” as appropriate.

2. Outcomes

The primary outcome was the rate of an “improved” or “worsened” status from baseline to 6 months postoperatively and the rate of a favorable outcome, defined by mMCs grade I/II, which was evaluated 6 months after surgery. Secondary outcomes were the rates of a “worsened” status from the preoperative period to the immediate period after surgery and an “improved” status from the immediate period after surgery to 6 months, as well as the all-cause/tumor-related mortality rate at 6 months postoperatively and during follow-up. We also recorded intraoperative bleeding, operation time, the appearance of new neurologic symptoms, cerebrospinal fluid (CSF) leakage, postoperative hemorrhage, and surgical site infection.

3. Statistical Analysis

Categorical variables are presented as number (%) and were compared using the chi-square test. If the minimum expected count (or frequency) was <5, we used Fisher exact test. To compare multiple factors of categorical variables, multiple comparisons were performed after factor analysis using the chi-square test. Continuous variables are expressed as median (interquartile range [IQR]) and were compared using the Wilcoxon rank-sum test. Primary and secondary outcomes were compared between younger and older patient groups. We constructed multivariable conditional logistic regression models adjusted for the following variables: preoperative mMCs grade (grade I/II or grade III/IV/V), degree of removal (biopsy, partial resection, subtotal resection, total resection), and pathological findings (ependymoma, hemangioblastoma, astrocytoma, cavernous

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malformations, undiagnosed, or others). The most important factor in determining the neurological and functional outcomes of IMSCT surgery is the preoperative neurologic status, and pathological type and removal rate are important prognostic factors. The thresholds for the mMCs grade before surgery were determined using the same threshold as that for the primary outcome. The effects of age group (young vs. old) were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). 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 survivors. Kaplan-Meier curves were created to estimate survival in groups classified by age. After evaluation of the proportional hazards assumption, between-group differences were assessed using the log-rank test for 10 years. The effects of the patient group (young vs. older) for all-cause/cause-specific death were estimated using Cox proportional hazard models and expressed as hazard ratios (HRs) with 95% CIs. We adjusted for the following clinically relevant variables to estimate the adjusted HR in the multivariable Cox proportional hazard models: preoperative mMCs grade (grade I/II or grade III/IV/V), degree of removal (biopsy, partial resection, subtotal resection, or total resection), and pathological findings (ependymoma, hemangioblastoma, astrocytoma, cavernous malformations, undiagnosed, or other). Additionally, a multivariate analysis incorporating comorbidities as covariates into the aforementioned adjustment factors was conducted to identify novel factors affecting patient overall survival. The subgroups for primary outcomes were as follows: preoperative mMCs grade (grade I/II or grade III/IV/V), tumor location (cervical level or below the thoracic level), degree of removal (total removal or nontotal removal), pathological findings (astrocytoma or nonastrocytoma), and postoperative treatment (observation or intervention). The subgroups for overall survival were as follows: history of cancer, heart disease, preoperative mMCs grade (grade I/II or grade III/IV/V), degree of removal (total removal or nontotal removal), pathological findings (astrocytoma or nonastrocytoma), and postoperative treatment (observation or intervention). In the subgroup analysis, these variables were dichotomized into 2 categories, as shown in the parentheses. For tumor location, we dichotomized the boundary spinal cord level that had potential to induce tetraplegia or paraplegia based on anatomical knowledge. The threshold of the degree of removal was described previously, implying that gross total removal was associated with a favorable prognosis. The threshold of pathological findings was based on a previous report that astrocytomas and other intramedullary tumors have different prognoses.

Some studies have defined the threshold for the mMCs grade before surgery to be grade II, based on a previous report that astrocytomas and other intramedullary tumors have different prognoses.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Adult patients (n = 841)</th>
<th>Younger patients (n = 658)</th>
<th>Older patients (n = 183)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44 (35–54)</td>
<td>72 (68–75)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>346 (52.6)</td>
<td>97 (53.0)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>22.1 (19.7–24.8)</td>
<td>22.3 (19.7–24.6)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Period of illness (mo)</td>
<td>7 (2–24)</td>
<td>8 (2–33.8)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Past history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of smoking</td>
<td>188 (29.6)</td>
<td>51 (28.3)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>92 (14.1)</td>
<td>86 (47.0)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31 (4.7)</td>
<td>26 (14.2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>54 (8.2)</td>
<td>46 (25.1)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>History of cancer</td>
<td>36 (5.5)</td>
<td>30 (16.4)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>10 (1.5)</td>
<td>16 (7.7)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Previous spinal surgery</td>
<td>54 (8.2)</td>
<td>19 (10.4)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Steroid use</td>
<td>21 (3.2)</td>
<td>13 (7.2)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Anticancer drug use</td>
<td>11 (1.7)</td>
<td>4 (2.2)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck, back, and lower back pain</td>
<td>304 (46.3)</td>
<td>70 (38.3)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Limb pain</td>
<td>277 (42.2)</td>
<td>78 (42.6)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td>586 (89.1)</td>
<td>155 (84.7)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Motor weakness</td>
<td>407 (61.9)</td>
<td>124 (67.8)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Walk disturbance</td>
<td>342 (52.0)</td>
<td>124 (67.8)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Bladder rectal disorder</td>
<td>199 (30.3)</td>
<td>74 (40.4)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Preoperative modified McCormick scale</td>
<td>2 (2–3)</td>
<td>2 (2–4)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Preoperative modified McCormick scale ≤ II</td>
<td>416 (63.2)</td>
<td>95 (51.9)</td>
<td>0.006</td>
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<tr>
<td>Preoperative Karnofsky Performance Scale</td>
<td>80 (70–90)</td>
<td>70 (50–80)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Radiological findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor length (mm)</td>
<td>26 (14.1–48)</td>
<td>27 (14.8–45.2)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>314 (47.7)</td>
<td>72 (39.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical and thoracic</td>
<td>80 (12.2)</td>
<td>22 (12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>215 (32.7)</td>
<td>52 (28.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic and lumbar</td>
<td>49 (7.5)</td>
<td>37 (20.2)</td>
<td></td>
<td></td>
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<tr>
<td>Tumor characteristics</td>
<td></td>
<td></td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Cystic</td>
<td>56 (8.5)</td>
<td>14 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td>325 (49.4)</td>
<td>100 (54.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>169 (25.7)</td>
<td>43 (23.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>103 (15.7)</td>
<td>26 (14.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5 (0.8)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of removal</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>42 (6.4)</td>
<td>25 (13.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial removal</td>
<td>81 (12.3)</td>
<td>27 (14.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal removal</td>
<td>75 (11.4)</td>
<td>29 (15.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total removal</td>
<td>460 (69.9)</td>
<td>102 (55.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The median preoperative mMCs grade and KPS scores were significantly worse for older than for younger patients (II [IQR: II–III] vs. II [IQR: II–IV], p < 0.001; and 80 vs. 70, p < 0.001, respectively). Patients with a preoperative mMCs grade of ≤ II were significantly fewer among older than among younger patients (63.2% vs. 51.9%, p = 0.006). With regard to radiological findings, although there was no significant between-group difference with respect to the tumor length (26 mm vs. 27 mm, p = 0.95) and tumor characteristics (p = 0.60), there were significantly fewer cervical lesions and more thoracolumbar lesions in older than in younger patients (47.7% vs. 39.3%, p = 0.04 and 7.5% vs. 20.2%, p < 0.001, respectively). With regard to the degree of removal, the percentage of biopsy was significantly higher and gross total removal was less common in older than in younger patients (6.4% vs. 13.7%, p = 0.001 and 69.9% vs. 55.7%, p < 0.001, respectively). Pathological findings showed fewer hemangioblastomas and a significantly higher proportion of astrocytomas in older than in younger patients (20.8% vs. 10.4%, p = 0.001 and 13.4% vs. 19.7%, p = 0.003, respectively). With regard to cervical lesions, there were significantly more hemangioblastomas in younger than in older patients (22.0% vs. 8.3%, p = 0.008). The use of chemotherapy was significantly more common in older than in younger patients undergoing postoperative treatment (1.0% vs. 4.1%, p = 0.004). The duration to the last follow-up was significantly shorter for older patients (48 vs. 30 months, p < 0.001).

2. Outcomes

The rates of “improved” and “worsened” status from before to 6 months after surgery were similar between groups (28.1% vs. 25.1%; crude OR [cOR], 0.86; 95% CI, 0.59–1.25; adjusted OR, aOR, 0.84; 95% CI, 0.55–1.28; 16.9% vs. 23.0%; cOR, 1.47; 95% CI, 0.98–2.20; aOR, 1.28; 95% CI, 0.83–1.97; respectively) (Fig. 1A). In the univariate analysis, the rate of mMCs grade I/II at 6 months after surgery was significantly lower for older than for younger patients (66.4% vs. 53.0%; cOR, 0.57; 95% CI, 0.41–0.80). Nevertheless, multivariate analysis showed no significant between-group difference (aOR, 0.77; 95% CI, 0.50–1.19). The rate of a “worsened” status from the preoperative period to the immediate postoperative period was not significantly different (24.1% vs. 20.2%; cOR, 0.80; 95% CI, 0.54–1.20; aOR, 0.83; 95% CI, 0.55–1.27). In the univariate analysis, the rate of “improved” status from the immediate postoperative period to postoperative 6 months was significantly lower for older than in younger patients (66.4% vs. 53.0%; cOR, 0.57; 95% CI, 0.41–0.80). Nevertheless, multivariate analysis showed no significant between-group difference (aOR, 0.77; 95% CI, 0.50–1.19). The rate of all-cause and tumor-related mortality rates at 6 months were higher for older than for younger patients (2.0% vs. 4.9%; cOR, 2.57; 95% CI, 1.08–6.10; 1.2% vs. 4.4%; cOR, 3.71; 95% CI, 1.37–10.0; respectively), but these effects did not remain after statistical adjustment (aOR, 1.28; 95% CI, 0.66–2.47; aOR, 1.68; 95% CI, 0.53–5.28; respectively). Overall survival and cause-specific

Table 1. Patient characteristics (Continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adult patients (n = 841)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger patients (n = 658)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Older patients (n = 183)</td>
<td></td>
</tr>
<tr>
<td>Pathological findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>254 (38.6)</td>
<td>58 (31.7)</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>137 (20.8)</td>
<td>19 (10.4)</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>88 (13.4)</td>
<td>36 (19.7)</td>
</tr>
<tr>
<td>Cavernous malformations</td>
<td>98 (14.9)</td>
<td>38 (20.8)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>11 (1.7)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Others</td>
<td>70 (10.6)</td>
<td>29 (15.9)</td>
</tr>
<tr>
<td>Postoperative therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>526 (83.8)</td>
<td>136 (80.0)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>24 (3.8)</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Radiation</td>
<td>30 (4.8)</td>
<td>10 (5.9)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6 (1.0)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Radiation and chemotherapy, n (%)</td>
<td>41 (6.7)</td>
<td>13 (7.7)</td>
</tr>
<tr>
<td>Last follow-up duration (mo)</td>
<td>48 (23.8–79.3)</td>
<td>30 (15–60) &lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).
survival are shown in Kaplan-Meier curves (Fig. 1B). The 10-year overall survival rate did not differ between groups (87.6% vs. 87.1%; crude HR [cHR], 1.56; 95% CI, 0.92–2.64; adjusted HR [aHR], 1.04; 95% CI, 0.61–1.77). The 10-year cause-specific survival rate was significantly lower in older than in younger patients (90.0% vs. 88.8%; cHR, 1.77; 95% CI, 1.01–3.13), with no significant difference after adjustment (aHR, 1.14; 95% CI, 0.64–2.03). In order to elucidate novel factors influencing overall survival, a multivariate analysis was performed. The findings demonstrated that the presence of a cancer history and heart disease independently served as prognostic factors (aHR, 3.04; 95% CI: 1.59–5.81 for cancer history and 4.76; 95% CI, 1.79–12.6 for heart disease) (Supplementary Table 1).

### 3. Safety Outcomes

There was no significant difference in intraoperative bleeding volumes between the groups (120 mL vs. 100 mL, p = 0.27) (Fig. 1A). The operation time was significantly shorter for older pa-
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Subgroup Analyses

Subgroup analyses of mMCs grade I/II at 6 months suggested that younger patients had better outcomes in almost all subgroups (Fig. 2A), excluding those with lesions below the thoracic spine level. Among the prognostic factors already reported and the dichotomized variables set up in this study, tumor localization at the cervical spine level (aOR, 0.51; 95% CI, 0.27–0.96) and pathological finding of astrocytoma (aOR, 0.19; 95% CI, 0.05–0.70) caused a difference in prognosis between younger and older patients. Furthermore, there was a tendency toward differences in preoperative mMCs (interaction effect, p = 0.05), although the differences were not statistically significant.

5. Sensitivity Analyses

In sensitivity analyses, we dichotomized the adults’ cohort at age 75 years (Supplementary Table 2). Sensitivity analyses for the primary outcomes were similar to the main results.

6. The Relationship Between Preoperative mMCs and mMCs at 6 Months After Surgery

In both younger and older patients, preoperative mMCs were significantly associated with mMCs at 6 months after surgery (younger patients: rho = 0.59, 95% CI, 0.55–0.63; older patients: rho = 0.68, 95% CI, 0.61–0.75) (Fig. 3A). There was no significant difference in the correlation coefficient between younger and older patients (p = 0.07). In both younger and older patients, preoperative mMCs accurately predicted favorable outcomes (younger patients: AUC = 0.81, 95% CI, 0.77–0.84; older patients: AUC = 0.84, 95% CI, 0.78–0.89) (Fig. 3B). There was no signifi-
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There were significant outcome differences between younger and older patients with astrocytomas who had preoperative mMCs of III (p = 0.03) (Fig. 4A). In the astrocytoma group, no older patients had favorable outcomes if their preoperative mMCs were III or higher and no younger patients had favorable outcomes if their preoperative mMCs were V (Fig. 4B). There were significant outcome differences between younger and older patients with astrocytomas who had preoperative mMCs of I, although there was only one case in the older group (p = 0.01) (Fig. 4B).

**DISCUSSION**

1. **Older and Younger IMSCTs Patients’ Characteristics**

To our knowledge, this retrospective study is the largest to...
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In this study, while the proportion of patients with diabetes mellitus was higher among older patients, with more patients taking steroids that could mask symptoms, there was no difference in the time from onset to presentation between groups. Primary glial tumors are reportedly more common in the elderly population (80%). Hemangioblastomas are less common, with an incidence of approximately 2%–15%, consistent with the high incidence of astrocytomas and low incidence of hemangioblastomas in older patients in the present study. While cavernous hemangiomas are uncommon in the elderly and reportedly present in < 10% patients aged ≥ 65 years, in our cohort, they accounted for 20% cases in the older patient group, suggesting that surgery for older cavernous hemangiomas may have been aggressively performed in Japan. Interestingly, in our cohort, the rate of thoracolumbar le-

Fig. 3. Relationship between preoperative modified McCormick scale (Pre-mMCs) and mMCs at 6 months after surgery. (A) The association between Pre-mMCs and mMCs at 6 months after surgery. (B) The diagnostic accuracies of preoperative mMCs in predicting favorable outcomes. (C) The distribution of Pre-mMCs and mMCs at 6 months after surgery. CI, confidence interval; AUC, area under the curve.
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Fig. 4. Relationship between preoperative modified McCormick scale (Pre-mMCs) and mMCs at 6 months after surgery, stratified by lesion site (A) and tumor type (B). mMCs, modified McCormick scale at 6 months after surgery.

sions was significantly higher for older patients, with fewer cases of cervical lesions. Depending on age, there may be differences in the localization of surgically treated IMSCTs, partly because of the higher incidence of hemangioblastomas in younger patients, who commonly exhibit cervical lesions. With regard to the extent of tumor removal, biopsies were more common while total tumor removal was significantly less common in older patients. Partly because of this, the operating time was significantly shorter in older patients, and the occurrence of new neurological symptoms, including worsening symptoms, to the extent that they did not appear on mMCs grade change, was significantly higher in younger patients. Furthermore, the between-group difference in new symptom occurrence remained significant after adjustment, suggesting that being older or younger is an independent factor for new symptoms. These results suggest that surgeons may intentionally choose less invasive treatments for older patients.

