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Reciprocal Changes Following Cervical Realignment Surgery

Jae-Koo Lee, Seung-Jae Hyun, Seung Heon Yang, Ki-Jeong Kim

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Over the last few decades, the importance of the sagittal plane and its contour has gained significant recognition. Through full-body stereoradiography, the understanding of compensatory mechanisms, and the concept of global balance and reciprocal change has expanded. There have been a few reports describing how cervical realignment surgery affects global spinal alignment (GSA) and global balance. Despite the research efforts, the concept of reciprocal change and global balance is still perplexing. Understanding the compensatory status and main drivers of deformity in a patient is vital because the compensatory mechanisms may resolve reciprocally following cervical realignment surgery. A meticulous preoperative evaluation of the whole-body alignment, including the pelvis and lower extremities, is paramount to appreciate optimal GSA in the correction of spinal malalignment. This study aims to summarize relevant literature on the reciprocal changes in the whole body caused by cervical realignment surgery and review recent perspectives regarding cervical compensatory mechanisms.

Keywords: Reciprocal change, Global alignment, Cervical spine, Deformity, Balance, Odontoid

INTRODUCTION

Over the last few decades, the importance of the sagittal plane and its contour has gained significant recognition. Through full-body stereoradiography, the understanding of compensatory mechanisms in patients with spinopelvic imbalance has progressed rapidly, and the concept of global balance and reciprocal change has expanded to the field of the cervical spine and lower extremities.1 The regions of the spine are intertwined through compensatory mechanisms. When a patient loses an adequate lumbar lordosis (LL), compensatory mechanisms are recruited to maintain an upright posture; cervical hyperlordosis, thoracic kyphosis (TK), pelvic retroversion, and knee flexion.2-7 The sagittal alignment regarding spinopelvic parameters and reciprocal changes in the thoracolumbar spine has been well documented.8-12

The essential function of global spinal alignment (GSA) is the maintenance of global balance, an upright posture, and a horizontal gaze.13 Thus, in the setting of thoracolumbar spinal deformity, cervical alignment is the final piece affected by GSA through compensatory mechanisms to maintain a horizontal gaze.4,13-18 Likewise, recent studies report that cervical kyphotic deformity showed compensatory changes in the thoracolumbar spine, analogous to the changes that occur in thoracolumbar deformity.19-23 At the regional level, the upper cervical spine compensates for C2–7 angle through the extension of C0–2, thereby maintaining the patient’s horizontal gaze.22-27

Understanding the compensatory status of a patient is vital because the compensatory mechanisms may resolve reciprocally following cervical realignment surgery which correlates with improved patient outcome.19,21 Despite the efforts, understanding and anticipating the reciprocal changes that occur following realignment surgery is perplexing. Further, a new approach should be taken into account to comprehend reciprocal changes. This study aims to summarize relevant literature on the reciprocal changes in the whole body caused by cervical realignment surgery and review recent perspectives regarding cervical compensatory mechanisms.
COMPENSATORY MECHANISMS OF THE SPINE AND GLOBAL BALANCE

It is critical to understand the compensatory mechanisms and global balance of the spine beforehand as reciprocal change is a dynamic phenomenon. The sagittal balance reflects the spine’s shape, allowing individuals to maintain a standing position with minimal muscle force. The spine adapts to different changes in order to stay in balance. The normal aging process induces truncal stooping. To adapt to morphological variations that occur in the spine, several compensatory mechanisms are implemented to maintain optimal GSA (Fig. 1). The aging-related deterioration of the GSA is compensated by supportive functions of the spine, pelvis, and lower limbs. The compensations happen to refrain from the anterior shifting of the gravity line (GL). The compensatory mechanisms do not occur simultaneously but are closely associated depending on the stiffness of the spine, musculature status, painful phenomena, and severity of the imbalance. All mechanisms integrate with different ways depending on each individual.

In patients with spinal pathologies, compensatory mechanisms from the thoracolumbar to the cervical spine and lower extremities occur in a staged fashion to maintain horizontal gaze and global balance. In patients with spinal deformity at any level, initial compensatory mechanisms usually initiate adjacent to the deformity. After the exhaustion of the adjacent compensatory reservoir, the next adjacent segments are subsequently recruited to maintain an erect posture and balance. Roussouly and Pinheiro-Franco hypothesized the following sequential mechanism of compensation of progressive kyphosis: (1) a normal stage with slight pelvic retroversion and the C7 plumb line (C7PL) over the sacral endplate, (2) a compensated stage, with a progressive loss of LL and pelvic retroversion to maintain the C7PL posterior to the femoral heads; and (3) a decompensated stage, wherein hip extension limits pelvic retroversion, which is compensated by knee flexion, and the C7PL passes forward to the femoral heads. With the hips maximally extended and the knees flexed, the last posture is well-known in severe kyphosis and is very uncomfortable and uneconomical. Accordingly, patients with thoracolumbar malalignment exhibit compensatory changes in the form of cervical hyperlordosis, posterior pelvic shift, ankle dorsiflexion, knee flexion, hip extension, and pelvic retroversion. In addition, recent investigations have shown that cervical alignment is also affected by GSA through compensatory mechanisms to maintain an upright posture and horizontal gaze. Changes in cervical kyphosis (CK) reduce TK to correct alignment and maintain cone of economy of global spinal balance. To compensate for CK, posterior shifting of the C7PL, a decrease in T1 slope (T1S), and an increase in LL occurs. Therefore, to truly understand a patient’s state of balance, it is necessary to evaluate GSA because the compensatory mechanism for global malalignment is present.

For an overall assessment of a patient with spinal imbalance, radiography of the entire spine with a standardized position (hands resting on collar bones) is mandatory. Radiographs to analyze the overall sagittal balance including the lower limbs can be made with the EOS imaging system (EOS Imaging, Paris, France). The EOS system was developed to overcome the limitations of conventional radiography by interdisciplinary investigators. Using the 3-dimensional bone external envelope technique, EOS allows bilateral long-length images (whole-body or localized) in either the standing or seated position, with overall enhanced image quality and a lower radiation dose for the patient. Through whole-body radiographs, our understanding of the global balance and reciprocal changes in the cervical spine and the lower extremities became more profound.

Global balance can be determined by the position of the GL, defined as a plumb line from the center of the acoustic meatus (CAM). The normal location of bony landmarks in standing whole-body radiographs in reference to the GL has been reported using the EOS imaging system (Fig. 2). It has been proposed...
Reciprocal Changes Following Cervical Realignment Surgery

Lee JK, et al.

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Compensatory mechanisms and reciprocal changes of the cervical spine

1. Reciprocal Changes in the Regional Cervical Spine

In patients with spinal deformity, initial compensatory mechanisms usually initiate adjacent to the deformity. The next adjacent segments will be subsequently recruited after the exhaustion of adjacent compensatory reservoir to maintain an erect posture and balance. Sequential linkage of correlation has been demonstrated in asymptomatic subjects between C0–2 angle, C2–7 angle, and T1S; C2–7 angle showed a negative correlation with both C0–2 and T1S. In CK patients, the upper cervical spine is recruited to maintain balance. Thus, at the regional level, kyphotic alignment of the subaxial cervical spine is known to be compensated by a lordotic upper cervical spine and vice versa, which illustrates a regional compensatory mechanism. The upper cervical spine is the most mobile segment, hence the compensatory mechanism of the upper cervical spine would allow a patient to maintain horizontal gaze.