2. Outcomes After IMSCT Surgery

The change in neurological findings due to surgery was not significantly different between groups. The rate of mMCs grade I/II at 6 months after surgery, which indicates a favorable out-
come, was lower for older patients, but the difference was not significant after adjustment. These results are consistent and robust, even though the definition of the older group was changed. The 10-year cause-specific survival rate was also significantly lower for older than for younger patients, with no significant difference after adjustment. The fact that significant differences disappeared after adjustment suggested that preoperative neurological findings were a major confounding factor for determining postoperative outcomes, as observed in previous studies.\textsuperscript{14-17} Actually, in our cohort, the preoperative mMCs grade was significantly worse in older patients. Furthermore, preoperative mMCs and mMCs at 6 months after surgery were significantly correlated in both groups, and preoperative mMCs were found to be a good predictor of favorable outcomes at 6 months in both groups.

Previous studies described the risk of postoperative neurological deterioration.\textsuperscript{29} Changes in functional status from the preoperative to the immediate postoperative period tended to be worse in younger patients, although the difference was not statistically significant. However, the recovery of functional status from the immediate postoperative period to postoperative 6 months was better in younger patients; this suggests better recovery in younger patients. There was no significant difference in the overall change in status after surgery up to 6 months postoperatively. In summary, although transient neurological deterioration was observed in younger patients because they were often selected for aggressive removal, their recovery was better than that of older patients. It remained unclear whether better neurological recovery after 6 months in younger patients depended on the effect of tumor removal or neuroplasticity or both.

3. IMSCT Surgical Indications in the Elderly

Our results indicated that history of cancer and heart disease are independent prognostic factors contributing to overall survival in patients with IMSCTs and should be considered when determining the indication for surgery. While not statistically significant, subgroup analysis suggested these conditions contributed to an increased risk rather in younger patients. This might indicate that a reciprocal association between length of morbidity history and better management of comorbidities in the older patients, but further research is needed in this regard. Subgroup analysis showed significantly more favorable outcomes in younger patients for cervical spine lesions and astrocytoma, without a significant difference in the interaction. There were significant outcome differences between younger and older patients, with the cervical lesion who had preoperative mMCs of III and with astrocytomas who had preoperative mMCs of I. In older patients, there were no favorable outcomes if their preoperative mMCs were V. In the astrocytoma group, no older patients had favorable outcomes if their preoperative mMCs were I and III or higher. The reason for the poor prognosis of cervical spine lesions in the elderly may partly be due to higher spinal cord lesions generally presenting with more extensive neurological symptoms and injuries at the cervical level allowing for considerably more spontaneous recovery than injuries at the thoracic level,\textsuperscript{30} and older patients have worse neuroplasticity than younger patients.\textsuperscript{31,32} If the tumor type can be determined preoperatively, the indication for surgery can be considered according to the above in older patients. Considering the challenges in achieving a differential diagnosis of IMSCT through preoperative assessment, and acknowledging that intraoperative rapid pathology exhibits only 70% concordance with definitive pathology specimens,\textsuperscript{33} it appears that surgical intervention may not be advisable for older patients presenting with a preoperative McCormick scale of V and a high suspicion of astrocytoma. Subgroup analysis showed significantly better overall survival in younger patients for mMCs of I/II, without a significant difference in the interaction. This indicates that surgical intervention in older IMSCTs patients who are neurologically independent preoperatively requires more attention than in younger patients. The indications for IMSCT surgery in older patients suggested by this study are summarized in Supplementary Fig. 2.

4. Limitations

Because of the nature of IMSCTs, it will continue to be ethically difficult to determine the efficacy of surgery in the elderly through randomized trials. We believe that our study might provide insight into the optimal treatment strategies for IMSCTs in the older population.

This study has several limitations, including the retrospective design. Each center decided to perform surgery, and only surgically treated cases were included. Therefore, we were unable to evaluate the clinical course of conservatively treated patients with IMSCTs in Japan, and the complete coverage rate was insufficient. Second, a 22% attrition rate was observed at the 6-month time point. These findings suggest inevitable selection bias. It is important to note that our results show no difference in the effectiveness of surgery between older and younger patients with IMSCTs, although they do not indicate homology. To our knowledge, this is the largest study of IMSCTs, but we cannot rule out the possibility of differences as the sample size increases. A large
prospective, multinational, longitudinal study on this issue needs to be conducted in the future.

CONCLUSION

We believe that a thorough evaluation of each individual's conditions such as preoperative neurological status, comorbidities, disease spinal level, and expected pathological diagnosis rather than age itself is crucial for determining the surgical indications for elderly patients with IMSCTs. By striving to minimize operative time, blood loss, and surgical complications, and avoiding overly aggressive total resection, we can enhance the safety and efficacy of the procedure. It is essential to consider the differences in recovery between older and younger patients. This comprehensive approach will contribute to more precise and appropriate surgical decision-making, ultimately leading to improved patient outcomes.

NOTES

Supplementary Material: Supplementary Tables 1, 2 and Figs. 1, 2 can be found via https://doi.org/10.14245/ns.2346390.195.

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: HK, KT, TE, MM; Data curation: HK, TE, MM; Formal analysis: KT; Funding acquisition: TE; Methodology: HK, KT; Project administration: HK, KT, TE, MM; Visualization: HK, KT, TE, MM; Writing - original draft: HK, KT; Writing - review & editing: HK, KT, SY, TE, KH, MM.


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Toshiki Endo: 0000-0002-5609-200X
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Supplementary Fig. 1. Study flowchart. Among the 1,080 patients initially enrolled in the registry, we excluded nonsurgical cases (n = 20), cases of spinal lipoma (n = 18) and myxopapillary ependymoma (n = 11), cases that underwent external decompression only (n = 1), and those that underwent surgery before 2008 (n = 3). We classified pediatric patients (< 18 years) (n = 58), younger patients (aged 18–64 years) (n = 739), and older patients (over 65 years) (n = 230), respectively. In total, 81 younger and 47 older patients did not have modified McCormick scale (mMCs) results at 6 months and were excluded from this analysis. Finally, 841 adult patients with available mMCs data at 6 months were examined in this analysis. There were 658 younger (78.2%) and 183 (21.8%) older patients.
Supplementary Fig. 2. Indications for intramedullary spinal cord tumor (IMSCT) surgery in older patients. GTR, gross total removal; STR, subtotal removal. Appendix: The ultimate determination regarding surgical indications remains at the discretion of the treating physician, and this algorithm should be regarded as a general guide rather than an inflexible rule. Older age is not an independent poor prognostic factor, but older patients should be informed that it is difficult to achieve the same degree of neurological recovery as younger patients. Older patients of preoperative mMC III with cervical lesions should be informed that approximately 40% of patients will have postoperative neurological deterioration. Older patients of preoperative mMCs II/IV suspected astrocytoma should be informed postoperative independence difficulties. A history of cancer or heart disease independently contributed to overall survival in patients with IMSCT and should be factored into surgical decision-making.
### Supplementary Table 1. Multivariate analysis incorporating comorbidities as adjustment factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients aged ≥ 65 years</td>
<td>0.70 (0.38–1.27)</td>
<td>0.24</td>
</tr>
<tr>
<td>History of cancer</td>
<td>3.04 (1.59–5.81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>4.76 (1.79–12.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Preoperative modified McCormick scale I/II</td>
<td>0.24 (0.14–0.42)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Degree of removal</td>
<td>-</td>
<td>0.003</td>
</tr>
<tr>
<td>Pathological findings</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
## Supplementary Table 2. Sensitivity analyses

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Adults under 75 years old (n = 787)</th>
<th>75 years or older (n = 54)</th>
<th>Crude OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved rate from the preoperative period to 6 months after surgery</td>
<td>218 (27.7)</td>
<td>13 (24.1)</td>
<td>0.83 (0.44–1.57)</td>
<td>0.56</td>
<td>0.85 (0.42–1.73)</td>
<td>0.66</td>
</tr>
<tr>
<td>Worsened rate from the preoperative period to 6 months after surgery</td>
<td>141 (17.9)</td>
<td>12 (22.2)</td>
<td>1.31 (0.67–2.55)</td>
<td>0.43</td>
<td>1.11 (0.55–2.26)</td>
<td>0.77</td>
</tr>
<tr>
<td>Modified McCormick scale grade I/II at 6 months after surgery</td>
<td>509 (64.7)</td>
<td>25 (46.3)</td>
<td>0.47 (0.27–0.82)</td>
<td>0.007</td>
<td>0.82 (0.39–1.74)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.
The Effect of Transitioning to Remote Working in Patients Affected by Chronic Low Back Pain: A Cross-Sectional Study

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Objective: To assess the effect of transitioning to remote working during the coronavirus disease 2019 pandemic in a population of adults affected by chronic low back pain (cLBP).

Methods: An online questionnaire was sent by email to teleworkers affected by cLBP. Demographic data, remote working features and tasks, and LBP burden were analyzed. The psychological burden of remote working was evaluated with the World Health Organization Five Well-Being Index and the Patient Health Questionnaire-2. LBP severity was evaluated using a visual analogue scale. LBP-related disability was assessed using the Oswestry Disability Index. The effect of LBP on working capacity was examined with the Occupational Role Questionnaire. Independent risk factors related to LBP worsening were identified using a multivariate logistic regression model.

Results: During remote working, LBP severity was significantly higher compared to previous in-person working (p < 0.0001), as well as average weekly work hours (p < 0.001). Furthermore, the risk of LBP worsening was associated with higher depression scores (odds ratio [OR], 1.38; 95% confidence interval [CI], 1.00–1.91; p = 0.048), increased stress levels (OR: 3.00, 95% CI: 1.04–8.65; p = 0.042), and being divorced (OR: 4.28, 95% CI: 1.27–14.47; p = 0.019). Conversely, living with others (OR: 0.24, 95% CI: 0.07–0.81; p = 0.021), and reporting unchanged stress levels (OR: 0.22, 95% CI: 0.08–0.65; p = 0.006) were associated with a lower risk of LBP worsening.

Conclusion: Our findings highlight key factors to consider for improving remote workers’ physical and mental wellbeing and decrease their LBP burden.

Keywords: Low back pain, COVID-19, Remote working, Teleworking, Pandemics, Occupational medicine

INTRODUCTION

Since December 2019, the pandemic outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an unprecedented global health issue, with > 574,000,000 cases and approximately 6,500,000 deaths worldwide.¹ Due to the high transmissibility of the coronavirus disease 2019 (COVID-19), personal-contact activities and short-distance interactions have been minimized to reduce viral dissemination during social and clinical encounters.² At the socioeconomic level,
this has prompted a profound reorganization of the working world with an increasing number of individuals working remotely from home. In a matter of months, several companies and employers shifted to “remote working” (also known as “telework,” “smart working,” “home working,” etc.), consisting in carrying out a job outside the workplace on a regular basis with the use of information technology. Yet, while preserving productivity and the prosecution of both public and private services, prolonged remote working has demonstrated to negatively impact on workers’ physical and mental wellbeing. Indeed, decreased physical activity and the sedentary lifestyle associated with social confinement and working from home have been related to a higher risk of several systemic and musculoskeletal disorders (MSDs), including chronic low back pain (cLBP).

Low back pain (LBP) is the main cause of disability worldwide, resulting in a huge medical burden and economic costs for the healthcare systems and society. Indeed, studies in European countries indicate that total costs associated with LBP vary between 0.1%–2% of the gross domestic product, with over 80% consisting in indirect costs due to the loss of productivity and disability payments. The main risk factors for LBP include aging, smoking, obesity, sedentary occupations, physical inactivity, and depression. Considering the impossibility to participate in leisure activities, increased time spent home and prolonged sitting during remote working, the prevalence and severity of LBP has significantly increased during the pandemic. However, it is still unclear how remote working impacts on individuals affected by LBP and how transitioning to this new work modality has influenced both work- and health-related outcomes.

The aim of this cross-sectional study was to investigate the effect of transitioning to remote working in an adult population affected by cLBP. We hypothesized that diverse working conditions, home office equipment as well as perceived advantages, disadvantages and impact on job satisfaction, productivity, well-being and stress may differentially influence the severity of LBP in this subset of workers.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Campus Bio-Medico University of Rome (approval number: 76/19 OSS ComEt CBM). Informed consent was obtained from all study subjects upon recruitment. The study was reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Supplementary Material 1).

1. Study Participants

A cross-sectional study was performed at Campus Bio-Medico University of Rome (Rome, Italy) through an online questionnaire. The target population consisted of working-age adults diagnosed with cLBP due to degenerative disc disease after attending the Spine Clinic of Campus Bio-Medico University Hospital Foundation (Rome, Italy). All patients underwent thorough history-taking and physical examination, as well as lumbar spine imaging evaluation to confirm the diagnosis (isolated axial LBP lasting ≥ 12 weeks associated with radiographic or magnetic resonance imaging evidence of intervertebral disc degeneration). Participants were recruited if they reported a history of cLBP and worked remotely from home in the previous 18 months. Eligible subjects were reached by phone and recruited after a thorough explanation of the study aims and methods and signature of the informed consent. Upon acceptance, a web-based questionnaire built with Google Forms (Google Inc., Mountain View, CA, USA) was sent by email to each participant. The questionnaire could be interrupted at any time, and the consent could be withdrawn by closing the browser. After 1 month, a reminder was sent to increase participants’ responsiveness. Data were collected from September 2021 to June 2022.

2. Study Questionnaire

The questionnaire was evaluated by a panel of experts belonging to different professional categories (3 orthopaedic surgeons, 1 occupational psychologist, 1 occupational doctor, and 2 remote workers who met the eligibility criteria for this study) who assessed its content, completeness, and level of comprehension. The questionnaire included 3 sections: (1) demographic and occupational information; (2) remote working features and tasks; (3) LBP burden.

In the first section, retrieved information included age, gender, civil status, highest qualification held, current field of work, specific job title, length of service, professional category, number of cohabitants, and number of minor children.

The second section investigated whether transitioning to remote working caused any changes in terms of tasks, work hours and salary compared to in-person working. In addition, information regarding workplace equipment (type of chair, desk, and devices), hours spent in standing and sitting position as well as perceived productivity, job satisfaction, stress level, and mental wellbeing during remote working were collected. More
specifically, participants were asked about their perceived productivity, job satisfaction and stress level during remote working compared to in-person working and answers were evaluated using a 3-point Likert scale ("increased," "unchanged," "decreased"). The psychological burden of remote working was evaluated with 2 validated scores: the World Health Organization Five Well-Being Index (WHO-5) measuring the level of illness\(^{15}\) and the Patient Health Questionnaire-2 (PHQ-2) measuring the frequency of depressed mood and anhedonia over the past 2 weeks.\(^{16}\) Eventually, advantages and disadvantages of remote working were evaluated.

The third section was focused on LBP severity and related disability, as well as its relationship with occupational tasks. More specifically, subjects were asked if their LBP worsened after transitioning to remote working, to what extent LBP caused work absence and how it affected their working activities. LBP severity was evaluated using a visual analogue scale (VAS). LBP-related disability was assessed using the Oswestry Disability Index (ODI).\(^{17}\) The effect of LBP on working capacity was examined with the Occupational Role Questionnaire (ORQ).\(^{18}\) The Italian version of the questionnaire was sent over and the English translated version is reported (Supplementary Material 2).

3. Bias

In order to achieve a homogeneous sample and avoid participants with self-diagnosed LBP, only patients with LBP due to intervertebral disc degeneration certified by an orthopaedic surgeon were included and personally contacted by the authors, thus reducing selection bias.

4. Sample Size

Considering the change of LBP severity as the primary outcome for sample size calculation, the minimal clinically important difference (MCID) for LBP on VAS was determined based on previous data.\(^{19}\) Assuming a power of 90% and an alpha of 0.05, a sample size of 50 individuals was calculated. To adjust for possible invalid questionnaire responses, considering a rate of 20%, the final sample size consisted of 60 subjects. After reaching the calculated sample size, additional eligible participants were included to increase the external validity of the study population.

5. Statistical Analysis

Descriptive statistics were applied to analyze the characteristics of the sample. Continuous variables were reported as mean ± standard deviation, whereas categorical variables were reported as absolute and percentage frequencies (n, n%). The normality of data distribution has been assessed upon confirmation of the central limit theorem and determined with the Wilk-Shapiro test. Continuous variable differences between timepoints (before and during remote working) in the same individuals was evaluated using the paired t-test. The individual association of each variable on worsening of LBP (determined as an increase on VAS > 2 following the start of remote working, corresponding to the MCID\(^{19}\)) was assessed with a logistic regression model. The independent variables considered were age, sex, civil status, number of cohabitants, number of minor children, work hours, % remote working, type of chair, type of desk, hours sitting, hours standing, productivity, stress, job satisfaction, WHO-5, PHQ-2, ODI, ORQ, and work. Odds ratio (OR) and 95% confidence intervals (CI) were estimated for each reference category. Formal analysis was conducted using the Stata 17.0 (StataCorp LLC, College Station, TX, USA). A p-value of < 0.05 was considered statistically significant.

RESULTS

The questionnaire was delivered to 136 participants and a total of 101 responses were received (response rate: 74.26%). Out of the filled questionnaires received, 8 were excluded because participants did not meet one of the inclusion criteria. Eventually, 93 questionnaires were included in the study (Fig. 1). Participants' characteristics are reported in Table 1.

After transitioning to remote working, 68 subjects (73.1%) retained the same tasks, 4 (4.3%) were assigned to new tasks, and 27 (29%) changed their working time. Indeed, a statistically significant increase of average weekly work hours during re-
Table 1. Study population characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.36 ± 10.11</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (52.7)</td>
</tr>
<tr>
<td>Female</td>
<td>44 (47.3)</td>
</tr>
<tr>
<td>Civil status</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>20 (21.5)</td>
</tr>
<tr>
<td>Married/cohabitee</td>
<td>58 (62.4)</td>
</tr>
<tr>
<td>Divorced</td>
<td>14 (15.1)</td>
</tr>
<tr>
<td>Widowed</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Highest qualification held</td>
<td></td>
</tr>
<tr>
<td>Secondary education</td>
<td>48 (51.6)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Master’s degree</td>
<td>25 (26.9)</td>
</tr>
<tr>
<td>Postgraduate degree</td>
<td>15 (16.1)</td>
</tr>
<tr>
<td>Field of work</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Public administration</td>
<td>19 (20.3)</td>
</tr>
<tr>
<td>Finance and insurance companies</td>
<td>10 (10.7)</td>
</tr>
<tr>
<td>Technical and scientific support</td>
<td>12 (12.8)</td>
</tr>
<tr>
<td>Telecommunications</td>
<td>15 (16.1)</td>
</tr>
<tr>
<td>Accommodation and catering</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Energy industry</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Manufacturing activity</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Computer industry</td>
<td>6 (6.6)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Length of service (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>6 (6.5)</td>
</tr>
<tr>
<td>1–5</td>
<td>15 (16.1)</td>
</tr>
<tr>
<td>6–10</td>
<td>12 (12.9)</td>
</tr>
<tr>
<td>11–15</td>
<td>10 (10.8)</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>50 (53.8)</td>
</tr>
<tr>
<td>Professional category</td>
<td></td>
</tr>
<tr>
<td>Intern</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Employee</td>
<td>72 (77.4)</td>
</tr>
<tr>
<td>Manager</td>
<td>8 (8.6)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (12.9)</td>
</tr>
<tr>
<td>No. of cohabitants</td>
<td>2.56 ± 1.28</td>
</tr>
<tr>
<td>No. of minor children</td>
<td>0.61 ± 0.88</td>
</tr>
<tr>
<td>No</td>
<td>57 (61.29)</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (38.71)</td>
</tr>
</tbody>
</table>

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

Fig. 2. Study participants reported an increase of average weekly work hours during remote working compared to previous in-person working. ***p < 0.001.

Table 2. Changes of working time during remote working compared to in-person working

<table>
<thead>
<tr>
<th>Regarding your working time during remote working, to what extent do you agree with the following?</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>My working hours frequently exceed the standard working time</td>
<td></td>
</tr>
<tr>
<td>Absolutely agree</td>
<td>18 (19.3)</td>
</tr>
<tr>
<td>Agree</td>
<td>24 (25.8)</td>
</tr>
<tr>
<td>Neither agree nor disagree</td>
<td>12 (12.9)</td>
</tr>
<tr>
<td>Disagree</td>
<td>27 (29.03)</td>
</tr>
<tr>
<td>Absolutely disagree</td>
<td>12 (12.9)</td>
</tr>
<tr>
<td>My working time is fragmented and unpredictable</td>
<td></td>
</tr>
<tr>
<td>Absolutely agree</td>
<td>8 (8.6)</td>
</tr>
<tr>
<td>Agree</td>
<td>22 (23.6)</td>
</tr>
<tr>
<td>Neither agree nor disagree</td>
<td>13 (13.9)</td>
</tr>
<tr>
<td>Disagree</td>
<td>34 (36.5)</td>
</tr>
<tr>
<td>Absolutely disagree</td>
<td>16 (17.2)</td>
</tr>
<tr>
<td>I am occasionally asked to work at night</td>
<td></td>
</tr>
<tr>
<td>Absolutely agree</td>
<td>8 (8.6)</td>
</tr>
<tr>
<td>Agree</td>
<td>22 (23.6)</td>
</tr>
<tr>
<td>Neither agree nor disagree</td>
<td>14 (15.05)</td>
</tr>
<tr>
<td>Disagree</td>
<td>31 (33.3)</td>
</tr>
<tr>
<td>Absolutely disagree</td>
<td>18 (19.3)</td>
</tr>
<tr>
<td>My working time did not substantially change</td>
<td></td>
</tr>
<tr>
<td>Absolutely agree</td>
<td>11 (11.8)</td>
</tr>
<tr>
<td>Agree</td>
<td>30 (32.2)</td>
</tr>
<tr>
<td>Neither agree nor disagree</td>
<td>15 (16.1)</td>
</tr>
<tr>
<td>Disagree</td>
<td>26 (27.9)</td>
</tr>
<tr>
<td>Absolutely disagree</td>
<td>11 (11.8)</td>
</tr>
</tbody>
</table>

(Continued)
mote working (38.09 ± 13.26) was reported compared to previous in-person working (34.98 ± 12.46, p < 0.001) (Fig. 2). A more detailed summary on the influence of remote working on working time is depicted in Table 2.

Most study participants (38, 40.9%) worked exclusively from home, while 18 (19.4%) worked > 50% of the time remotely and 37 (39.8%) worked ≤ 50% of the time from home. With regard to the home office setup, 65 (69.9%) declared to have a dedicated workstation, 6 (6.5%) shared their workstation with others, while 22 (23.7%) did not have a fixed workstation. In terms of workstation equipment, 22 participants (23.7%) had a chair with fixed feet not adjustable in height and inclination, 4 (4.3%) had a rolling chair not adjustable in height and inclination, 17 (18.3%) had a rolling chair adjustable in height but not in inclination, 20 (21.5%) had a rolling chair adjustable in height and inclination and 12 (12.9%) possessed an ergonomic chair. Most subjects (69, 74.2%) owned a fixed desk, 5 (5.4%) had a height-adjustable desk and 19 (20.4%) declared not to have a specific workstation but to work anywhere without preferences. In terms of digital devices, 80 (86%) utilized a laptop, 11 (11.8%) a desktop and only 2 (2.2%) a tablet. Sixty-five participants (69.9%) considered these devices to be adequate for their working tasks, while the remainder (28, 30.1%) affirmed they were insufficient for their activities. The latter lamented about limited connectivity (4, 12.1%), inadequateness of digital devices (9, 27.3%), deficient sharing software and tools (5, 15.2%) and, most of all, insufficient ergonomic supports (25, 75.8%). As for the role of the employers in supplying the workers with their home office equipment, 45 (48.4%) were provided with digital devices but not with other items (i.e., chair, desk etc.), 10 (10.8%) were provided with both digital devices and furniture, while the remainder (38, 40.8%) declared to have equipped their home office in total autonomy without the support of their employer.

During an average remote working day, participants spent 7.37 ± 2.16 hours sitting and 1.97 ± 1.6 hours standing. Compared to in-person working, participants considered their productivity to be increased (50, 53.8%), decreased (8, 8.6%), or unchanged (35, 37.6%). Similarly, their stress level was increased (32, 34.4%), decreased (32, 34.4%), or unchanged (29, 31.2%). Furthermore, 29 subjects (31.2%) affirmed that their work satisfaction increased, while it decreased in 26 (28%) and remained unchanged in 38 (40.9%).

In terms of advantages of remote working, the most renowned benefit was reduced commuting time (84, 90.4%), followed by higher organizational flexibility (61, 65.6%), increased family time (52, 55.9%), higher autonomy (43, 46.2%), and higher focus while working (32, 34.4%). On the contrary, the main disadvantages were lack of social interactions with colleagues (70, 75.3%), difficulty in separating work and family environments (47, 50.5%), higher distractions within the domestic environment (33, 35.5%), lower involvement in organizational and administrative changes at work (26, 28%), technical issues with digital devices (27, 29%), lower support and interaction with superiors (17, 18.3%), communication problems (18, 19.4%), and activity planning issues (11, 11.8%). The average WHO-5 score was 13.31 ± 5.25, which is indicative of a nearly poor wellbeing, while the average PHQ-2 score was 1.85 ± 0.6. Additional outcome measures of the psychosocial burden of remote working are summarized in Table 3. When asked if willing to continue with remote working after the pandemic, 48 participants (51.6%) answered “yes, as much as possible,” 31 (33%) “occasionally” and the remainder answered “no” due to organizational difficulties (3, 3.2%), increased costs (1, 1.1%), lack of social interaction (5, 5.4%), increased distractions (2, 2.2%) and higher workload (3, 3.2%).

After having started remote working, 54 participants (58.1%)...
reported a worsening of their LBP and 24 (25.8%) that LBP was unchanged; only 15 (16.1%) affirmed that their LBP improved compared to in-person working. Indeed, LBP severity was significantly higher (5.29 ± 2.16) compared to previous in-person working (3.21 ± 2.19, p < 0.0001) (Fig. 3) after transitioning to remote working, with an average ORQ of 30.4/100 and an ODI of 22.55/100. While LBP did not cause work absence in 37 subjects (39.8%), 38 (40.9%) were absent for less than 10 days, 15 (16.1%) between 10 and 24 days and 3 (3.2%) between 25 and 99 days.

A multivariate logistic regression model was built to examine the association between worsening of LBP after starting remote working and several independent variables (Table 4). Interestingly, participants who were married/cohabitees (OR, 0.24; 95% CI, 0.07–0.81; p = 0.021) or reported an unchanged job satisfaction (OR, 0.22; 95% CI, 0.08–0.65; p = 0.006) showed a significantly lower risk of LBP deterioration. On the other hand, higher depression scores (OR, 1.38; 95% CI, 1.00–1.91; p = 0.048), an increased stress levels (OR, 3.00; 95% CI, 1.04–8.65; p = 0.042), and being divorced (OR, 4.28; 95% CI, 1.27–14.47; p = 0.019) were associated with a significantly higher risk of LBP worsening.