After cervical realignment surgery, reciprocal changes ensue. If the alignment is inadequate, it intensifies the compensatory mechanisms. When realignment surgery is adequately performed, it often leads to the relaxation of compensatory mechanisms. Hyperlordotic positioning of the upper cervical spine leads to a kyphotic alignment of the subaxial spine to maintain balanced cervical alignment. After a patient recovers optimal cervical lordosis (CL), C0–2 angle reciprocally decreases. Concurrently, Lafage et al. reported that correction of sagittal cervical deformity (CD) led to reciprocal relaxation of the established CD compensatory mechanisms such as C0–2 hyperlordosis and thoracic hypokyphosis. Furthermore, the preoperative Neck Disability Index (NDI) had a significant correlation with preoperative C0–2 range of motion (ROM) and reserve of extension (ROE). Relaxation of compensatory mechanisms was found to be associated with improvement in patients’ reported clinical

Fig. 2. Normative offset distances between bony landmarks and the gravity line. Positive values denote locations anterior to the gravity line and negative values indicate locations posterior to the gravity line. CAM, center of the acoustic meatus; CI, confidence interval.

that the optimal goal of a truly balanced spine is to maintain the head over femoral heads, suggesting that the position of the head is an important driver of true spinal balance. Recent investigations revealed that the mean offset distance from the center of gravity (COG) to the CAM was 0, and was not affected by aging. It suggests that when the global alignment gradually deteriorates with age as aging induces truncal stooping (Fig. 1), the change is compensated in order to maintain both horizontal gaze and global balance. Loss of lordosis and an increase in pelvic tilt were induced by the posterior shift of the lower lumbar vertebrae and sacrum, to maintain optimal positioning of the GL above the COG.
outcomes. The inclusion of ROM and ROE, as it is associated with patient-reported outcomes, can help to better understand this complex condition at a regional level.

2. Reciprocal Changes and Global Balance Following Cervical Realignment Surgery

Traditionally, a balanced spine is defined as whether spino-pelvic parameters, including the C7PL, are adequate. The C7PL was used to measure sagittal trunk balance as a virtual COG rather than GL, as it is generally concordant with GL in general populations and is a pragmatic tool to estimate sagittal trunk balance. However, the spine can be in balance (compensated), but spino-pelvic parameters can be inadequate. Even though C7PL is an easy method to estimate sagittal balance, its discordance with the GL has been widely recognized. When the distance between the GL and C7PL exceeds 30 mm, it is defined as occiput-trunk (OT) discordance. True GSA cannot be assessed using C7PL when there is OT discordance. Patients with CD are unable to accomplish OT concordance by extending the cervical segment. A posterior shifting of C7PL is therefore necessary for optimal positioning of the head. Following C7PL posterior shifting, subsequent thoracolumbar alignment compensation takes place. Hence, the concept of global balance utilizing GL was implemented to assess patients undergoing cervical realignment surgery.

Only a handful of research has been conducted regarding how cervical realignment surgery reciprocally affects GSA. It has first been reported that surgical correction of CK leads to an increase in preoperatively decreased T1S and TK, but did not influence lumbar or pelvic parameters. However, a recent study reported 2 different groups of CD patients with different compensatory mechanisms based on the preoperative location of the C7PL (Fig. 3): the head-balanced type and the trunk-balanced type. According to the C7PL value, the former was balanced globally while the latter was balanced below the trunk. In detail, the head-balanced patients were those with a posterior shifting of the C7PL but with optimal GL location. The head-balanced group is balanced globally, including the head, with hyper-lumbar lordosis, and a low T1S. Trunk-balanced patients are unable to shift the C7PL posteriorly, have upper-limit pelvic incidence–LL values, and have normal T1S.

The primary goal of cervical realignment surgery is to achieve OT concordance. Once OT concordance is achieved, subsequent thoracolumbar alignment changes occur to harmonize GSA, showing that cervical reconstruction can restore both cervical deformities and GSA. Subsequently, thoracolumbar alignment changed to harmonize the entire spinal alignment. Although mild CD affects adjacent segments, a severe CD can alter even the lumbar segments. Cervical realignment surgery induces reciprocal changes and restores both cervical and global balance. Correction in the head-balanced group resulted in anterior shifting of C7PL, a subsequent increase in T1S and TK, and a decrease in LL.

FUTURE APPLICATIONS OF RECIPROCAL CHANGES FOLLOWING CERVICAL REALIGNMENT SURGERY

1. In Regional Cervical Balance

A significant chain of correlation has been demonstrated in asymptomatic subjects between C0–2 angle, C2–7 angle, and T1S. T1S has been suggested as a key factor in understanding cervical alignment. In a given T1S, an adequate C2–7 angle is necessary in order to maintain optimal head balance. If CL is insufficient to match a given T1S, the dens tilts forward, resulting in an increase in C2 slope (C2S) (Fig. 4). Lee et al. introduced a novel concept of odontoid parameters, similar to the inverted pelvic parameters (Fig. 5). A significant chain of correlation is noted between cervical and odontoid parameters. Linear regression analysis demonstrated a significant correlation of C2–7 angle with odontoid incidence (OI), OT, and T1S, which suggests that in a given T1S, the structural characteristics of the dens affect optimal cervical alignment in each individual. They indicated a large OI decreased C2–7 angle to preserve the optimal head position and horizontal gaze.
As OI is a constant and fixed value, the odontoid parameters could provide a concrete anatomical base for understanding cervical alignment from the cephalad end.

To understand the clinical role of the odontoid parameters, we analyzed the correlation between patient-reported health-related quality of life and odontoid parameters in patients who underwent a multilevel posterior cervical fusion. First of all, the postoperative NDI showed a significant correlation with both OT ($r = -0.37$, $p < 0.05$) and OI ($r = -0.40$, $p < 0.05$). Secondly, a cutoff value of $20^\circ$ for the T1S-CL corresponds to OT of $0^\circ$ in a linear regression model ($r^2 = 0.702$, $p < 0.001$). Lastly, a significant correlation between OI and ROM of both C1–2 ($r = 0.37$, $p < 0.05$) and C0–2 ($r = 0.46$, $p < 0.01$) has been observed.

Based on these results, we postulated that depending on OI of a patient, the clinical impact of anterior tilting of the dens may differ as the resulting OT is distinct. At a given C2S, patients with a larger OI have a larger OT, which helps to retain the COG of the odontoid process more posteriorly, withholding it from losing balance (Fig. 4). It can be assumed that the threshold of imbalance differs in each individual. Also, ROM and ROE of the upper cervical spine are associated with improved clinical outcomes. OI is positively correlated with C1–2 extension angle, C1–2 ROM, and C0–2 ROM, concurrent with a previous biomechanical study. The reserve to extend the upper cervical spine is related to the anatomical characteristics of the dens. A patient with a larger OI can be assumed to have a larger compensatory reservoir or ROE. As a result, a patient with a larger OI can maintain a positive OT, which is significantly correlated with an improved NDI score. Therefore, implementing the odontoid parameters will aid in a better understanding of the reciprocal changes in the cervical spine in the future.

2. In Global Spinal Balance

Reciprocal changes following cervical realignment surgery in CD patients exhibit different patterns depending on whether they have an adequate compensatory reservoir in the thoraco-

Fig. 4. Schematic drawings illustrating the different spatial orientations of the dens with an identical C2 slope and different odontoid incidence values. (A) A dens with a straight curvature is conducive to a small odontoid incidence, prone to anterior tilting of the center of the dens. (B) A dens with a lordotic curvature can maintain the center of the dens more posteriorly.