### DISCUSSION

The COVID-19 pandemic has profoundly reshaped the daily routines of workers throughout the world. To reduce the risk of disease transmission, remote working has been implemented on a global scale across nearly all industry sectors, including governments, educational and information services, business companies and several more.\(^{20}\) While promoting safety and guaranteeing the continuity of production activities, working from home has also raised significant concerns regarding workers’ performance, health and wellbeing.\(^{21}\) These aspects may be related to several factors, such as inadequate environmental conditions within the home workspace (lighting, noise, comfort, etc.),\(^{22}\) decreased concentration due to poor proxemics, lack of social interactions, and several more.\(^{23}\) In addition, the sedentary lifestyle and physical inactivity imposed by remote working also importantly increase the risk of non-communicable diseases\(^{24}\) and MSDs, including cLBP.\(^{7}\)

LBP is a multifaceted condition affecting nearly every worker at least once in their life.\(^{25,26}\) According to the biopsychosocial model, cLBP is determined by the complex interplay between biological factors (intervertebral disc degeneration associated with aging, obesity, overload, etc.) and psychosocial factors, including depression, social isolation, catastrophizing, and

### Table 3. Changes of working time during remote working compared to in-person working

<table>
<thead>
<tr>
<th>During remote working, how often do you feel…?</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without company</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>12 (12.9)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>38 (40.8)</td>
</tr>
<tr>
<td>Never</td>
<td>43 (46.2)</td>
</tr>
<tr>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>26 (27.9)</td>
</tr>
<tr>
<td>Never</td>
<td>62 (66.6)</td>
</tr>
<tr>
<td>Isolated from others</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>11 (11.8)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>38 (40.8)</td>
</tr>
<tr>
<td>Never</td>
<td>44 (47.3)</td>
</tr>
</tbody>
</table>

### Table 4. Statistically significant associations between low back pain worsening and study variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Civil status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabitee</td>
<td>0.24</td>
<td>0.07–0.81</td>
<td>0.021</td>
</tr>
<tr>
<td>Divorced</td>
<td>4.28</td>
<td>1.27–14.47</td>
<td>0.019</td>
</tr>
<tr>
<td>Job satisfaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>0.22</td>
<td>0.08–0.65</td>
<td>0.006</td>
</tr>
<tr>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>3.00</td>
<td>1.04–8.65</td>
<td>0.042</td>
</tr>
<tr>
<td>Depression</td>
<td>1.38</td>
<td>1.00–1.91</td>
<td>0.048</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
misperceptions about the relationship between pain, health, work, and societal obstacles.27

In this cross-sectional study, we performed a multidimensional evaluation of the interaction between demographic and work-related factors with cLBP in an adult population working from home. We found that the severity of LBP significantly increased after beginning remote working compared to in-person working and was accompanied by an ODI score corresponding to a degree of moderate disability,17 with more than half of participants reporting sick leaves due to LBP. More interestingly, we found that the risk LBP worsening was significantly associated with several factors, including being divorced, depression, and having reported increased stress levels with remote working. Conversely, living with others or reporting unchanged job satisfaction seemed to protect against the risk of LBP deterioration. Hence, the increased severity of LBP in this specific population may be explained by several reasons. Indeed, it is widely accepted that cLBP is more prevalent among office workers and that prolonged sitting (>7 hours) is directly associated with a higher risk of developing LBP.28 Due to its sedentary nature and the lack of adequate workplace conditions, remote workers are often affected by LBP.29 In a study by Matsugaki et al.,30 a positive correlation between telework hours and the risk of LBP was described in workers reporting a poor work environment. Indeed, as per ours and other reports,31,33 home offices often lack good illumination, noise isolation, appropriately sized screens and ergonomically friendly chairs and desks, with a substantial amount of individuals not having a dedicated workstation or even working at shared desks or from their beds.32 The use of adjustable chairs and desks allows to work in a comfortable position and is recommended to reduce the overload on the cervical and lumbar spine, thus reducing the risk of neck pain and LBP.33 Likewise, having a dedicated workspace that is not intended for other uses reduces the probability of being interrupted by distractions, therefore increasing work productivity and reducing stress.22 This is particularly important for workers living with others and having young children, which are often required to pause their tasks due to family duties.34 Therefore, it is not surprising that we found a statistically significant increase of approximately 3 weekly work hours during remote working compared to in-person working in our population. This is in line with the study of Awada et al.,21 who reported a daily increment of approximately 90 minutes per day while working from home. In this report, longer hours were mainly reported by individuals with school age children and that adjusted their work hours to fit their family routine. Remote working is often aggravated by a drastic reduction of social interactions as well, which has been claimed by most participants in this and other studies.21,31 Indeed, reduced communication with both coworkers and employers has been shown to negatively impact on work productivity, job satisfaction, and stress.21 Furthermore, the prolonged stay at home may contribute to depressed and anxious feelings,35 with sentiments of loneliness and failure of work expectations, especially in subjects living alone. Notably, these psychosocial traits are widely known to increase the risk of cLBP,36 which may partially explain the increased risk of LBP worsening in divorced workers and in individuals with higher WHO-5 and PHQ-2 scores in our study. On the other hand, remote working is characterized by several advantages that have been advocated by most participants, including reduced commuting time, higher organizational flexibility, increased family time and higher autonomy. Indeed, even if all these factors have not shown a direct link with LBP, they have been associated with reduced stress, increased mental health and wellbeing and, in turn, higher job satisfaction.37 Collectively, these aspects may support the desire to continue with remote working after the pandemic expressed by >80% of the study participants. As remote working is increasingly heard to be "here to stay," several implementations should be considered to promote remote workers’ mental and physical wellbeing. With regards to workstation equipment, it is mandatory to sensitize employers about the relevance of guaranteeing an appropriate work environment at home by directly supplying workers with the ergonomic supports needed,21 as they usually need to arrange themselves their home office without any logistic or economic support. Daily routines and schedules should be created in order to optimize work hours, dedicate time to physical activity and avoid family-work conflicts.33 Interactions with coworkers and reports to employers should be encouraged to increase job satisfaction, productivity and engagement.38 Nevertheless, as also highlighted by our findings, more efforts at the policy level are required to coordinate workplace interventions, measures, and actions within organizations to prevent MSDs with a multidimensional approach.39,40

This study has some limitations. Firstly, caution should be used in generalizing the results of this study. As the study population is entirely from Italy, it might not be representative of the working population of other countries, despite the homogenous distribution of age, sex, and field of work. Furthermore, while internal validity and compliance with inclusion criteria was guaranteed by direct recruitment of participants by the research team, biases may have been introduced by convenience sampling and the cross-sectional design of the study. Indeed, the
lack of determination of causal relationship between variables over different timepoints may further decrease the generalizability of our results.

CONCLUSION

The COVID-19 pandemic has significantly changed the world of work with a radical shift towards remote tasks without the need to perform in-person workplace activities. However, the sedentary lifestyle, reduced physical activity, poorer workspace conditions and decreased social interactions associated with remote working may also increase the severity of LBP in individuals working from home. In this study, we reported that workers affected by LBP significantly worsened and had increased work hours after starting remote working. Furthermore, the risk of LBP deterioration was associated with being divorced or living with others, higher ill-health and depression scores, and having reported an unchanged or decreased job satisfaction as well as increased stress levels. Considering the likely integration of remote working in everyday life in the next future, it is essential to plan specific interventions to promote physical and mental wellbeing of remote workers.

NOTES

Supplementary Materials: Supplementary Materials 1 and 2 can be found via https://doi.org/10.14245/ns.2346510.255.

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Detection of Glioma-Related Hotspot Mutations Through Sequencing of Cerebrospinal Fluid (CSF)-Derived Circulating Tumor DNA: A Pilot Study on CSF-Based Liquid Biopsy for Primary Spinal Cord Astrocytoma

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Objective: Although cerebrospinal fluid (CSF)-based liquid biopsy was proved to be practical in molecular analysis of intracranial gliomas, liquid biopsy of primary intramedullary astrocytoma was rarely reported. Given the distinct genomic profiles between primary intramedullary glioma and intracranial astrocytoma, whether the feasibility of CSF-based molecular analysis of intracranial gliomas can be replicated in primary spinal cord astrocytoma needs to be investigated. The aim of this pilot study is to evaluate the feasibility of molecular analysis of primary intramedullary astrocytoma through sequencing CSF-derived circulating tumor DNA (ctDNA).

Methods: Two grade IV diffuse midline gliomas, 1 grade II, and 1 grade I astrocytoma were included. Intraoperative collection of peripheral blood and CSF samples was conducted, along with postoperative collection of matched tumor tissues. A panel covering the 1,021 most common driver genes of solid tumors was used for targeted DNA sequencing.

Results: CSF-derived ctDNA was detected in 3 CSF samples (2 grade IV diffuse midline gliomas and 1 grade I astrocytoma), 5 mutations were found in both tumor tissues and CSF samples, while 11 mutations and 20 mutations were detected exclusively in tumor tissues and CSF samples, respectively. Importantly, hotspot genetic alterations, including H3F3A K28M, TP53, and ATRX, were identified in CSF and the average mutant allele frequency was often higher in CSF than in tumor tissues.

Conclusion: CSF-based liquid biopsy showed potential feasibility for molecular analysis of primary intramedullary astrocytoma through sequencing of ctDNA. This approach may assist in diagnosis and prognostic evaluation of this rare spinal cord tumor.

Keywords: Astrocytoma, Circulating tumor DNA, Spinal cord, Intramedullary, Liquid biopsy

INTRODUCTION

Liquid biopsy via biofluid sampling, such as blood, ascites, hydrothorax, cerebrospinal fluid (CSF) etc., was increasingly used to analyze molecular profile of tumors. Various tumor-derived molecules, including proteins, nucleic acids, and extracellular vesicles etc., can serve as biomarker platform for liquid biopsy. Among these, circulating tumor DNA (ctDNA), which is shed by necrotic or apoptotic tumor cells into body fluid, has gained traction in recent years. Sequencing ctDNA can describe the mutational landscape of tumor. Importantly, mutation analysis by ctDNA hold several advantages over that by traditional...
tissue biopsy, including mini-invasion, dynamic monitoring and capturing global tumor genome. In central nervous system tumor, CSF is considered the optimal carrier of ctDNA shed by brain tumor compared to blood due to blood-brain barrier. As expected, CSF-derived ctDNA has been successfully and increasingly used to assess molecular profile of brain gliomas. However, the utility of CSF-derived ctDNA in mutation analysis of primary spinal cord astrocytoma, the second common intramedullary glioma, has been seldomly reported. Given that the clinical characteristics and molecular profile of primary spinal cord astrocytoma were reported to be different from its intracranial counterpart, it was suspected that the feasibility of mutation analysis through sequencing CSF-derived ctDNA in intracranial glioma could be reproduced in primary spinal cord astrocytoma.

Here, we report results from a pilot study in patients with primary spinal cord astrocytoma aiming to evaluate the practicality of molecular analysis through sequencing of CSF-derived ctDNA.

MATERIALS AND METHODS

1. Patients

Four patients with primary intramedullary tumor underwent surgical treatment in Xuanwu Hospital, Capital Medical University and postoperative pathology confirmed astrocytoma. Tumor grade was classified according to 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System by 2 independent neuropathologists. Formalin-fixed, paraffin-embedded tumor samples were obtained postoperatively for genomic DNA extraction. Matched peripheral blood (PB) samples were obtained at the time of anesthetic induction and CSF was collected upon opening dura and prior to tumor resection (Fig. 1). Demographic data and clinicoradiological features were collected. Follow-up data until June, 2020 were available. Overall survival was defined as the duration from the date of the diagnosis to the date of final follow-up or death. This study was approved by the Clinical Research Ethics Committee of Xuanwu Hospital (2022020). All participants gave written informed consent.

2. Sample Preparation: Sample Processing and DNA Extraction

More than 10 mL of PB and 7–10 mL CSF were collected from each patient using cell-free DNA (cfDNA) collection tubes (Streck, Omaha, NE, USA) at room temperature before receiving any treatment. PB samples and CSF samples were processed within 3 days after gathering, and centrifuged at 2,500 g for 10 minutes, then moved to microcentrifuge tubes and centrifuged at 16,000 g for 10 minutes to remove remaining cellular debris. Peripheral blood lymphocytes (PBLs) generated from the first centrifugation were gathered as germline control samples. Plasma, CSF supernatant and PBLs were stored at -80°C. The DNA of PBL was extracted using the DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany). Circulating cfDNA was isolated from 1.6–2.8 mL plasma and 7–10 mL CSF using QIAamp Circulating Nucleic Acid Kit (Qiagen). DNA concentration was measured with the Qubit fluorometer using dsDNA HS kit (Life Technologies, Carlsbad, CA, USA), and the size of cfDNA fragments were assessed using the Agilent 2100 BioAnalyzer and DNA HS kit (Agilent Technologies, Santa Clara, CA, USA).

3. Targeted Sequencing: Sequencing Library Construction and Hybridization Capture-Based Sequencing

Before library construction, genomic DNA were sheared into 200–250 bp fragments with a Covaris S2 instrument (Covaris, LLC, Woburn, MA, USA). Indexed Illumina NGS libraries were prepared from PBL germline and circulating DNA using the KAPA Library Preparation Kit (Kapa Biosystems, Wilmington, MA, USA). For cfDNA, after end repairing and A-tailing, well-designed adapters with unique identifiers were ligated to both ends of the double-stranded cfDNA fragments. The SeqCap EZ Library system (Roche NimbleGen, Madison, WI, USA) was used for target enrichment. All libraries were hybridized to cus-
tom-designed biotinylated oligonucleotide probes (IDT, Coralville, IA, USA) covering 1.6 Mbp of the genome. The captured genomic regions included the most common driver genes of solid tumors, including glioma. We chose their entire exome regions to construct the basic panel. Next, genomic regions relevant to the effects of chemotherapy, targeted drugs, and immunotherapy per available clinical and preclinical research were added to the panel. Finally, high-frequently mutant regions recorded in the Catalogue of Somatic Mutations in Cancer (COSMIC, http://cancer.sanger.ac.uk/cosmic) and The Cancer Genome Atlas (TCGA, https://cancergenome.nih.gov/) were involved. All included 1,021 genes are shown in Supplementary Table 1. Captured DNA fragments were amplified after hybrid selection and then pooled into several multiplexed libraries. Sequencing was performed using the MGISEq-2000 sequencing system (BGI, Shenzhen, China) according to the manufacturer's guideline.

4. Raw Data Processing
After removal of terminal adaptor sequences and low-quality reads (> 50% N rate, > 50% bases with Q < 5), remaining reads were mapped to the reference human genome (hg19) and aligned using Burrows-Wheel Aligner (version 0.7.12-r1039, http://bio-bwa.sourceforge.net/) with default parameters, followed by duplicate reads identification using Picard's Mark Duplicates tool (https://software.broadinstitute.org/gatk/documentation/tooldocs/4.0.3.0/picard_sam_markduplicates_MarkDuplicates.php). Base quality recalibration and local realignment were conducted by the Gene Analysis Toolkit (GATK, https://www.broadinstitute.org/gatk/).

5. Mutation Identification
Somatic single-nucleotide variations and insertions or deletions of small fragments (Indels) were called by MuTect algorithm (https://software.broadinstitute.org/gatk/documentation/tooldocs/3.8-0/org_broadinstitute_gatk_tools_walkers_cancer_m2_MuTect2.php). PBL sequencing data were used to filter germline mutations. All reliable alterations were supported by ≥ 5 high-quality sequencing reads (mapQthres > 30, base-Qthres > 30). Multiple single-nucleotide polymorphism databases (dbSNP, https://www.ncbi.nlm.nih.gov/projects/SNP/; 1000G, https://www.1000genomes.org/; ESP6500, https://evs.gs.washington.edu/; ExAC, http://exac.broadinstitute.org/; self-built SNP database) were used to ensure the accuracy of somatic detection.

RESULTS

1. Clinicoradiological Features
All the 4 patients underwent biopsy only. Postoperative histological morphology confirmed astrocytoma, and integrating with molecular pathology, final pathological diagnosis revealed 2 diffuse midline glioma (DMG), H3 K27M-mutant (WHO IV), 1 grade II diffuse astrocytoma, 1 grade I diffuse astrocytoma. Mean age was 22.3 years (range, 18–28 years). The duration of symptom was 1 month and 2 months for the 2 patients with high-grade astrocytoma, respectively, while the duration of symptom was 10 months and 60 months for patient with grade I and grade II astrocytoma, respectively. Of the 4 spinal cord astrocytomas, 2 confined to the thoracic region, 1 in cervical region, and 1 involved holocord. The 2 patients with DMG received postoperative radiotherapy and chemotherapy with Temozolomide, while the remaining 2 patients did not receive postoperative adjuvant treatment. At the last follow-up, 2 patients (DMG) died with an average survival time of 12 months, while the remaining 2 patients were alive with an average survival time of 42 months. Clinicoradiological features were showed in Table 1 and preoperative MRI were showed in Fig. 2.

2. Tumor-Specific Mutations Detected in CSF-Derived ctDNA
CSF-derived tumor DNA was identified in 3 CSF samples (2 DMGs and 1 grade I astrocytoma) and was sequenced to an av-

Fig. 2. Preoperative contrast-enhanced magnetic resonance imaging (MRI). (A, D) Radiological characteristics of the 2 patients with diffuse midline gliomas. (B) MRI of the patient with World Health Organization (WHO) I grade astrocytoma. (C) MRI imaging of the patient with WHO II grade astrocytoma.
average depth of 1,039 (range, 100–2,041). The median mutant allele frequency (MAF) was 3.65% (range, 0.74%–84.84%). At least 1 tumor mutation was identified in these 3 CSF samples. The most frequently mutated genes were TP53 (3/4), H3F3A K27M (2/4), APC (1/4), ZFHX3 (1/4), SETD2 (1/4), NOTCH2 (1/4), BLM (1/4), NCOR1 (1/4), PIK3R1 (1/4), CD5L (1/4), KRAS (1/4), EGFR (1/4), BRAF (1/4), MLL3 (1/4), PTEN (1/4) and CDKN1A (1/4). The average MAF of these mutated genes were TP53 53.83%, H3F3A K27M 36.53%, ATRX 21.75%, APC 4.30%, ZFHX3 (4.36%), SETD2 (4.70%), NOTCH2 (7.11%), BLM (5.80%), NCOR1 (5.95%), PIK3R1 (1.49%), CD5L (0.74%), KRAS (7.02%), EGFR (3.38%), BRAF (5.34%), MLL3 (1.85%), PTEN (1.46%) and CDKN1A (21.05%), respectively (Supplementary Table 2).

3. Concordance of Molecular Profile Between Paired Tissues and CSF Samples

Using the targeted sequencing approach, a total of 16 somatic mutations were identified in the 2 DMGs tissues, while no mutation was determined in grade I and grade II tumor tissues, respectively; average sequencing depth was 340 (range, 186–452) and the average MAF was 22.36% (Fig. 3A). In 3 CSF samples with detectable ctDNA, 28 somatic mutations were identified, the average MAF was 13.84%; of those, 5 of 28 mutations (17.86%) were shared between tumor tissues and CSF (Fig. 3B, C); the average MAF of the 5 variants detected in CSF was 52.9% (range, 30.0%–84.8%) compared to that of 36.4% (range, 16.1%–91.0%) in tumor tissues (Fig. 3D–F). Twenty-three mutations and 11 mutations were detected exclusively in CSF and tumor tissues, respectively (Fig. 3C). No tumor mutation was identified in matched blood.

**DISCUSSION**

Primary spinal cord astrocytoma is a rare disease. Different from its intracranial counterpart, intramedullary astrocytoma rarely receives gross total resection without neurological deficit, due to poorly defined margins between the tumor and normal spinal cord, as well as the highly dense nerve fiber tracts in the spinal cord. Therefore, less-invasive diagnostic methodology and postoperative longitudinal monitoring of residual tumor in molecular level have clinically practical value and may help clinicians evaluate treatment response. Blood-based liquid biopsy has been used in clinical practice for assessing several noncentral nervous system tumors, including lung cancer, colorectal cancer, pancreatic cancer, melanoma and others.\(^{10-15}\) As to cen-
Detection of ctDNA in Primary Intramedullary Astrocytoma

Cheng L, et al.

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tral nervous system tumor, molecular analysis via CSF-derived ctDNA was emergingly confirmed to be feasible in brain glioma in proof-of-principle studies\textsuperscript{7,16-19}, which may pave the way for the application of CSF-derived ctDNA to assess the molecu-

Fig. 3. (A) Average mutant allele fraction of mutations detected in tumor tissues, cerebrospinal fluid (CSF) and blood, respectively. (B) Mutational characteristics and concordance between CSF and tumor tissues, molecular biomarkers associated with survival and diagnosis, such as \textit{H3F3A K27M}, \textit{TP53}, and \textit{ATRX}, were detected in CSF. (C) Five mutations were shared in CSF and tumor tissues, number of mutations detected in CSF were more than that in tumor tissue. (D–F) The mutant allele frequency (MAF) of the 5 mutations shared in CSF and tumor tissues was frequently higher in CSF than that in tumor tissues. DMG, diffuse midline glioma; WHO, World Health Organization.
lar characteristics of primary spinal cord astrocytoma. However, given the distinction in genetic profiles between intramedullary glioma and cranial glioma, especially in terms of MAF, the MAF in spinal cord astrocytoma is likely to be low due to the fact that most spinal astrocytomas occur in children and young-aged populations. Therefore, further investigation is warranted to determine the feasibility of applying CSF-derived ctDNA to evaluate the genetic profile of primary spinal cord astrocytoma.

In this pilot study, concordance of genetic alteration detected in paired tissues and CSF samples was evaluated. The results showed that 5 mutations shared in tumor tissues and CSF samples, but 11 mutations detected in tumors tissues were not identified in CSF; additionally, 23 mutations were exclusively detected in CSF. The concordance rate was lower than that in brain/brainstem gliomas. Of note, in spite of the low concordance rate, genetic mutations in H3F3A, TP53, and ATRX, which were hotspot mutations found in spinal cord astrocytoma and were diagnostic and prognostic markers of glioma, could be detected in CSF-derived ctDNA using next-generation sequencing approach and showed favorable concordance with tissue-based testing. Particularly, H3F3A K27M, the representative diagnostic marker of DMG, was identified in CSF samples of the 2 patients with DMG, suggesting that CSF-based H3F3A K27M testing has the potential to serve as a noninvasive method for the diagnosis of DMG. Although H3F3A K27M does not exclusively occur in DMG, other gliomas, such as glioblastoma, can also harbor this mutation, the clinicoradiological features of primary spinal cord DMG and glioblastoma are distinct. Therefore, noninvasive-multimodal diagnostic modality integrating CSF-based liquid biopsy of H3F3A K27M with clinicoradiological parameters, rather than CSF-based H3F3A K27M testing alone, hold promise for the differential diagnosis of DMG in lieu of traditional biopsy and real-time monitoring of tumor recurrence and response.

Additionally, of the mutations shared in tumor tissues and CSF, the MAF in CSF was frequently higher than that in tumor tissues, which may be attributed to intratumoral heterogeneity or sampling bias via biopsy. Consequently, mutation analysis based on tumor tissues obtained via a biopsy could not provide comprehensive mutation assessment of all tumor sites, while ctDNA has been proven to be a reliable source for intratumoral heterogeneity analysis, due to ctDNA is shed from the various heterogeneous tumor clones. Additionally, molecular analysis using biopsy-obtained tumor tissues with a low proportion of tumor cells might be prone to error. That is why several mutations were exclusively detected in CSF.

Fig. 3. (A) Average mutant allele fraction of mutations detected in tumor tissues, cerebrospinal fluid (CSF) and blood, respectively. (B) Mutational characteristics and concordance between CSF and tumor tissues, molecular biomarkers associated with survival and diagnosis, such as H3F3A K27M, TP53, and ATRX, were detected in CSF. (C) Five mutations were shared in CSF and tumor tissues, number of mutations detected in CSF were more than that in tumor tissue. (D–F) The mutant allele frequency (MAF) of the 5 mutations shared in CSF and tumor tissues was frequently higher in CSF than that in tumor tissues. DMG, diffuse midline glioma; WHO, World Health Organization. (Continued)
Several factors likely contribute to the detectability of ctDNA in CSF. Tumor grade and location were reported to be highly associated with the detectability of ctDNA in CSF.\textsuperscript{7,18} From a technological standpoint, the quantity of ctDNA released into CSF by high-grade glioma and tumor that abut a CSF reservoir is more likely to be sufficient for detection. In our study, one patient with grade I astrocytoma showed positive ctDNA in CSF. While the patient had a 28-month history of primary spinal cord lesion and MRI showed the tumor almost involved totally cross-sectional spinal cord and adjacent leptomeningeal enhancement, thus, complete exposure to CSF reservoir likely contributes to positive detection of ctDNA in CSF. Of note, in our study, all CSF samples were collected intraoperatively from the site of tumor rather than through lumbar puncture. CSF circulates in spinal canal, therefore, it's hypothesized that the anatomical location of CSF collection has no impact on the detectability of ctDNA. Consistently, the study by Miller et al.\textsuperscript{17} revealed the genomic profiles of CSF samples collected in different locations were highly concordant. Thus, molecular analysis in CSF collected via lumbar puncture is clinically feasible.

To our knowledge, this is the first study exclusively focused on the feasibility of CSF-derived ctDNA in evaluating the molecular profile of primary spinal cord astrocytoma to date. ctDNA could be detected in CSF from primary spinal cord astrocytoma. However, given that only 4 patients were included, the concordance of molecular profiles between paired tissues and CSF samples needs further investigation in large sample-sized study. Favorably, hotspot genetic alterations that could assist molecular diagnosis or prognostic evaluation for gliomas, such as H3F3A K27M, TP53, ATRX, etc. could be identified in CSF, indicating that extraction and sequencing of CSF-derived ctDNA hold promising potential in assisting differential diagnosis or prognostic assessment of spinal cord lesions.

**CONCLUSION**

CSF-derived ctDNA could be detected in patients with primary spinal cord astrocytoma. Molecular analysis through sequencing of CSF-derived ctDNA hold promise in assisting with the diagnosis and prognostic evaluation for primary spinal cord astrocytoma.

**NOTES**

**Supplementary Materials:** Supplementary Tables 1 and 2 can be found via https://doi.org/10.14245/ns.2346210.105.

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Proteomic Comparison of Paraspinal Muscle Imbalance Between Idiopathic Scoliosis and Congenital Scoliosis

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Objective: This study aims to compare the proteomic profiles of paraspinal muscle imbalance between idiopathic scoliosis (IS) and congenital scoliosis (CS).

Methods: Bilateral paraspinal muscles of 5 pairs of matched IS and CS patients were collected. Proteome patterns of paraspinal muscles were established. Differentially expressed proteins (DEPs) in paraspinal muscles between the convexity and the concavity were screened out. DEPs shared by both IS and CS and IS-specific DEPs were identified. Bioinformatic analyses of DEPs were performed.

Results: Among 105 DEPs identified in IS, 30 displayed predominant expression on the convexity, whereas other 75 exhibited predominant expression on the concavity. DEPs in IS were mainly enriched in calcium ion binding and DNA binding in gene ontology (GO) term and glycolysis/gluconeogenesis and purine metabolism in Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway. Among 48 DEPs identified in CS, 25 were predominantly expressed on the convexity and 23 on the concavity. DEPs in CS were mainly enriched in receptor activity and immune response in GO term and glycolysis/gluconeogenesis and cellular senescence in KEGG pathway. Comparison of DEPs between IS and CS identified only 8 proteins shared by both types of scoliosis. Among the 97 IS-specific DEPs, 28 were predominantly expressed on the convexity and 69 on the concavity. IS-specific genes were enriched in calcium ion binding and protein glycosylation in GO term and glycolysis/gluconeogenesis and hypertrophic cardiomyopathy in KEGG pathway.

Conclusion: IS and CS exhibit proteomic imbalance in bilateral paraspinal muscles but share few similarities. Paraspinal muscle imbalance in IS might not be the consequence of spinal deformities.

Keywords: Idiopathic scoliosis, Congenital scoliosis, Paraspinal muscle imbalance, Proteomic profile, Differentially expressed proteins, Bioinformatic analysis

INTRODUCTION

As the most common type of scoliosis, idiopathic scoliosis (IS) affects approximately 1%–3% of the population, which differs between regions and races. The course of disease deteriorated progressively in more than 60% of patients. As the most common nonoperative treatment, bracing is effective in preventing curve progression in a certain proportion of IS patients. However, brace treatment is mainly used for patients with a Cobb angle of more than 25 degrees. For patients at the early stage of the disease, effective intervention is in lack. To develop early interventions, exploring the cause of IS is essential. Unlike congenital scoliosis (CS), no remarkable vertebra abnormalities were observed in IS. Currently, multiple theories have been put forward to interpret the pathogenesis of IS, including the nervous system equilibrium dysfunction theory, hormone theory, genetic theory, etc. Nervous system equilibrium dysfunction may bring about the imbalance of paraspinal muscles, the effector of nervous system. The asymmetric distribution and methylation level of estrogen receptors in bilateral paraspinal muscles were observed.
in IS.\textsuperscript{10-12} As for genetic theory, single nucleotide polymorphisms in several genes that were asymmetrically expressed in bilateral paraspinal muscles were identified in IS.\textsuperscript{13-16} Based on above theories, paraspinal muscle imbalance is supposed to participate in the pathogenesis of IS.

Various methods were used to decipher paraspinal muscle imbalance in IS. For instance, imageological techniques, such as ultrasound and magnetic resonance imaging (MRI), verified the differences between bilateral paraspinal muscles regarding cross-sectional area and muscle volume.\textsuperscript{17-20} Asymmetrical myoelectric activity was observed by electromyography.\textsuperscript{21} Histological analyses showed differences between the concavity and the convexity in the size, density and distribution of myofibers.\textsuperscript{22,23} Although relevant research has mushroomed, whether paraspinal muscle imbalance is the primary cause or secondary change of scoliosis in IS has yet to be determined. To clarify the causality between paraspinal muscle imbalance and scoliosis, more precise methods are required. Recently, transcriptome sequencing has been used to identify differentially expressed genes (DEGs) in bilateral paraspinal muscles in IS.\textsuperscript{24,25} Although several crucial DEGs were identified in IS, the difference of global gene expression profile in bilateral paraspinal muscles between IS and CS remains unclarified. Besides, to our knowledge, research on paraspinal muscle imbalance in IS from the aspect of proteome is in lack.

Herein, we utilized data-independent acquisition (DIA) proteomics to analyze differences in paraspinal muscles between the convex and concave sides in IS. Besides, CS was taken as the control. As is known, differences in paraspinal muscles between the convex and concave sides in CS are supposed to be changes due to genetic factors for skeletal deformities or changes secondary to skeletal deformities. Comparison of paraspinal muscle imbalance between IS and CS may help to eliminate differentially expressed proteins (DEPs) in bilateral paraspinal muscles secondary to scoliosis, and thereby screen out DEPs specific for IS, which may give some enlightenments for the pathogenesis of IS.

**MATERIALS AND METHODS**

1. Participants

IS patients and CS patients receiving surgical treatment by one senior surgeon (Prof. Shen) from January 2022 to December 2022 in Peking Union Medical College Hospital were enrolled in this study. The inclusion criteria for IS were as follows: (1) Age at surgery ranged from 10 to 18 years old. (2) Adolescent idiopathic scoliosis with thoracic curve as the major curve. (3) Primary surgery via posterior spinal instrumentation. The inclusion criteria for CS were: (1) Age at surgery ranged from 10 to 18 years old. (2) Apex of the curve located at T5/6 disc to T11/12 disc. (3) Posterior spinal fusion as the first surgery with no previous nonfusion surgeries or revision surgery. (4) Intra-spinal abnormalities, including split cord malformation, syringomyelia and tethered spinal cord, were excluded using computed tomography scans and MRI. (5) Without a definite genetic diagnosis. Then IS patients and CS patients were matched according to age (≤ 1 year), sex and the location of apex (≤ 1 segment). Patient selection strategy was described in Fig. 1.

This study was performed according to the Helsinki Declaration and approved by the Institutional Review Board of Peking Union Medical College Hospital (K4136). A written informed consent was obtained from all subjects.