Fig. 5. Schematic drawing of the odontoid parameters. (A) Odontoid incidence (OI): the angle between the line perpendicular to the C2 endplate at its midpoint and the line connecting this point to the center of the odontoid process (the center of a circle with an anterior/posterior border and the apex of the dens as a tangent). Odontoid tilt: the angle created by a line running from the C2 endplate midpoint to the center of the odontoid process and the vertical axis (VRL) C2 slope: the angle between the C2 endplate and a horizontal line (HRL). (B) Inverse illustration demonstrating similarity with the pelvic parameters.
lumbar spine.19 In our practice, we divide patients into 2 CD subgroups; compensated and decompensated (Fig. 6). In patients with compensated CK (i.e., head-balanced, Fig. 4A, B), the posteriorly shifted C7PL before surgery shifts anteriorly after correction. Subsequently, TK and T1S increase while LL decreases. In contrast, no significant changes in thoracolumbar alignment occur in patients with decompensated patients (i.e., trunk-balanced, Fig. 6C, D) following realignment surgery. While T1S and TK decrease, spinopelvic and lower extremity parameters remain constant. In a previous study of these 2 groups, patients with decompensated CK showed decreases in T1S and TK, but no changes occurred in spinopelvic and lower extremity parameters. In addition, the C0–1 and C1–2 angles became kyphotic and less lordotic, respectively, after surgery.19 No changes were observed in the pelvic and lower extremity parameters in both groups.19 As specific implications, a selective cervical correction would be possible for the compensated subtype, whereas both cervical and thoracic correction would be necessary for the decompensated subtype.19

CONCLUSION

The cervical spine is still one of the most understudied and least understood parts of the spine. It is crucial to identify the drivers of CD and each compensatory mechanism connected with the deformity. Analyzing the compensatory mechanisms such as C0–2 hyperlordosis, posterior thoracolumbar malalignment, or thoracic hypokyphosis in isolation can be mistaken for a surgical indication or even a sign of deformity. Spine surgeons should recognize and accurately address the regional drivers of the deformities for optimal treatment. A meticulous preoperative evaluation of the whole-body alignment, including the pelvis and lower extremities, is paramount to appreciate optimal GSA in the correction of spinal malalignment. This study adds to the literature by advocating whole-body analysis for all CD patients. The proverb, “Do not miss the forest for the trees.” is helpful to understand the malalignment of the spine. Furthermore, it has been challenging for spine surgeons and researchers to predict reciprocal changes following realignment surgery. Expanding our ability to not only simulate postoperative alignment of the fused segments but also methodically and systematically predict reciprocal changes in the unfused segments is crucial. A future approach to CD needs to take reciprocal changes in the thoracolumbar spine, as well as the cervical spine to provide optimal planning of realignment surgery and achieve ideal cervical alignment.

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Reciprocal Changes Following Cervical Realignment Surgery

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Classification(s) of Cervical Deformity

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Cervical spine deformities (CSD) are complex surgical issues with currently heterogeneous management strategies. The classification of CSD is still an evolving field. Rudimentary classification schemas were initially proposed in the late 20th century but were largely informal and based on the underlying etiology (i.e., postsurgical, traumatic, or inflammatory). The first formal classification schema was proposed by Ames et al. in 2015 who established a standard nomenclature for describing these deformities. This classification system established 5 deformity descriptors based on curve apex location (cervical, cervicothoracic, thoracic, craniovertebral junctional, and coronal deformities) and 5 deformity modifiers which helped surgeons utilize a standard language when discussing CSD patients. Koller et al. in 2019 subsequently established a classification system for patients with rigid cervical kyphosis based on regional and global sagittal alignment. Most recently, Kim et al. in 2020 proposed an updated classification system utilizing dynamic cervical spine imaging to guide surgical treatment of CSD patients. It identified 4 major groups of deformities – (1) those with “flat-neck” deformities caused by cervical lordosis T1 slope mismatch; (2) those with focal kyphotic deformities between 2 cervical vertebrae; (3) those with cervicothoracic deformities caused by large T1 slope; and (4) those with coronal deformities. Group 2 deformities most often required combined anterior-posterior approaches with short constructs, and group 3 deformities most often required posterior-only approaches with 3-column osteotomies.

Keywords: Cervical spine deformity, Cervical kyphosis, Spinal deformity

INTRODUCTION

Cervical spine deformities (CSD) can significantly hinder patient quality of life.1,2 Despite the complex surgical management required, the rarity and relative paucity of data has resulted in heterogeneous management of patients with cervical deformities. Although other spinal deformities have benefited from established classifications,3-7 the classification of CSD is an evolving field. Recent attempts at classifications of CSD by large multi-institution studies, are helping to guide surgical treatment of these complex deformity cases.8-10

HISTORICAL CLASSIFICATION

Given the relative rarity of CSD, there was sparse literature describing the management of these deformities throughout the 20th century. Much of the early literature regarding treatment of cervical deformities, however, described anecdotal management strategies for isolated types of secondary cervical deformity. These included traumatic,11,12 postlaminectomy,13-18 neuromuscular,19 and inflammatory.20,21 Consequently, early attempts at classifying CSD were based entirely on the underlying etiology of the deformities, not radiographic characteristics or treatment. Yasuoka et al.22 was among the first to explicitly classify cervical deformities as: congenital, neuromuscular, traumatic, oncologic, inflammatory, and idiopathic. This classification was proposed in the setting of creating exclusion criteria for their analysis of postlaminectomy cervical deformities. No treatment-guiding classification were proposed at this time.

MODERN CLASSIFICATION

1. Ames Classification

The first codified classification system for CSD was published in 2015 by Ames et al. and the International Spine Study Group. The goal of this schema was to provide a unified nomenclature
system for patients with CSD. This followed similar attempts to unify nomenclature for cervical spine osteotomies and soft tissue releases.33

The Ames classification was created utilizing a modified Delphi panel of experts who identified pertinent classification criteria based on static radiographs.4 Classification using the Ames schema requires full-length standing anteroposterior (AP) and lateral films of the spine and dedicated AP and lateral films of the cervical spine.24 The Ames classification system consists of 5 deformity descriptors with 5 deformity modifiers (Fig. 1). Deformity descriptors included 3 sagittal deformity groups: “C” for curves with apex deformity in the cervical spine, “CT” for curves with apex deformity at the cervicothoracic junction, and “T” with apex deformities in the thoracic spine. The other 2 classifications were “S” for coronal deformities (defined as a C2–7 cobb angle of greater than or equal to 15 degrees), and “CVJ” for deformities primarily at the craniovertebral junction.

The 5 deformity modifiers included: (1) a sagittal vertical axis (SVA) modifier, measured by the difference in C2–7 SVA; (2) a horizontal gaze modifier, measured by the chin-brow vertical angle; (3) a cervical lordosis (CL) modifier, measured by T1 slope (T1S) subtracted by CL; (4) a myelopathy modifier using the modified Japanese Orthopedic Association scores; and (5) a thoracolumbar spinal deformity modifier using the validated SRS-Schwab Classification Modifier.5 The respective grading scales for each modifier can be seen in Fig. 1. The validation study for the Ames classification showed strong intraobserver reliability.

The Ames classification provided a unified nomenclature system for deformity surgeons to use when discussing patients, and improvement in the cervical modifiers of the Ames classification has been correlated with improved postoperative radiographic alignment.8,26,27 This classification was not based on health-related quality of life metrics, however, and the classification does not guide treatment.28 Another limitation of this classification was that it relies exclusively on static radiographs. For management of CSD, dynamic radiographs are crucial to help determine the required number of osteotomies and soft tissue procedures needed for ultimate deformity correction and fusion.29-32

Since the publication of the Ames criteria, several validations studies have demonstrated the correlation between advanced Ames deformity modifiers and progressive deformity.33-36 Subsequent literature has also demonstrated the clinical importance of stratifying deformities by rigidity, achieving global sagittal balance with regional alignment, and correcting of cervical alignment in extension.32,37,38

![Fig. 1. Ames Classification for cervical spine deformity - deformities broken down into 5 deformity descriptors with 5 subsequent modifiers to account for sagittal vertical axis, horizontal gaze, cervical lordosis (CL), myelopathy, and overall SRS-Schwab classification (T, thoracic; L, thoracolumbar/lumbar; D, double curve; N, no coronal curve). CBVA, chin-brow vertical angle; TS, T1 slope; mJOA, modified Japanese Orthopedic Association; PI, pelvic incidence; LL, lumbar lordosis.](https://doi.org/10.14245/ns.2245864.392)
2. Koller-ECSRS Classification