2. Specimens Collection, Processing and Storage

After general anesthesia, patients were lied in prone position. Then a standardized posterior median approach was taken to expose bony structures. Muscle samples were obtained from bilateral multifidus muscles at the apical region of the major curve. To ensure the symmetry of samples collected, deep muscles adjacent to spinous process, which covers vertebral lamina at the apical vertebra were collected. All procedure were conducted by a senior surgeon (Prof. Shen) specialized in spinal deformity.

After collection, muscles were washed with precooled phosphate buffer saline to remove blood cells. Then samples were dissected into suitable size and immersed in AllProtect preservation solution of nucleic acids and proteins in animal tissues (Beyotime Biotechnology, Shanghai, China) at 4°C overnight. Tissues were then transferred to -80°C for storage until use.

3. Protein Extraction, Quality Control, and Digestion

Protein extraction was performed by the filter-aided sample preparation procedure. Briefly, tissues with the size of approximately 3 mm × 3 mm × 3 mm were grinded in liquid nitrogen and lysed with lysis buffer containing sodium dodecyl sulfate (SDS) and dithiothreitol (4% SDS [Sigma-Aldrich, St. Louis, MO, USA], 1 mM DL-Dithiothreitol [Sigma-Aldrich], 100 mM Tris–HCl [Sigma-Aldrich], pH 7.6). After ultrasonication for 5 minutes, the lysates were incubated at 95°C for 15 minutes and with ice-bath for 2 minutes. Then the lysates were centrifuged at 12,000 g for 15 minutes at 4°C to remove insoluble cellular debris. The supernatants were obtained and mixed with sufficient iodoacetamide (Solarbio, Beijing, China). After alkyl-
Proteomic Comparison Between IS and CS


Proteomic Comparison Between IS and CS


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Proteomic Comparison Between IS and CS

Proteomic Comparison Between IS and CS

Proteomic Comparison Between IS and CS

Proteomic Comparison Between IS and CS

1.51 Operated scoliosis by prof. Shen in PUMCH (2022.01–2022.12)

57 IS

11 Age < 10 or > 18

Excluded

39 CS

11 Age < 10 or > 18

Excluded

10 IS

47 IS

11 UT or TL/L curve as main curve

Excluded

28 CS

11 UT or TL/L curve as main curve

Excluded

36 IS

2 Revision surgery

Excluded

21 CS

2 Revision surgery

Excluded

34 IS

Matching conditions:

Age within 1 year

Same sex

Apex location within 1 segment

21 CS

13 CS

10 IS

Excluded

9 CS

1 With a definite genetic diagnosis

5 IS

5 CS

2 With intraspinal abnormalities

Matching conditions:

Age within 1 year

Same sex

Apex location within 1 segment

5 IS

5 CS

Fig. 1. Flowchart showing the recruitment of participants in this study. 5 pairs of IS patients and CS patients were selected from scoliotic patients receiving corrective surgery by Prof. Shen in PUMCH in 2022 and matched according to age, sex and apex location. PUMCH, peking union medical college hospital; IS, idiopathic scoliosis; CS, congenital scoliosis; UT, upper thoracic; TL/L, thoracolumbar/lumbar.

ation at room temperature for 1 hour in darkness, samples were mixed with 4 volumes of precooled acetone (Solarbio) and incubated at -20°C for 120 minutes. Precipitates were collected via centrifugation at 12,000 g for 15 minutes at 4°C, followed by washing with 1-mL precooled acetone (Solarbio). Then the precipitates were completely dissolved in Dissolution Buffer (8 M Urea, Solarbio; 100 mM tetraethylammonium bromide, Solarbio; pH 8.5).

Protein concentration was quantified via the Branford method, according to the manufacturer’s instructions (Beyotime Biotechnology, Shanghai, China). Then samples of 20 μg total protein were used for protein quantification and SDS-poly acrylamide gel electrophoresis (Solarbio).

After quantification, 100 μg total protein of each samples was digested into peptides. Briefly, each protein samples were added to 100-μL dissolution buffer. Samples were then reacted with trypsin and 100 mM tetraethylammonium bromide (Solarbio) at 37°C for 4 hours, followed by digestion with trypsin and calcium chloride (Solarbio) overnight. Then formic acid (FA; Sigma-Aldrich) was added to adjust the pH of digested samples under 3. After centrifugation at 12,000 g for 5 minutes at room temperature, the supernatant was collected and loaded to the C18 desalting column. Then the column was washed with washing buffer (0.1% FA, Sigma-Aldrich; 3% acetonitrile, Sigma-Aldrich) for 3 times. After that, elution buffer (0.1% FA, Sigma-Aldrich; 70% acetonitrile, Sigma-Aldrich) was added and the eluents were collected and lyophilized.

4. Peptide Fractionation

Lyophilized samples were resolved in mobile phase buffer A (2% acetonitrile, Sigma-Aldrich; pH 10). Then samples were centrifugated at 12,000 g for 10 minutes at room temperature. Fractionation were performed using L-3000 HPLC system (Arc Scientific, Syracuse, NY, USA) connected with Waters BEH C18 column (4.6 × 250 mm, 5 μm). Then samples were subjected to the column. Gradient elution was performed with different proportions of mobile phase buffer A and buffer B (98% acetonitrile, Sigma-Aldrich; pH 10). After fractionation, samples were lyophilized, followed by dissolved in 0.1% FA (Sigma-Aldrich).

5. Data-Dependent Acquisition- and DIA-Based LC-MS/MS

The data-dependent acquisition (DDA) and DIA liquid chro-
matography–mass spectrometry/mass spectrometry (LC-MS/MS) analyses were performed using an EASY-nLC 1200 UPLC system (Thermo Fisher Scientific, Waltham, MA, USA) coupled with a Q Exactive HF-X mass spectrometer (Thermo Fisher Scientific). Samples were added with indexed retention time (iRT) peptides (Biognosys, Schlieren, Switzerland) according to manufacturer’s instructions. Peptides of 1 μg were loaded onto the self-produced precolumn. Gradient elution was then conducted with different proportions of mobile phase buffer A (0.1% FA, Sigma-Aldrich) and buffer B (80% acetonitrile, Sigma-Aldrich; 0.1% FA, Sigma-Aldrich). For DDA mode, parameters were set as follows: full scan range, 350 to 1,500 m/z; MS1 scan resolution, 120,000 at 200 m/z; automatic gain control (AGC) target value, $3 \times 10^4$; maximum ion injection time (MIIT), 80 msec. The top 40 precursor ion with the highest abundance were screened out, fragmented using higher energy collisional dissociation, followed by MS2 analysis. Parameters for MS2 were set as follows: scan resolution, 15,000 at 200 m/z; AGC target value: $5 \times 10^4$; MIIT, 45 msec; normalized collision energy: 27%.

6. MS Data Analysis

Raw data of DDA were searched against the National Center for Biotechnology Information database (1492129-1492124-Homo_sapiens. fasta; 130184 sequences) using Spectronaut Pulsar X software (Biognosys AG, Schlieren, Switzerland). Parameters for the searches were as follows: mass tolerance for precursor ion, 10 ppm; mass tolerance for product ion, 0.02 Da; maximum of missed cleavage sites, 2; fixed modification, carbamidomethyl; dynamic modification, oxidation of methionine; N-terminal modification, acetylation. Retrieval results were further filtered by Spectronaut Pulsar X software (Biognosys AG) to select identified peptide spectrum matches (PSMs) with the confidence level greater than 99%. Identified PSMs were then subjected to the verification of false discovery rate (FDR) for the removal of peptides and proteins with FDR greater than 1%. Then the DDA spectral library was established.

DIA data was imported into Spectronaut Pulsar X software (Biognosys AG). By search DDA spectral library, qualitative and quantitative analysis of peptides were implemented. Parameters set for DIA analysis were as follows: retention time correction, dynamic iRT; precursor ion Q value cutoff, 0.01.

7. Grouping and Comparison

Samples collected from the convex and concave sides in IS patients were classified as the IST group and ISA group, respectively. To investigate proteomic imbalance of paraspinal muscles in IS, comparison between the IST group and ISA group were conducted. Samples collected from the convex and concave sides in CS patients were classified as the CST group and CSA group, respectively. To investigate proteomic imbalance of paraspinal muscles in CS, comparison between the CST group and CSA group were conducted. Upregulation was defined as a higher expression of DEPs on the convex side than the concave side, whereas downregulation was defined as a lower expression of DEPs on the convex side than the concave side. To determine IS-specific proteomic profile, DEPs in paraspinal muscles between the convex and concave sides in IS were compared with that in CS. After the elimination of DEPs with the same trend in bilateral paraspinal muscles shared by both IS and CS, the remaining DEPs in IS were defined as the IS-specific DEPs.

8. Bioinformatic Analysis

Fold change $>1.5$ and $<0.67$ were set to identify DEPs between groups, with a $p$-value of $<0.05$ determined by independent $t$-test. Volcano plot and hierarchical clustering heatmap with R package (version 3.4.3) were used to analyze DEPs. Gene ontology (GO) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis and Interpro (IPR) domain annotation were performed using R ver. 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) to explore functional enrichment of DEPs. Cytoscape (ver. 3.8.2) were utilized to construct protein–protein interaction (PPI) network and screen out hub proteins.

9. Statistical Analysis

Clinical data were analyzed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation and compared by independent $t$-test or Mann-Whitney U-test. Categorical variables were presented as percentages (%) and compared by chi-square test. Proteomic data were processed by Spectronaut Pulsar X software (Biognosys AG) with default settings, and the FDR was also set as 1%. Proteomic analysis between groups were compared by independent $t$-test. A $p$-value of $<0.05$ was considered statistically significant. Hypergeometric test was applied for enrichment analyses of GO terms, KEGG pathways and IPR domains, with a $p$-value of $<0.05$ was considered significant.

RESULTS

1. Patient Characteristics

A total of 5 IS patients and 5 CS patients were matched in this
study (Table 1). Average age for IS group and CS group were 13.8 ± 0.8 and 13.0 ± 1.2 years old, respectively, with no statistical difference between groups (p < 0.05). There were 4 females in each group (p < 0.05). No significant differences were observed in major curve-related parameters, including curve length, Cobb angle and the location of apical vertebra (All p < 0.05).

Table 1. Comparison of clinical data between patients with idiopathic scoliosis and congenital scoliosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>IS</th>
<th>CS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>13.8 ± 0.8</td>
<td>13.0 ± 1.2</td>
<td>0.262†</td>
</tr>
<tr>
<td>Sex (female%)</td>
<td>80</td>
<td>80</td>
<td>1.000‡</td>
</tr>
<tr>
<td>Major curve length (no. of vertebrae)</td>
<td>6.4 ± 0.9</td>
<td>5.8 ± 2.4</td>
<td>0.589§</td>
</tr>
<tr>
<td>Major curve Cobb angle (°)</td>
<td>52.6 ± 7.9</td>
<td>52.4 ± 9.6</td>
<td>0.972†</td>
</tr>
<tr>
<td>Apical vertebra/sampling site</td>
<td>8.6 ± 0.9</td>
<td>9.0 ± 1.4</td>
<td>0.723§</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or unless otherwise indicated.

IS, idiopathic scoliosis; CS, congenital scoliosis.

†Independent t-test. ‡Chi-square test. §Mann-Whitney U-test.

2. Proteomic Analysis of Paraspinal Muscle Imbalance in IS

Comparison of paraspinal muscles on the convex and concave sides identified 105 DEPs in IS (Fig. 2A). Among these DEPs, 30 exhibited higher expression on the convex side than the concave side; while the remaining 75 DEPs displayed lower expression on the convex side than the concave side (Fig. 2B). According to GO annotation of biological process, DEPs in IS were enriched in calcium ion binding, DNA binding, and et al. (Fig. 2C). KEGG analysis revealed the enrichment of DEPs in IS in various pathways, including glycolysis gluconeogenesis, purine metabolism, hypertrophic cardiomyopathy, et al. (Fig. 2D). IPR domain annotation revealed that DEPs in IS were enriched in Vitamin K epoxide reductase and calsequestrin (Fig. 2E). Subcellular distribution of DEPs in IS identified 89 nodes and 405 edges. Top 10 hub proteins in protein-protein interaction network of IS: IST, paraspinal muscles on the convex side idiopathic scoliosis; ISA, paraspinal muscles on the concave side idiopathic scoliosis; IS, idiopathic scoliosis; DEP, differentially expressed protein; BP, biological process; MF, molecular function; PWWP, Pro-Trp-Trp-Pro motif.

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Fig. 2. Comparison of proteomic profiles between the IST group and ISA group. (A) Hierarchical clustering heatmap based on 105 DEPs in IS. (B) Volcano plot shows that 75 DEPs were highly expressed in the ISA group and 30 were highly expressed in the IST group. (C) Gene ontology (GO) analysis indicates functional enrichment of DEPs in IS in biological processes, such as protein glycosylation, and molecular functions including calcium ion binding and DNA binding. (D) Kyoto Encyclopedia of Genes and Genomes analysis reveals the enrichment of DEPs in IS in pathways, including glycolysis gluconeogenesis, purine metabolism, etc. (E) IPR analysis indicates the enrichment of DEPs in IS in Vitamin K epoxide reductase, calsequestrin, et al. (F) Subcellular distribution of DEPs in IS. (G) Protein-protein interaction network of DEPs in IS identified 89 nodes and 405 edges. (H) Top 10 hub proteins in protein-protein interaction network of IS: IST, paraspinal muscles on the convex side idiopathic scoliosis; ISA, paraspinal muscles on the concave side idiopathic scoliosis; IS, idiopathic scoliosis; DEP, differentially expressed protein; BP, biological process; MF, molecular function; PWWP, Pro-Trp-Trp-Pro motif.
Fig. 2. Comparison of proteomic profiles between the IST group and ISA group. (A) Hierarchical clustering heatmap based on 105 DEPs in IS. (B) Volcano plot shows that 75 DEPs were highly expressed in the ISA group and 30 were highly expressed in the IST group. (C) Gene ontology (GO) analysis indicates functional enrichment of DEPs in IS in biological processes, such as protein glycosylation, and molecular functions including calcium ion binding and DNA binding. (D) Kyoto Encyclopedia of Genes and Genomes analysis reveals the enrichment of DEPs in IS in pathways, including glycolysis/gluconeogenesis, purine metabolism, etc. (E) IPR analysis indicates the enrichment of DEPs in IS in Vitamin K epoxide reductase, calsequestrin, etc. (F) Subcellular distribution of DEPs in IS. (G) Protein-protein interaction network of DEPs in IS identified 89 nodes and 405 edges. (H) Top 10 hub proteins in protein-protein interaction network of IS. IST, paraspinal muscles on the convex side in idiopathic scoliosis; ISA, paraspinal muscles on the concave side in idiopathic scoliosis; IS, idiopathic scoliosis; DEP, differentially expressed protein; BP, biological process; MF, molecular function; PWWP, Pro-Trp-Trp-Pro motif. (Continued)
2E). Subcellular localization of DEPs in IS indicated that 22 proteins localized in cytoplasm, 17 in nucleus, 9 in mitochondrion, 8 in cytoskeleton, 7 in plasma membrane and 5 in centrosome (Fig. 2F). Global analysis of DEPs in IS identified 89 nodes and 405 edges involved in PPI network (Fig. 2G). The top 10 hub proteins were myosin light chain 11 (MYL11), troponin C2, fast skeletal type (TNNC2), troponymosin alpha-1 chain isoform Tpm1.2st (TPM1.2st), troponin I2, fast skeletal type (TNNI2), actinin alpha 3 (ACTN3), ATPase sarcoplasmic/endoplasmic reticulum Ca\textsuperscript{2+} transporting 1 (ATP2A1), myosin light chain 1 (MYL1), nebulin (NEB), myozenin 1 (MYOZ1), and myosin-binding protein C2 (MYBPC2) (Fig. 2H).