Building upon the unified nomenclature provided by the Ames Classification, Koller et al.\(^9\) and the European Cervical Spine Research Society (ECSRS) established a treatment-guiding algorithm for patients with rigid cervical kyphosis (CK). In 2019, this research group conducted a 10-year, multicenter retrospective review of patients with rigid CK who underwent surgical correction. In this review, Koller-ECSRS classified patients into 4 deformity types based on regional and global alignment in patients: types A-D (Fig. 2). They subsequently described the surgical techniques most often used for correction of each deformity. Deformity type A corresponded to patients with cervical/cervicothoracic kyphosis with maintained global alignment. Type B corresponded to cervical/cervicothoracic kyphotic deformities with concomitant global imbalance. Type C corresponded to cervicothoracic kyphotic deformities with inadequate compensatory CL and persistent global imbalance. Type D corresponded to patients with appropriate CL and maintained global alignment. Koller et al.\(^9\) found that this classification schema had clinical implications. Patients with type A deformities were significantly more likely to require a combined anterior/posterior surgical approach, while patients with type C deformities were more likely to undergo posterior-only correction. Type C deformities also required the highest-grade osteotomies for adequate deformity correction.

The Koller-ECSRS classification created a useful classification system for patients with rigid CK that emphasized regional and global alignment. Like the Ames classification, however, the Koller-ECSRS classification solely utilized static radiographs. Moreover, the Koller classification simply reported the most common surgical techniques utilized by their cohort of surgeons with limited discussion on the biomechanical reason for these strategies.

3. Kim Classification

Given the Ames and Koller-ECSRS classifications’ reliance on static radiographs and limited ability to guide surgical correction, Kim et al. and the International Spine Group Study in 2020 published a new classification schema based on a multi-institution 2-step cluster analysis study of patients with severe CSD. The Kim classification schema utilized dynamic cervical spine imaging to create a treatment-guiding classification schema for CSD.\(^10\) Classification utilizing the Kim schema requires full-length standing AP and lateral spine radiographs and dedicated AP, lateral, flexion, and extension cervical spine radiographs. The Kim classification identified 4 distinct classes of CSD: (1) “flat-neck” deformities; (2) focal kyphotic deformities; (3) cervicothoracic deformities; and (4) coronal deformities (Fig. 3).\(^39\) Of note, coronal deformities were rare among the patient cohort and treatment recommendations were unable to be made.\(^10,39\)

To identify the structural etiology behind these CSD subtypes and recommend treatment options, the Kim classification validation study analyzed changes in T1S, C2–7 SVA, T1S-CL,
and maximum kyphosis between neutral and extended neck lateral radiographs. This isolated the source of deformity in each group and allowed recommendations for necessary fusion levels (Table 1).

Regarding group 1 deformities, the Kim classification identified a mainly cervicothoracic curve was secondary to significant CL-T1S mismatch. Treatment for group 1 flat-neck deformities is heterogenous in terms of anterior versus posterior approach however these deformities most often require fusions from C2 to a high-thoracic lowest instrumented vertebrae (LIV).

Regarding group 2 deformities, the main driver was identified as extremely large T1S ( > 50°). Surgical treatment for these patients most often requires an isolated posterior approach with an extended constructs extending to a LIV in the midthoracic to high-lumbar region. These patients frequently require 3-column osteotomies for adequate deformity correction.10

The Kim classification has also shown high intraobserver reliability and is currently the only codified CSD classification system which both utilizes dynamic cervical spine imaging and guides treatment approaches.10,39

CONCLUSION

Given the rarity of CSD patients, classifications of these deformities are still evolving. Historical classifications of CSD focused on the etiologies of these conditions but did not provide

Table 1. Kim classification of cervical deformities with structural etiology and technique for surgical correction10,39

<table>
<thead>
<tr>
<th>Deformity group</th>
<th>Structural etiology</th>
<th>Surgical approach</th>
<th>Fusion construct length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat-neck</td>
<td>CL-T1S mismatch</td>
<td>Heterogeneous</td>
<td>High thoracic</td>
</tr>
<tr>
<td>Focal kyphosis</td>
<td>Isolated 2 vertebral kyphosis</td>
<td>Combined anterior/posterior</td>
<td>Isolated cervical</td>
</tr>
<tr>
<td>Cervicothoracic</td>
<td>T1S &gt; 50°</td>
<td>Posterior w/ frequent 3 column osteotomy</td>
<td>Mid thoracic – high lumbar</td>
</tr>
<tr>
<td>Coronal</td>
<td>Unable to assess given limited sample size</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T1S, T1 slope.

Fig. 3. Three groups of sagittal deformities identified by Kim et al.10 Dynamic images are utilized to identify the etiology of the deformity as well as plan surgical correction. “Ext” indicates extended neck lateral radiographs. Lat, lateral; Ext, extension; AP, anteroposterior.
much clinical insight. The first unified classification schema, the Ames classification, was created in 2015 which provided a unified nomenclature for describing CSD using static radiographs but did not provide treatment recommendations. The Koller-ECSRS classification subsequently utilized static radiographs to classify and guide treatment of CK based on regional and global sagittal alignment. More recently, the Kim classification was created utilizing dynamic cervical spine imaging to help guide CSD surgical planning.

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Surgical Strategies and Perioperative Considerations for Cervical Deformity With Cerebral Palsy: A Comprehensive Review of the Literature

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The complex nature of the cervical spine makes surgical intervention challenging when treating cervical deformity in patients with cerebral palsy (CDCP). However, few studies have investigated the unique characteristics of cerebral palsy that create the need for surgery, the most effective surgical strategies, and the possible perioperative complications. The intended benefit and the potential risk of postoperative complications must be considered when deciding to operate for CDCP. Because the approach and correction strategy depend on the type of cervical deformity, as well as the patient’s comorbidities and functional status, a customized strategy is needed. Perioperatively, botulinum toxin injections and muscle division techniques can help control excessive involuntary movements and improve the spinal fusion success rate. Surgical intervention for CDCP requires a multidisciplinary approach, and the information presented in this article is intended to help in the perioperative management and surgical treatment of CDCP.

Keywords: Cervical vertebrae, Surgical procedures, Postoperative complications, Cerebral palsy

INTRODUCTION

Patients with cerebral palsy (CP) demonstrate involuntary and repetitive neck movements and are more likely to develop cervical deformity (CD) or cervical myelopathy (CM).¹-⁵ The excessive involuntary movements in CP cause early degenerative changes (degenerative discs, herniated intervertebral discs, osteophytes) as well as spinal instability.⁶,⁷ Accelerated degeneration and continuous motion in the cervical spine eventually result in CM, which can further complicate a patient’s already compromised neurological function and severely limit their autonomy.⁸-¹¹ In addition, static anatomical factors (i.e., bones or ligaments) can result in problems with stenosis, and dynamic factors (i.e., nerves or muscles) are related to problems of incoordination.⁶,¹⁰,¹²-¹⁶ Since the cervical spine has a wide range of motion and complex functions, these factors can generate a wide range of disorders and alignment pathologies necessitating surgical treatment.⁶,¹³ Although cervical spine deformities in CP have unique characteristics and substantially impact patients’ quality of life, few comprehensive studies have focused on CD in patients with CP (CDCP). In a previous report, spinal deformities were present in 20% to 70% of CP patients, depending on the severity of the disease.¹⁷ Once neurological deterioration due to CM or CD has developed in patients with CP, conservative treatments are ineffective and surgical intervention is required.¹⁰,¹⁸ However, the diagnosis of CDCP and surgical interventions for CDCP are challenging, and the incidence of postoperative complications is 2–3 times higher than that of CD in patients without CP.¹⁹ Therefore, we reviewed the existing literature on the characteristics and surgical strategies for CDCP including preoperative and postoperative management.
ETIOLOGY AND PATHOPHYSIOLOGY