3. Proteomic Analysis of Paraspinal Muscle Imbalance in CS

Forty-eight DEPs in bilateral paraspinal muscles were detected in CS patients (Fig. 3A). Higher expression of 25 DEPs on the convex side than the concave side were observed. The remaining 23 DEPs exhibited lower expression on the convex side than the concave side (Fig. 3B). GO analysis revealed that DEPs in CS were enriched in receptor activity in the category of molecular function and immune response in the category of biological process (Fig. 3C). Analysis of KEGG pathway suggested the enrichment of DEPs in CS in glycolysis/gluconeogenesis, cellular senescence, Kaposi’s sarcoma-associated herpesvirus infection and biotin metabolism (Fig. 3D). IPR domain annotation showed that the enrichment of DEPs in CS in various domains including methyltransferase, NNMT/PNMT/TEMT, phosphoglycerate kinase, frataxin/CyaY, etc. (Fig 3E). Subcellular localization of DEPs in CS revealed the distribution of 9 proteins in cytoplasm, 6 in nucleus, 4 in plasma membrane, 4 in cytoskeleton, 3 in mitochondrion and 3 in extracellular space (Fig. 3F). PPI network of DEPs in CS displayed 43 nodes and 69 edges (Fig. 3G). The top

Fig. 3. Comparison of proteomic profiles between the CST group and CSA group. (A) Hierarchical clustering heatmap based on 48 DEPs in CS. (B) Volcano plot shows that 25 DEPs were highly expressed in the CSA group and 23 were highly expressed in the CST group. (C) Gene ontology (GO) term analysis indicates functional enrichment of DEPs in CS in immune response and receptor activity. (D) Kyoto Encyclopedia of Genes and Genomes pathway analysis reveals the enrichment of DEPs in CS in glycolysis/gluconeogenesis, cellular senescence, etc. (E) IPR domain analysis exhibits the enrichment of DEPs in CS in methyltransferase, NNMT/PNMT/TEMT, phosphoglycerate kinase, et al. (F) Subcellular distribution of DEPs in CS. (G) Protein-protein interaction network of DEPs in CS identified 43 nodes and 69 edges. (H) Top 10 hub proteins in protein-protein interaction network of CS. CST, paraspinal muscles on the convex side in congenital scoliosis; CSA, paraspinal muscles on the concave side in congenital scoliosis; CS, congenital scoliosis; DEP, differentially expressed protein; BP, biological process; MF, molecular function; TMPIT, transmembrane protein induced by tumor necrosis factor alpha; NNMT/PNMT/TEMT, nicotinamide N-methyltransferase/phénylthanolamine Nmethyltransferase/thioether S-methyltransferase; DUF1731, domain of unknown function 1731; AMOP, adhesion-associated domain in MUC4 and other proteins.

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Fig. 3. Comparison of proteomic profiles between the CST group and CSA group. (A) Hierarchical clustering heatmap based on 48 DEPs in CS. (B) Volcano plot shows that 25 DEPs were highly expressed in the CSA group and 23 were highly expressed in the CST group. (C) Gene ontology (GO) term analysis indicates functional enrichment of DEPs in CS in immune response and receptor activity. (D) Kyoto Encyclopedia of Genes and Genomes pathway analysis reveals the enrichment of DEPs in CS in glycolysis/gluconeogenesis, cellular senescence, etc. (E) IPR domain analysis exhibits the enrichment of DEPs in CS in methyltransferase, NNMT/PNMT/TEMT, phosphoglycerate kinase, et al. (F) Subcellular distribution of DEPs in CS. (G) Protein-protein interaction network of DEPs in CS identified 43 nodes and 69 edges. (H) Top 10 hub proteins in protein-protein interaction network of CS. CST, paraspinal muscles on the convex side in congenital scoliosis; CSA, paraspinal muscles on the concave side in congenital scoliosis; CS, congenital scoliosis; DEP, differentially expressed protein; BP, biological process; MF, molecular function; TMPIT, transmembrane protein induced by tumor necrosis factor alpha; NNMT/PNMT/TEMT, nicotinamide N-methyltransferase/phenylethanolamine Nmethyltransferase/thioether S-methyltransferase; DUF1731, domain of unknown function 1731; AMOP, adhesion-associated domain in MUC4 and other proteins. (Continued)
10 hub proteins were glyceraldehyde-3-phosphate dehydrogenase, titin, myosin heavy chain 4, parvalbumin, protein phosphatase 3 catalytic subunit alpha, PDZ (PSD-95, Dlg, and ZO-1/2) and LIM (Lin11, Isl-1, and Mec-3) domain 7, succinate-CoA ligase guanosine diphosphate-forming subunit beta, cullin 4A, cyclin dependent kinase 6 and phosphoglycerate kinase 1 (PGK1) (Fig. 3H).

Table 2. Differentially expressed proteins with the same trend in bilateral paraspinal muscles of both IS and CS

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Expression in IS</th>
<th>Expression in CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoglycerate kinase 1</td>
<td>PGK1</td>
<td>Convex &lt; Concave</td>
<td>Convex &lt; Concave</td>
</tr>
<tr>
<td>Cullin-4A isoform 1</td>
<td>CUL4A</td>
<td>Convex &lt; Concave</td>
<td>Convex &lt; Concave</td>
</tr>
<tr>
<td>Phosphoglucomutase-1 isoform 1</td>
<td>PGM1</td>
<td>Convex &lt; Concave</td>
<td>Convex &lt; Concave</td>
</tr>
<tr>
<td>Myosin-binding protein C, fast-type</td>
<td>MYBPC2</td>
<td>Convex &lt; Concave</td>
<td>Convex &lt; Concave</td>
</tr>
<tr>
<td>PDZ and LIM domain protein 7 isoform 1</td>
<td>PDLIM7</td>
<td>Convex &lt; Concave</td>
<td>Convex &lt; Concave</td>
</tr>
<tr>
<td>Armadillo repeat-containing protein 1 isoform 1</td>
<td>ARMC1</td>
<td>Convex &gt; Concave</td>
<td>Convex &gt; Concave</td>
</tr>
<tr>
<td>Kelch-like protein 34</td>
<td>KLHL34</td>
<td>Convex &gt; Concave</td>
<td>Convex &gt; Concave</td>
</tr>
<tr>
<td>PDZ and LIM domain protein 7 isoform 4</td>
<td>PDLIM7</td>
<td>Convex &lt; Concave</td>
<td>Convex &lt; Concave</td>
</tr>
</tbody>
</table>

IS, idiopathic scoliosis; CS, congenital scoliosis; Convex < Concave, a higher expression in paraspinal muscles on the concave side than that on the convex side; Convex > Concave, a higher expression in paraspinal muscles on the convex side than that on the concave side.

Fig. 4. Bioinformatic analysis of DEPs shared by IS and CS. (A) Hierarchical clustering heatmap based on 8 DEPs shared by IS and CS. (B) Volcano plot shows that 2 DEPs shared by IS and CS were highly expressed in the IST group and 6 were highly expressed in the ISA group. (C) Gene ontology (GO) analysis indicates functional enrichment of DEPs shared by IS and CS in protein binding, carbohydrate metabolic process, etc. (D) Kyoto Encyclopedia of Genes and Genomes analysis reveals the pathway enrichment of DEPs shared by IS and CS in glycolysis/gluconeogenesis, nucleotide excision repair, etc. (E) Interpro analysis exhibits domain enrichment of DEPs shared by IS and CS in phosphoglycerate kinase, PDZ domain, etc. (F) Subcellular distribution of DEPs shared by IS and CS. IST, paraspinal muscles on the convex side in idiopathic scoliosis; ISA, paraspinal muscles on the concave side in idiopathic scoliosis; IST, vs. ISA, shared, differentially expressed proteins in paraspinal muscles between the convex and concave sides in idiopathic scoliosis shared by congenital scoliosis; DEP, differentially expressed protein; IS, idiopathic scoliosis; CS, congenital scoliosis; BP, biological process; MF, molecular function; BTB, broad-complex, tramtrack and bric a brac; PDZ, PSD-95, Dlg, and ZO-1/2.

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4. Identification of DEPs in Bilateral Paraspinal Muscles Shared by Both IS and CS

Comparison of DEPs in bilateral paraspinal muscles in IS and that in CS was performed. Only 8 DEPs with same trend in both IS and CS were identified (Table 2). Among DEPs shared by both IS and CS, 6 exhibited lower expression in paraspinal muscles on the convex side than that on the concave side; while the expression of the remaining 2 DEPs were higher on the convex side than that on the concave side in IS (Fig. 4A, B). GO annotation demonstrated that DEPs shared by both groups were
Fig. 5. Bioinformatic analysis of IS-specific DEPs. (A) Hierarchical clustering heatmap based on 97 IS-specific DEPs. (B) Volcano plot shows 69 DEPs were highly expressed in the ISA group and 28 were highly expressed in the IST group. (C) Gene ontology (GO) analysis indicates functional enrichment of IS-specific DEPs in biological processes, such as protein glycosylation, and molecular functions, such as calcium ion binding, protein glycosylation, etc. (D) Kyoto Encyclopedia of Genes and Genomes analysis reveals the pathway enrichment of IS-specific DEPs in glycolysis/gluconeogenesis, hypertrophic cardiomyopathy, purine metabolism, etc. (E) Interpro analysis exhibits domain enrichment of IS-specific DEPs in Vitamin K epoxide reductase, calsequestrin, et al. (F) Subcellular distribution of IS-specific DEPs. (G) Protein-protein interaction network of IS-specific DEPs identified 82 nodes and 350 edges. (H) Top 10 hub proteins in protein-protein interaction network of IS-specific DEPs. IST vs. ISA specific, differentially expressed proteins in paraspinal muscles between the convex and concave sides specific in idiopathic scoliosis; DEP, differentially expressed protein; IS, idiopathic scoliosis; BP, biological process; MF, molecular function; BTB, broad-complex, tramtrack and bric a brac; PWWP, Pro-Trp-Trp-Pro motif.

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Proteomic Comparison Between IS and CS


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Vitamin K epoxide reductase
Calcium-binding/EF-hand
p53-like transcription factor, DNA-binding
Rel homology-dimerisation domain
Rel homology
ATPase, P-type-cation-transporter, N-terminal
ATPase, P-type-cation-transporter, C-terminal
Spectrin repeat
Cytoplasm protein (27.03%)
Nucleus protein (20.27%)
Mitochondrion protein (12.16%)
Plasma membrane protein (9.46%)
Cytoskeleton protein (6.76%)
Endoplasmic reticulum protein (5.41%)
Golgi apparatus protein (2.70%)
Lysosome protein (2.70%)
Endosome protein (2.70%)
Golgi apparatus protein (1.35%)

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erate kinase, PDZ domain, alpha-D-phosphohexomutase, C-terminal, et al. (Fig. 4E). Among DEPs shared by both groups, 3 were localized in cytoplasm, 3 in nucleus and 2 in cytoskeleton (Fig. 4F). A tight correlation between PGK1 and phosphoglucomutase-1 isoform 1 was observed in PPI network, which corresponds with the enrichment of DEPs in carbohydrate metabolic process in GO annotation and glycolysis/gluconeogenesis pathway in KEGG analysis.

5. Identification of DEPs in Bilateral Paraspinal Muscles Specific for IS

Comparison of DEPs in bilateral paraspinal muscles in IS and that in CS identified 97 DEPs specific for IS, which account for 91.5% of all DEPs in paraspinal muscles between the convex side and concave side in IS (Fig. 5A). Among those IS-specific DEPs, 69 exhibited lower expression on the convexity than the concavity; while the expression of the remaining 28 DEPs were higher on the convexity than that on the concavity (Fig. 5B). GO analysis indicated that these IS-specific DEPs were enriched in calcium ion binding, protein glycosylation, DNA binding, et al. (Fig. 5C). KEGG pathway analysis showed the enrichment of IS-specific DEPs in multiple pathways, including glycolysis/gluconeogenesis, hypertrophic cardiomyopathy, purine metabolism, et al. (Fig. 5D). IPR annotation exhibited the enrichment of IS-specific DEPs in functions including Vitamin K epoxide reductase, calsequestrin, etc. (Fig. 5E). Subcellular localization of IS-specific DEPs showed that 20 proteins distributed in cytoplasm, 15 proteins in nucleus, 9 in mitochondrion, 7 in plasma membrane, 5 in the cytoskeleton, and 5 in the centrosome (Fig. 5F). Comprehensive analysis of IS-specific DEPs identified a total of 82 nodes and 350 edges involved in PPI network (Fig. 5G). The top 10 hub proteins were MYL11, TNNC2, TPM1.2st, TNNI2, ATP2A1, ACTN3, MYL1, NEB, MYOZ1, and tropomyosin alpha-1 chain isoform Tpm1.5cy (TPM1.5cy) (Fig. 5H).

DISCUSSION

This study first described paraspinal muscle imbalance in IS and CS from the aspect of proteome. Comparison of DEPs in paraspinal muscles between the concave and convex sides revealed low similarity in DEPs between IS and CS. Therefore, it is inferred that paraspinal muscle imbalance in gene expression in IS seems not to be changes secondary to the deformity.

Researches about paraspinal muscle imbalance in IS have emerged since decades ago. General observation during surgery indicates the imbalance of muscle volume and fatty infiltration in bilateral paraspinal muscles. To verify this discovery, various imaging methods were undertaken. For instance, ultrasound examination indicated a greater muscle thickness on the concavity. Detection of paraspinal muscles in IS with MRI showed a greater cross-sectional area and muscle volume on the concavity. MRI also demonstrated more severity of fatty infiltration on the concavity than that on the convexity. Except for asymmetrical distribution between the concave side and convex side, fatty infiltration in paraspinal muscles of IS also has other typical properties. The severity of fatty infiltration on the concavity of the curve increases gradually from the end vertebra towards the apex. A significant effect of the medial-to-lateral distribution was also observed, with more severe fatty infiltration in the medial (multifidus) than the lateral (erector spinae). Overall, multifidus at the apex on the concavity was speculated as the most severely affected area. Therefore, multifidus muscles at the apical region were selected as the main focus in this study. In addition to conventional imaging modalities, novel technologies were also used to evaluate paraspinal muscle imbalance in IS. X-ray fluorescence demonstrated the asymmetric distribution of metal ions in bilateral paraspinal muscles of IS patients, with higher concentrations of calcium, zinc and copper, on the concavity than the convexity. Detection of back muscles with infrared thermography in IS revealed higher infrared emissivity and temperature on the concavity than the convexity. However, whether CS patients share similar imbalance in above parameters has not been elucidated. Different from imaging methods, histological examinations analyzed paraspinal muscle imbalance in IS from microcosmic aspect. Muscles on the convexity possess a greater cross-sectional area and myonuclei density than that on the concavity. Asymmetrical distribution of myofiber types in bilateral paraspinal muscles was also observed, with a higher proportion of type I fiber and lower proportion of type II fiber on the convexity. Besides, higher levels of fatty involution and fibrosis were observed on the concavity. Yet histological comparison of paraspinal muscle imbalance between IS and CS is lacking. Electromyogram was widely applied to evaluate myoelectric activity of paraspinal muscles. Despite of the existence of some contrary reports, most studies reported that electromyogram parameters, such as motor unit action potential and root mean square amplitude, on the convexity were higher than that on the concavity in IS. Nevertheless, researches on myoelectric activities of paraspinal muscles in CS are rare.