CDCP usually presents with a rigid and severe curve of the cervical spine with dystonic muscle characteristics. Furthermore, the characteristics of CDCP differ from those of non-CP patients with degenerative CM.6 The primary pathologic factors that lead to serious disability include: (1) compression of neural elements caused by canal stenosis from excessive spondylotic changes and (2) severe dynamic instability of the spine induced by sustained involuntary movements and malalignment of the cervical spine.20 Studies have found that CM occurs at a younger age in patients with CP (generally in their 40s) whereas it is most common in non-CP patients in their 50s.21,22 Although the precise incidence of CDCP has not been reported, the incidence of CDCP varies according to the type of CP.23 There are 3 major types of CP: spastic (70%–80%), dyskinetic (athetoid/dystonic, 10%–20%), and ataxic (5%–10%). A mixed combination of the 3 types can also occur.14,24-27 Spastic CP is the most common type, but those with dyskinetic (athetoid/dystonic) CP are at much higher risk for cervical canal narrowing in the early years of the disease.22 In some studies, cervical spinal stenosis (CSS) and instability causing CD or CM were found to be more frequent in patients with dyskinetic (athetoid) CP than in a control group.3,21,28-30 The authors hypothesized that increased muscle tone, poor head control, and abnormal gait patterns lead to abnormal shearing forces that contribute to development of CSS and a much higher prevalence of symptomatic CSS in patients with dyskinetic (athetoid) CP.21,28,30 Guettard et al.31 reported that 31% of adults with dyskinetic CP developed CM or CD, all after the age of 36 years, and another recent study found that 7.5% of adults with spastic CP had symptomatic CSS.32 Radiological studies demonstrated that patients with dyskinetic CP exhibited an 8-fold higher frequency of cervical disk degeneration, spondylosis, and significant canal narrowing than control subjects.3,33

ANATOMICAL CONSIDERATIONS

Because severe degenerative changes occur with CDCP, the normal anatomical structure is greatly altered, which may cause difficulties for the spine surgeon. Therefore, caution is required when using instruments and with screw insertion. Since it is important for the operator to be aware of any anatomical changes created by the CDCP, many spine surgeons depend on continuous fluoroscopy or a navigation system during surgery to ensure accurate screw insertion and prevent neurovascular complications. The early onset of degenerative lesions in CDCP was well described by Harada et al.3 in a radiological study of over 180 patients with CP compared with control subjects. Disc degeneration occurred in 51% of the patients, an 8-fold higher frequency than in the control group. In addition, at the C3–4 and C4–5 levels, there was listhetic instability in 17% and 27% of the patients, respectively, with a 6-fold and 8-fold higher frequency than in the control subjects. There was also a significantly higher incidence of cervical canal narrowing in the patients with CP, especially at the C4 and C5 levels. In a recent study by Kim et al.,35 disc/facet degeneration was more progressed and lateral mass (LM) height was smaller in the CP group. However, the LM thickness and width were larger in the CP group at the midcervical level. The pedicle inner diameter, which we defined as the inner cancellous diameter, was significantly smaller in patients with CP. In addition, pedicle sclerosis was more frequent, and the range of cervical motion was smaller in the CP group than in the control group. Kato et al.10 reported that pedicle sclerosis, a wide transverse angle, and a LM deformity were frequently observed in patients with CP. Since the deformation of the cervical spine anatomy, which is the target during screw insertion, can cause a critical breach during surgery, understanding the various anatomical changes is most important in CDCP surgery.

SURGICAL DECISION PROCESS

A basic and important point in planning the surgical intervention is determining the position of the spinal deformity.34 Lee et al.35 proposed a surgical treatment strategy based on the T1 slope (T1S) and cervicothoracic junction (CTJ) angle (Fig. 1). When the T1S is normal and the CTJ angle is normal, the deformity is located in the cervical spine.35 The correction should be at the lower cervical spine (including pedicle subtraction osteotomy) when the T1S is normal and the CTJ angle is kyphotic.35 A high T1S and kyphotic CTJ angle mean the deformity is at the upper thoracic spine, and a high T1S and normal CTJ imply that the correction should be performed at the middle or lower thoracic spine.35 Furthermore, in cervical deformities, evaluation of the flexibility and rigidity of the cervical spine should be performed preoperatively, as the results may determine the approach, technique, and range of the surgery.36 If the cervical spine is flexible and is not ankylosed, based on a clinical examination and imaging studies including dynamic x-rays, an anterior-alone or posterior-alone correction strategy may be used.36 If the cervical spine is rigid without ankylosed facets or
Fig. 1. Surgical planning for fixed cervical deformities based on the location of the deformity using the T1 slope and the cervicothoracic junctional (C5–T3) angle. CTJ, cervicothoracic junction; ant., anterior; post., posterior; TL, thoracolumbar; PSO, pedicle subtraction osteotomy; VCR, vertebral column resection; SPO, Smith-Petersen Osteotomy.\(^{35}\)

has prior instrumentation, an anterior-alone strategy may be sufficient.\(^{36}\) Although anterior-alone surgery can be considered in CDCP, ankylosed facets are often present; therefore, it is rare to perform anterior-alone surgery. If the anterior spinal column is rigid with ankylosed facets, a combination of anterior and posterior strategies may be needed to correct the deformity.\(^{36}\) It is also important when planning deformity surgery in cervical kyphosis to locate the apex of the cervical kyphosis (C0–2 or C3–T1).\(^{6}\) In a craniovertebral junction (C0–1–2) deformity, craniovertebral junctional osteotomy is indicated when the deformity is irreducible and results in severe pain, functional impairment, or neurological impairment that cannot be relieved with a surgical decompression and/or stabilization procedure alone.\(^{6}\) When the apex of the cervical spine deformity is localized at the subaxial spine (C3–T1), surgeons may choose one of several surgical options according to curve flexibility (flexible vs. rigid) as well as the location of the apex of kyphosis (C3–C6 vs. C7–T1).\(^{5}\)

**SURGICAL METHODS**

The most important surgical objectives for treatment of CDCP are adequate decompression of the spinal cord and nerve roots, stabilization of the cervical spine, alignment correction, and a good postoperative clinical outcome.\(^{6,37,38}\) Recent advances in medical technology have led to the development of improved internal fixation methods that promote stronger initial mechanical stability with anterior plating or posterior screw fixation.\(^{49}\) However, surgery for CDCP remains a challenge due to the risk of perioperative instrumentation failure, nonunion, deformity progression, poor bone quality, and neurological deterioration caused by repetitive involuntary neck movements and deformity of the cervical spine.\(^{36,40}\) Several surgical procedures have been described, including posterior decompression without fusion and spinal arthrodesis via anterior, posterior, or circumferential approaches.\(^{20,41,42}\) In our review of the literature, most surgeons agreed that strong fixation was essential for the surgical treatment of CDCP. However, there was not a consensus on the appropriate surgical method.

1. **Combined Anterior-posterior Approach With Instrumented Fusion**

   The anterior approach generally included releasing the disc, osteophytes, and uncovertebral joints, as well as corpectomies if indicated.\(^{36}\) When the CD is rigid with ankylosed facets, a combined anterior-posterior (AP) fusion strategy may be applied.\(^{43}\) Kim et al.\(^ {44}\) reported that combined AP fusion resulted in a superior fusion rate at 3 years postoperatively compared to posterior-alone fusion in patients with CP (26 of 28 patients, 93% vs. 22 of 35 patients, 63%; \(p = 0.02\)). Visual analogue scale (VAS) scores for postoperative posterior neck pain (5.7 vs. 2.8, \(p = 0.02\)) and the incidence of instrument-related complications (21% vs. 60%; \(p = 0.01\)) were also significantly lower in the combined AP fusion group 3 years postoperatively compared to posterior-alone fusion in patients with CP. Onari et al.\(^ {45}\) demonstrated that combined AP fusion can effectively improve neurological function in patients with CP and cervical spondylotic myelopathy (CSM) (CP-CSM), even in those with severe involuntary movements. Lee et al.\(^ {3}\) demonstrated that patients with CP-CSM who underwent deformity correction had better clinical outcomes than patients who did not undergo deformity correction. In addition to adequate cord decompression, stabilization of the cervical spine is the most important surgery-related goal in CP-CSM, and highly rigid fixation is required.\(^ {50,44}\) Some authors have argued that correction of CP-CSM deformities, including translational and angular deformities, is important and may require the reinforcement of posterior structures.\(^ {7,43}\) In a retrospective review of 36 patients with CP and myelopathy who underwent CD correction surgery, Grosso et al.\(^ {46}\) found that a greater degree of focal kyphosis correction was associated with improved neurological outcomes.