The development of molecular biotechnology provides a possibility to resolve paraspinal muscle imbalance in IS from the
aspect of gene expression. Genetic association studies identified exceeding 20 susceptible genes in IS. Some of those genes exhibit differential expression in bilateral paraspinal muscles in IS. For instance, Xu et al.13 demonstrated a higher expression of \(LBX1\) on the convexity than that on the concavity. However, no differential expression of \(LBX1\) in bilateral paraspinal muscles of CS patients was observed. By targeting MyoD to regulate myogenesis, \(LBX1\) is implicated in the etiology of IS. Similar to \(LBX1\), expressions of other genes in Wnt pathway, such as \(CTNNB1\) and \(PAX3\), show similar difference in IS but no significant difference in CS.35,36 In addition to genes in Wnt pathway, the expression of \(SOCS3\) in IS and CS was also reported. In IS patients, paraspinal muscles on the convexity exhibited a higher expression of \(SOCS3\) than the concavity, whereas no difference in \(SOCS3\) expression in bilateral paraspinal muscles was observed in CS patients.14 Unlike above genes, the expression of \(GPR126\) was higher in paraspinal muscles on the concavity than that on the convexity in IS.15 Howbeit, \(GPR126\) expression in paraspinal muscles did not differ between the concave side and the convex side in CS.

Apart from genomic technologies, transcriptome sequencing was also applied for the detection of paraspinal muscle imbalance in IS. Jiang and colleagues identified 40 DEGs between the concave and convex sides of paraspinal muscles in IS.24 Of the 40 DEGs, \(ADIPOQ\) exhibited a higher expression on the concavity than the convexity in IS, whereas the expression of \(H19\) was higher on the convexity than the concavity. However, neither \(ADIPOQ\) or \(H19\) displayed differential expression between the concaved and convexed sided paraspinal muscles in CS. Moreover, differential expression of \(ADIPOQ\) and \(H19\) in bilateral paraspinal muscles is correlated with curve severity and the age at initiation. Luo et al.25 also performed transcriptome analyses and identify 58 DEGs of bilateral paraspinal muscles in IS. They demonstrated that \(TENT5A\) expression was higher on the convex side than that on the concave side. Although the pivotal role of \(TENT5A\) in myogenesis and muscle fiber maturation, whether \(CS\) shares similar differential expression of \(TENT5A\) in paraspinal muscles between the concave and convex sides with IS still remains unclear.

As is known, proteins are the main executors of cellular functions. Herein, we applied DIA proteomic sequencing to decipher paraspinal muscle imbalance in IS. GO analysis indicated the enrichment of DEPs in this study in calcium ion binding and DNA binding, whereas DEGs identified in the research of Luo and colleagues mainly enriched in extracellular space, glucose metabolic process, and glucose homeostasis.25 KEGG analysis demonstrated that DEPs in this study enriched in glycolysis/gluconeogenisis, in line with the report of Jiang et al.24 IPR domain analysis indicated the enrichment of DEPs in IS in calsequestrin. Calsequestrins participate in muscle contraction through the regulation of calcium storage in the sarcoplasmic reticulum. Calsequestrin 1 is mainly expressed in type II myofibers, whereas calsequestrin 2 is mainly expressed in type I myofibers and cardiomyocytes. In this study, a higher expression of calsequestrin 1 and a lower expression of calsequestrin 2 were observed on the concavity, which may to some degree reflect the asymmetric side distribution of different types of myofibers in IS. All the top 10 hub proteins in the PPI network of DEPs in IS are involved in muscle functions, including muscle contraction and myofibrillogenesis.

It should be pointed out that proteomic analysis of paraspinal muscle imbalance in IS patients only failed to distinguish potential primary DEPs from DEPs secondary to the deformity. To screen out DEPs secondary to scoliosis, bilateral paraspinal muscles in CS were also subjected to proteomic sequencing. It is widely acknowledged that paraspinal muscle imbalance in CS is secondary to the primary vertebral malformations, though genetic causes for skeletal deformities may also bring about muscle lesions in CS. Enrichment of DEPs in glycolysis/gluconeogenesis pathway was observed in CS, similar to that in IS. Besides, DEPs are also enriched in other pathways, including cellular senescence, Kaposi’s sarcoma-associated herpesvirus infection and biotin metabolism. GO analysis showed that DEPs in CS were enriched in immune response and receptor activity. Among the top 10 hub proteins in the PPI network of DEPs in CS, titin, myosin heavy chain 4 and parvalbumin are involved in muscle contraction, whereas PDZ and LIM domain 7 participates in actin cytoskeleton organization.

Obviously, functional enrichments of DEPs in IS are quite different from that in CS. In fact, there is low similarity in DEPs between IS and CS, with only 7.6% of DEPs in IS shared by CS. Except for 8 DEPs shared by both IS and CS, other DEPs in IS were deemed to be specific. These IS-specific DEPs are enriched in calcium ion binding and DNA binding in GO annotation and glycolysis/gluconeogenesis in KEGG pathway. Considering that almost all hub proteins in the PPI network of DEPs in IS are enriched in muscle contraction, it is inferred that the process of muscle contraction, which depends on the release of calcium from sarcoplasmic reticulum and energy supply, may play an important role in paraspinal muscle imbalance in IS.

This study provides comprehensive proteomic landscapes of...
paraspinal muscles and identified proteomic characteristics of paraspinal muscle imbalance in both IS and CS. Further comparison of DEPs between IS and CS helps to exclude changes in bilateral paraspinal muscles secondary to spinal deformities, which set great obstacles for clarification of the causal relationship between paraspinal muscle imbalance and IS. The identification of DEPs specific for IS provides the basis for future study exploring pivotal genes for paraspinal muscle imbalance in IS and the role of paraspinal muscle imbalance in the pathogenesis of IS. Through restoring the expressions of pivotal genes, targeted therapy may be able to correct paraspinal muscle imbalance, thereby preventing the progression of IS. However, this study still has several limitations. First, sample sizes in this study are relatively small, though patients in IS group and CS group were well-matched regarding age, sex and apex location. Second, this study only identified proteomic differences in paraspinal muscle imbalance between IS and CS, and thus offer some indirect basis for the speculation that paraspinal muscle imbalance might be the cause of IS rather than the consequence. Third, this study only provided a general landscape of differential proteome specific for paraspinal muscle imbalance in IS, further research is required to identified key proteins responsible for paraspinal muscle imbalance in IS.

CONCLUSION

This study demonstrates that differences in proteomic profile in paraspinal muscles between the convex and concave sides are common in both IS and CS. However, IS shares low similarity in DEPs in bilateral paraspinal muscles with CS, suggesting that spinal deformities may not be the principal cause of paraspinal muscle imbalance in IS.

NOTES

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Robotic-assisted (RA) surgery is becoming increasingly common in spine surgery, many literatures have been accumulated and showed the advantage of accuracy, radiation reduction, efficiency, future applications over traditional open surgery or even conventional minimally invasive surgery.1–3 By using advanced imaging techniques and computer-assisted navigation, the surgeon can plan and execute the procedure with a high degree of precision, which can help reduce the risk of complications and improve outcomes. The potential advantage of RA cervical spine surgery is greater accuracy and precision. Recently the robot assisted cervical spine surgery has been studied, some studies have suggested that RA cervical spine surgery may offer several advantages over traditional surgery.

The paper “Robotics in Cervical Spine Surgery: Feasibility and Safety of Posterior Screw Placement”4 proved this line of research using meta-analyses, to evaluate the feasibility and safety of RA screw placement on cervical spine surgery. This paper reviewed systematically total 7 studies; 1 randomized controlled trial,3 3 comparative cohort studies, and 3 case series.4–9 This paper concluded that the RA cervical pedicle screw fixation is safe and feasible on the result of optimal and clinically acceptable cervical screw placement accuracy were 88.0% and 98.4% respectively.

Though the accuracy is highly enough reported in recent reports, there is several reasons why the RA cervical pedicle screw placement is still challenging procedures to be cautious in the practice.

Current status of U.S. Food and Drug Administration (FDA) regulation for the RA cervical pedicle screw placement reflect the current status of the clinical acceptable accuracy of several kind of robotic systems.10 Several robotic systems have had FDA clearance for use in the cervical spine: the ExcelsiusGPS (Globus Medical, Audubon, Pennsylvania, PA, USA), the Cirq Robotic Alignment Module (Brainlab, Munich, Germany) but such use requires simultaneous intraoperative fluoroscopic confirmation or imaging workflow for real-time...
Commentary on "Robotics in Cervical Spine Surgery"

Yi S

The unique features of cervical spine are complex anatomy encasing vertebral artery and larger spinal cord, skiving on the bony surface, more mobile segments highly affected by patient’s position and surgical manipulation, smaller dimension, more convergent trajectory for pedicle screw and musculature than the other spine, which has more potential risk than thoraco-lumbar-sacral spine if the robotic errors exceed some extent of limit. The neurovascular complication by misplacement of cervical screws would be more catastrophic than the other spine. The main advantage of minimally invasive RA thoracolumbar surgery is the percutaneous screw insertion without using fluoroscopy or navigation, avoiding radiation hazards and restriction of unnecessary hand movement along the axis of screw insertion, minimizing destructive procedures. But the cervical pedicle screw placement is usually performed in open procedures, cannot be easily done by percutaneous technique at this moment due to the difficulty in localizing optimal anatomical landmark, few available percutaneous cervical screws system, except posterior C1–2 transarticular screw placement which can be done by percutaneously in skin entry, but not be done in bone entry actually.

RA cervical spine surgery is controversial though recent articles showed favorable results. The accuracy of surgical robot itself is reliable enough in submillimeter level. But the current technical limitations, which cannot visualize virtual image over cervical anatomy in real time, resulted in unwillingness of RA cervical surgery. Surgeons should understand the possible errors and consequences beyond robotic system. To be confident for the RA cervical spine surgery, real-time visualization or tracking system for real anatomical landmark to be coordinated by robotic system should be achieved, which is not introduced yet in current technologies.

In the current state, the robotic system has benefit clearly on identifying the ideal entry point and trajectory for accurate screw insertion based on the 3-dimensional CT reconstructions in cervical spine, especially in the patient of complex deformity. The preoperative planning leads to higher efficiency saving surgical time. Ultimately, the decision to undergo RA cervical spine surgery should be based on a careful evaluation of the patient’s individual anatomy and circumstances, as well as the skillful experience of the surgeon performing the procedure.

While this paper concluded a promising result, we look forward to a larger series before conclusions can be made about the safety and accuracy of its use with instrumentation in the cervical spine. The RA cervical spine will become essential, reliable and standard procedures when the accuracy supported by real-time anatomical information, the cost effectiveness, efficiency, special surgical instruments allowing RA percutaneous procedures are realized in the near future.

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Letter to the Editor

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The Fine Line Between Simplicity and Oversimplification: Comparing the Risk Analysis Index and 5-Factor Modified Frailty Index as Frailty Assessment Tools

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To the Editor,

Occam’s Razor insinuates that the premise with the fewest assumptions, or the most straightforward explanation, should be selected when presented with competing hypotheses.1 While this principle has frequently proven helpful in numerous disparate fields,1 it is essential to exercise caution when applying it to healthcare-related decisions (e.g., preoperative frailty risk assessment). Frailty risk assessment plays a pivotal role in perioperative management, as it empowers clinicians to identify high-risk patients who would benefit from preoperative optimization and multidisciplinary planning.2,3 Nonetheless, inaccurate frailty risk assessments can lead to inappropriate care plans, increased expenditures, and potentially adverse patient outcomes through erroneously understating the actual risk.4 Two prevalent frailty screening tools frequently utilized in neurosurgical practices are the Risk Analysis Index (RAI)2,5 and the 5-factor Modified Frailty Index (mFI-5) (Fig. 1).3 We aim to draw the neurosurgery workforce’s attention to the potential pitfalls of exclusively relying on Occam’s Razor when implementing frailty interventions. Additionally, we emphasize the importance of a thorough assessment method, as there are instances when Hickam’s Dictum takes precedence over parsimony.

The mFI-5 evaluates patients based on 5 specific parameters: diabetes, hypertension, functional dependence, chronic obstructive pulmonary disease, and congestive heart failure.3 The mFI-5 is advantageous due to its simplicity and ease of implementation.3 However, it also has certain drawbacks, such as its potential to overlook other critical aspects of frailty and oversimplification of complex cases, consequently leading to suboptimal care plans.3,5 Despite this the mFI-11, an extended, comorbidity-based frailty measure version of the mFI-5, is the most commonly reported frailty index, garnering considerable attention in the neurosurgery spine literature.6 RAI is an alternative screening tool that evaluates a patient’s overall health status based on various factors, including age, functional dependence, and comorbidities.1,2 RAI offers several advantages, such as its ease of use and integration into clinical workflows.7-10 Studies in the neurosurgery literature, encompassing a wide range of routinely
performed procedures, such as spinal, cranial, and functional surgeries, demonstrate that the RAI consistently exhibits superior discrimination compared to mFI-5, and greater patient age. Moreover, in these studies the RAI has been shown to be more effective in predicting a wide variety of adverse outcomes. Consider a hypothetical scenario in which an 85-year-old female spine patient is entirely dependent and requires social support. Her medical history includes renal cancer, dialysis, unintentional weight loss, diminished appetite, and pronounced dyspnea. Utilizing RAI, this patient receives a score of 55, classifying her as "very frail." In contrast, when assessed using the mFI-5, she obtains a score of 1, classifying her as "typical." This discrepancy illustrates the potential oversimplification of the patient's risk when relying solely on the mFI-5, which may result in a missed opportunity for perioperative optimization and tailored care planning to address her specific perioperative needs. Moreover, RAI offers a distinct advantage due to its broad spectrum of scores, which allows users to adopt tailored cutoffs suitable for diverse applications. These tailored cutoffs can be adapted according to the prevalence of frailty within a specific patient population and the resources available for the intervention.

The demonstrated superiority of RAI in predicting various adverse outcomes calls for neurosurgical practices to reconsider their exclusive reliance on mFI-5 for preoperative frailty risk assessment. While the mFI-5 can provide valuable information about a patient's comorbidities during preoperative planning, incorporating the RAI may yield a more comprehensive and accurate evaluation of a patient's frailty status. This transition will guarantee a thorough assessment and well-informed decision-making process. Ultimately, adopting a more rigorous approach to frailty risk assessment will not only enhance patient outcomes but also elevate the overall quality of care.

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