2. **Posterior Approach With or Without Instrumented Fusion**

   Combined AP fusion surgery has the advantage of correcting...
Sagittal alignment and promoting solid fusion, but for CDCP, this method may also carry a significant medical comorbidity burden. Consequently, some authors reported that a single operation with a posterior approach rather than a staged operation was also an effective treatment for CDCP. Moreover, a report that autofusion inside the disc or anterior vertebral bony bridging was observed in 86% of intervertebral levels without anterior surgery also supports this view. In a retrospective study of 31 patients with CP and cervical disorder, Watanabe et al. showed that posterior cervical fusion alone using pedicle screw constructs had a high fusion rate and good clinical outcomes without correction loss. Furuya et al. reported that subaxial pedicle instrumentation achieved good surgical outcomes for patients with CP. Demura et al. demonstrated that laminoplasty and pedicle screw fixation for CDCP had contributed to favorable stability and clinical outcomes at >10 years of follow-up. The authors also reported that a C2–7 Cobb angle (from 11.9° of kyphosis to 0.8° of lordosis) could only be corrected with posterior surgery. In addition, Zhou et al. reported that laminoplasty with LM screw fixation was an effective treatment for CSM in patients with athetoid CP. Clinical outcomes such as the mean VAS score (p < 0.01) and Neck Disability Index score (p < 0.01) had significant decreases after surgical intervention. Several studies reported that decompression without fusion or laminoplasty is not recommended because of repetitive abnormal cervical movement, adjacent segment instability, and progression of spondylosis. However, Harada et al. suggested that cervical laminoplasty may be an effective and less invasive surgical method for selective patients, especially for those with a low level of involuntary movements and no remarkable cervical kyphosis or instability. In that study, the recovery rate based on Japanese Orthopedic Association (JOA) scores in the laminoplasty group was significantly higher than that of the fusion group (p = 0.02), whereas the C2–7 Cobb angle did not improve postoperatively.

3. Additional Perioperative Procedures

CDCP can demonstrate a poor course during and after surgery due to involuntary repetitive movements and an abnormal increase in muscle tone of the cervical spine. Even after a successful operation, CDCP is associated with a higher incidence of postoperative complications such as pseudoarthrosis or instrument failure (broken or dislodged screw) due to involuntary movements. In order to partially compensate for these limitations and to improve spinal stability after the operation, additional techniques can be performed before and after surgery for CDCP.

1) Splenius and sternocleidomastoid muscle cutting

Muscle division aims to reduce involuntary movement by directly destroying overactive muscles. Matsuo performed muscle release for catatonic torticollis and neck strain in patients with CP and showed good clinical outcomes after the procedure. Ueda et al. reported that cervical laminoplasty combined with muscle release for the treatment of CM due to CP was effective in simplifying postoperative therapy and improving JOA scores. These muscle release methods were performed by cutting the splenius capitis and semispinalis muscles at the attachments to the occipital bone posteriorly. Anteriorly, the left and right splenius and sternocleidomastoid (SCM) muscles (including the sternal and clavicular branches) were cut 2 cm central to the clavicle.

2) Botulinum toxin injection

Botulinum toxin injection was the most widely used intervention in patients with CP. Pharmacokinetically, botulinum toxin binds to the cholinergic nerve endings of the neuromuscular junction, thereby reducing the release of acetylcholine, blocking neuromuscular transmission and reducing muscular overactivity. Thus, botulinum toxin injection can be very effective in controlling spasmodic torticollis perioperatively in patients with cervical dystonia. Anderson et al. reported improvement in 89% of patients receiving injections. The median time after injection to the onset of benefit was 7 days, with a peak benefit at day 14. The median duration of the benefit was approximately 9 weeks. The use of botulinum toxin to control cervical movements perioperatively has been reported in the surgical literature since 1996. Previous studies demonstrated that botulinum toxin decreased involuntary neck movements, facilitating postoperative spinal fusion and prevention of possible complications and reoperation. Kim et al. reported that botulinum toxin injections significantly lowered the incidence of a second operation in a 5-year follow-up study of 24 patients with athetoid CP.

3) Cervical traction

Prior to surgical correction of a deformity, cervical traction may be tried. A trial of 3 to 5 days of traction may be sufficient to reduce the deformity. However, if the deformity does not reduce with traction after 5 days, additional traction time or weight is unlikely to benefit the patient.
PERIOPERATIVE COMPLICATIONS AND RISK FACTORS

The decision to pursue surgery in CDCP should balance the intended outcome with the potential risk of complications. Providing accurate and up-to-date information on the known complications of cervical surgeries for CDCP will allow for improved informed consent and better standards for reimbursement. The postoperative complications for correction of CDCP were various, including neurologic deterioration, instrument failure, pseudoarthrosis or nonfusion, and revision. Samdani et al. recently reported a 39% complication rate in 127 patients with CP who underwent spinal fusion. Yasay et al. reported that spinal deformity surgery in 257 patients with CP with >2 years of follow-up had a 36% rate of major postoperative complications with a spine-related reoperation rate of 14.0%. When compared to CD without CP, surgical treatment in patients with CP was associated with higher rates of perioperative and postoperative complications. This is likely due to differences in the comorbidities and surgical complexities of the 2 populations. Kim et al. demonstrated that a CSM-CP group had significantly more overall postoperative complications than the control group (45.7%, 16 of 35 patients vs. 20.0%, 7 of 35 patients; p = 0.021). Specifically, the incidence of adjacent segment disease (20.0%, 7 of 35 patients vs. 2.9%, 1 of 35 patients; p = 0.018) and of revision (17.1%, 6 of 35 patients vs. 0%, 0 of 35 patients; p = 0.003) were significantly higher in the CP group. Moreover, more postoperative complications occurred in the fixed CD group than in the control group (31.3%, 5 of 16 patients vs. 5.3%, 1 of 19 patients; p = 0.037). Scheer et al. reported significant differences in complication rates for different approaches (anterior approach, 27.3%; posterior approach, 68.4%; combined approach, 79.3%). Among patients with CP, these results were likely because surgical invasiveness, need for surgical release, and utilization of osteotomies significantly increased in those with fixed cervical kyphosis compared to those with semi-rigid or flexible kyphosis. The occurrence of a major perioperative complication lengthened both intensive care unit (ICU) and hospital stays. In addition, most patients with CP have substantial comorbidities and postoperative medical complications can impact the patient’s prognosis. These considerations should be adequately addressed before and after surgery. In an observational study by Yasay et al., the most common postoperative medical complications in 257 patients with CP related to wound healing (n = 16, 6.2%), pulmonary issues (n = 28, 10.9%), and prolonged ventilator support (n = 21, 8.2%). Samdani et al. reported complications categorized as pulmonary 29.9% (38 of 127 patients), gastrointestinal 18.9% (24 of 127 patients), other medical (coagulopathy and severe hypotension) 11.8% (15 of 127 patients), and wound infection 4.7% (6 of 127 patients). Since the incidence of postoperative complications is much higher in a CDCP group than in a general patient group, and because unexpected complications are also more likely to occur, serious consideration is required before surgery and a more detailed observation of the patient’s symptoms is required after surgery.

The factors that affect the postoperative prognosis for CDCP are diverse and are different from those of non-CP patients with CD. In previous studies, the risk factors for postoperative complications in CDCP were analyzed. Better clinical outcomes were reported if early surgical therapy was conducted. In general, it was reported that CM or CD in patients with CP often progress in the 30- to 40-year age range. However, if unexplained neurologic deterioration or changes occur before then, the clinician should suspect myelopathy even at a relatively young age. Greater clinical attention to neurological deterioration, even subtle symptoms in individuals with CP, contributes to better outcomes. Conversely, a decrease in abnormal movements must be considered an alarming sign, even though it could be interpreted as an improvement. Other retrospective studies have found a significant negative correlation between developmental cervical spinal canal stenosis and recovery rate based on the modified JOA score (p = 0.01). Samdani et al. reported that the risk factors for postoperative complications in CDCP included larger preoperative kyphosis (p = 0.05), staged procedures (p < 0.05), a lack of antifibrinolytic use (p < 0.05), and increased estimated blood loss (p < 0.05), with the latter being an independent predictor of a major perioperative complication. Jackson et al. showed that staged and combined AP fusions were associated with longer operative times, hospital stays, ICU stays, and days intubated. Although some studies have reported that combined AP fusion increases complications, a recent study by Jackson et al. demonstrated no difference in major complication rates according to the type of approach.

ADDITIONAL CONSIDERATIONS

Strict postoperative immobilization should be maintained for 3 months with a Philadelphia collar or a cervicothoracic orthosis to prevent sustained abnormal tonicity or involuntary movement of the neck. Some authors recommend a halo vest for up to 6 months for postoperative immobilization with particular attention to the potential risk of skull fractures. Even
when the postoperative prognosis is good, long-term follow-up is essential in CDCP.\textsuperscript{1,2} In a radiographic analysis, Demura et al.\textsuperscript{47} found that 35% (proximal) and 21% (distal) of the adjacent segments showed a progression in degeneration of more than one grade after 10 years. More than 90% of the patients who underwent magnetic resonance imaging showed progressive disc degeneration on either side after 10 years.

CONCLUSION

Surgical treatment of CDCP can be challenging. Early diagnosis and intervention, as well as planning an appropriate surgical approach can improve the neurological function and clinical outcomes in CDCP. Understanding the unique characteristics of CDCP helps the surgeon decide on the appropriate surgical procedure. The decision to operate in CDCP should consider the intended benefits and the potential risk of postoperative complications. Additional perioperative management, such as the appropriate use of SCM cutting or botulinum toxin injections, can be effective, and long-term follow-up can help the patient's postoperative progress.

NOTES

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Defining Cervical Sagittal Plane Deformity – When Are Sagittal Realignment Procedures Necessary in Patients Presenting Primarily With Radiculopathy or Myelopathy?

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Objective: It remains unclear whether cervical sagittal deformity (CSD) should be defined by radiographic parameters alone versus both clinical and radiographic factors, and whether radiographic malalignment by itself warrants a CSD corrective surgery in patients who present primarily with neurologic symptoms.

Methods: We administered a survey to a group of expert surgeons to evaluate whether radiographic parameters alone were sufficient to diagnose CSD, and in which scenarios surgeons recommend a CSD realignment procedure versus addressing the neurologic symptoms alone.

Results: No single radiographic criteria reached a 50% threshold as being sufficient to establish the diagnosis of CSD. When asymptomatic radiographic malalignment was present, a sagittal deformity correction was more likely to be recommended in patients with myelopathy versus those with radiculopathy alone. The majority of surgeons recommended deformity correction when symptoms of cervical deformity were present in addition to radiographic malalignment (85% with deformity symptoms and radiculopathy, 93% with deformity symptoms and myelopathy).

Conclusion: There is no consensus on which radiographic and/or clinical criteria are necessary to define the presence of CSD. We recommend that symptoms of cervical deformity, in addition to radiographic parameters, be considered when deciding whether to perform deformity correction in patients who present primarily with myelopathy or radiculopathy.

Keywords: Kyphosis, Spinal cord compression, Cervical spine deformity, Radiculopathy, Myelopathy, Deformity correction

INTRODUCTION

Cervical sagittal deformity (CSD) is an extremely disabling condition that can have a myriad of etiologies including congenital, degenerative disease, posttraumatic, iatrogenic, and inflammatory, among others.¹ CSD can cause symptoms from the deformity itself, such as difficulty holding one’s head upright with an inability to maintain horizontal gaze, neck pain, and difficulty swallowing in severe cases. In addition to the symptoms related to the spinal malalignment, CSD can often also be associated with symptoms of radiculopathy and/or myelopathy from cervical nerve root or spinal cord compression. Indeed, CSD itself may be a cause of cervical myelopathy in certain situations from draping of the spinal cord over anterior pathology...
causing an increase in longitudinal spinal cord tension.\textsuperscript{2,3}

While there are several radiographic parameters commonly cited in the literature as inclusion criteria for entry into studies on CSD,\textsuperscript{4} the question remains as to whether these parameters are sufficient to warrant a diagnosis of CSD in clinical practice. Many patients present with radiculopathy or myelopathy in the setting of sagittal alignment that is not "perfect," but do not have a severe chin-on-chest deformity that obviously requires concomitant correction. Indeed, there have been many publications examining the postoperative outcomes of cervical deformity patients utilizing a large multicenter database with the following inclusion criteria: cervical kyphosis C2–C7 Cobb angle > 10°; cervical scoliosis C2–7 coronal Cobb angle > 10°, C2–7 sagittal vertical axis (cSVA) > 4 cm, or chin-brow vertical angle > 25°.\textsuperscript{5-8} Despite these radiographic definitions, it remains unclear whether patients who meet those radiographic criteria of cervical deformity actually require concomitant cervical deformity correction when they present primarily with symptoms of myelopathy and/or radiculopathy.

To begin to answer this question, we surveyed an international group of experienced cervical deformity surgeons on several clinical scenarios to determine if there is consensus as to (1) the definition of a cervical sagittal plane deformity in clinical practice, and (2) when a myelopathy/radiculopathy patient with radiologic malalignment merits additional CSD correction with its associated risks, versus when a smaller procedure to only treat the myelopathy and/or radiculopathy is sufficient.

MATERIALS AND METHODS

A survey (Supplementary Material) was distributed through REDCap (Project REDCap, Vanderbilt University) to 82 expert cervical spine surgeons (current and past Board Members from the Cervical Spine Research Society [CSRS], CSRS Asia Pacific, and CSRS Europe, as well as those who have published extensively in CSD) with differing experience, training background (neurosurgery vs. orthopaedic surgery), and practice environment (university setting vs. private or hospital employed). The questions, developed by the authors of this study, were designed to determine whether the current published radiographic criteria were sufficient alone to establish a diagnosis of CSD or whether other clinical and physical exam factors were also thought to be necessary in the diagnosis of CSD. We also presented several clinical vignettes to determine which radiographic parameters would require correction in the setting of clinical signs and symptoms such as radiculopathy, myelopathy, axial neck pain, and difficulty holding one’s head upright.

Statistical analyses were performed using the R ver. 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Chi-square analyses in Tables 1 and 2 were used to assess whether participants showed a preference for one option over another (i.e., significantly differed from an equal split across options).

RESULTS

We received survey responses from 41 surgeons (33 orthopaedic surgeons, 8 neurosurgeons) with 93% working in an academic environment. 35 surgeons (85%) were from North America, 2 (5%) were from Europe, and 4 (10%) were from Asia. Forty-one percent of surgeons had 6–15 years of experience and 59% had 16+ years of experience (mean, 19.7 ± 9.0 years). Eighty percent of the surgeons devote greater than 50% of their surgic-
Table 3. Is the radiographic criteria or clinical symptom listed below, by themselves, sufficient to establish a diagnosis of cervical sagittal deformity?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2–7 SVA, &gt;4 cm</td>
<td>16 (39)</td>
<td>25 (61)</td>
</tr>
<tr>
<td>C2–7 kyphosis &gt;10°</td>
<td>13 (32)</td>
<td>28 (68)</td>
</tr>
<tr>
<td>CBVA &gt;25°</td>
<td>20 (49)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>Difficulty holding head upright</td>
<td>10 (24)</td>
<td>31 (76)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

SVA, sagittal vertical axis; CBVA, chin-brow vertical angle.

The question of when cervical deformity (i.e., neck pain associated with difficulty holding one’s head upright, 68% of surgeons still felt this combination was insufficient to establish the diagnosis of CSD.

1. Definition of Cervical Sagittal Plane Deformity in Clinical Practice

The survey results demonstrate that CSD remains difficult to define, as no single radiographic criteria (each of which alone has commonly been used as an inclusion criterion for entry into studies on cervical deformity surgery) reached even a 50% threshold as being sufficient to establish a diagnosis of CSD in clinical practice (Table 3). Even when all 3 of these radiographic criteria were combined with patient-reported symptoms of difficulty holding one’s head upright, 68% of surgeons still felt this combination was insufficient to establish the diagnosis of CSD.

2. When Does a Patient Presenting Primarily With Myelopathy and/or Radiculopathy in the Setting of Radiographic Malalignment Merit Additional CSD Correction With Its Associated Risks?

An extensive sagittal deformity correction procedure beyond that needed to just treat the neurologic disorder was much more likely to be recommended in patients with myelopathy and asymptomatic radiographic malalignment (51%; Table 1) versus those with radiculopathy and asymptomatic radiographic malalignment (10%; Table 2). However, despite that, only 51% recommended extensive deformity correction even in those with myelopathy and asymptomatic radiologic malalignment. The presence of neck pain did not substantially change the recommendation for either radiculopathy (17%) or myelopathy (54%) patients.

When examining proportions, surgeons were more likely to recommend extensive deformity correction in both radiculopathy and myelopathy patients when they had concomitant symptoms of deformity (i.e., neck pain associated with difficulty holding one’s head upright) along with radiologic malalignment (radiculopathy 85%, myelopathy 93%).

DISCUSSION

Our study shows that there is poor consensus amongst a group of worldwide cervical spine surgery experts on the definition of CSD. Similarly, the indications for a sagittal plane corrective procedure versus a procedure designed to simply address the myelopathy and/or radiculopathy remains a topic of debate. Although, degenerative cervical disorders causing myelopathy and radiculopathy are common, symptomatic CSD requiring corrective surgery is relatively more rare, especially when compared to thoracolumbar spinal deformity.13 The question of when cervical sagittal realignment procedures are needed is important because CSD procedures are typically more extensive than procedures for degenerative cervical pathology, require fusion of a greater number of motion segments, more often involve combined anterior and posterior approaches, more commonly require osteotomies, and have a higher rate of complications.10–15

On the other hand, while operations to simply treat radiculopathy and/or myelopathy are often less invasive than CSD procedures, they may potentially have the risk of undertreating the problem and not addressing all potential pain generators or dynamic neurologic compression. In this study, we found that no single radiographic or clinical criteria by itself was sufficient to establish a diagnosis of CSD. In those with asymptomatic radiographic malalignment, we found that expert surgeons are much more likely to recommend a sagittal realignment procedure when patients have myelopathy compared to radiculopathy. However, even in that setting, deformity correction was recommended by only 51% of surgeons. Finally, surgeons were much more likely to recommend deformity correction surgery in patients with concomitant symptoms of sagittal plane deformity (93% for those with myelopathy, 85% for those with radiculopathy). These results suggest that clinical symptoms of deformity should be strongly considered in clinical decision-making, rather than relying solely on radiographic alignment criteria alone.

Our understanding of CSD is still evolving as we gain more insight into normative cervical and thoracolumbar alignment.16–19 While it is well known that degenerative cervical conditions have significant negative effects on health-related quality of life (HRQoL), it remains unclear as to what extent CSD itself negatively affects HRQoL. As there are no current widely-adopted specific CSD HRQoL instruments, we do not have a full understanding...
of the impact of CSD that is independent of the negative effects that myelopathy and radiculopathy have on HRQoL. Further, it has been shown that approximately one-third of the asymptomatic population has a kyphotic alignment of the cervical spine.\(^20,21\) Given this, it is somewhat surprising that we found only 32% of expert surgeons felt that C2–7 kyphosis \(>10^\circ\) was sufficient to establish a diagnosis of CSD. Although cervical kyphosis is frequently present in asymptomatic individuals, sagittal malalignment is very poorly tolerated in the thoracolumbar spine and lumbar kyphosis is less commonly present in normal, asymptomatic patients.\(^22\) It is known, however, that kyphotic cervical alignment in the presence of anterior compressive disease increases longitudinal cord tension and there may be less dorsal migration of the cord with posterior decompression.\(^23,24\) Even with this in mind, not all patients need to achieve the same amount of lordosis after a cervical spine fusion procedure. Passias et al. reported on the relationship between myelopathy, surgical deformity correction, and patient-reported outcomes (PROs) and found no relationship between PRO improvement and cervical-specific sagittal alignment measures.\(^25\) Other studies have suggested an association between postoperative cervical lordosis minus T1 slope and worsened disability after cervical deformity correction.\(^26\) Given these somewhat disparate results, it is safe to say that we do not yet fully understand which patients require lordotic alignment after cervical reconstruction. Rather than the amount of overall cervical lordosis, the final C2 tilt or C4 tilt may ultimately prove to be more important with regards to restoring normal alignment, but this will need further prospective validation.\(^20,27\) In this study, we sought to specifically focus on cervical radiographic parameters that have been widely published in literature to date, but certainly understand the value in discussing additional parameters as more evidence is obtained over time.

In addition to cervical lordosis, C2–7 SVA \(<4\) cm has been reported as an important measure of sagittal alignment. However, it is not clear what the target C2–7 SVA should be for all patients undergoing cervical spine surgery. Normal C2–7 SVA has been reported to be \(16.8 \pm 11.2\) mm.\(^28\) Previous studies have reported that C2–7 SVA \(>4\) cm is associated with worsened PROs after multilevel posterior cervical deformity surgery,\(^29\) and this criterion is part of the comprehensive cervical spine deformity classification system which was proposed by Ames et al.\(^30\) Although these studies certainly suggest that a C2–7 SVA of \(<4\) cm may be beneficial to achieve in those undergoing cervical deformity correction, they should not necessarily be interpreted as meaning that all patients with radiculopathy or myelopathy need to have a value \(<4\) cm to achieve an optimal outcome. By contrast, in a recent study by Karamian et al.\(^30\) of patients undergoing 1–3 level anterior cervical disectomy and fusion, those with a preoperative C2–7 SVA of \(>4\) cm actually had greater improvement in Neck Disability Index scores postoperatively versus those with a C2–7 SVA \(<4\) cm, even though the SVA values remained \(>4\) cm in the former group and \(<4\) cm in the latter. In other words, in patients with primarily radiculopathy or myelopathy, C2–7 SVA may not necessarily be a major driver of outcomes. Further, given that C2–7 SVA is dynamic and is affected not only by the intrinsic cervical alignment but also by other postural factors (thoracolumbar spinal alignment, lower extremity compensation, etc.), it should not be solely relied upon when planning a cervical sagittal corrective procedure. Accordingly, we found that only 39% of experts felt that C2–7 SVA was sufficient to establish a diagnosis of CSD, although 93% of surgeons felt it important to normalize C2–7 SVA along with the other radiographic parameters when cervical deformity correction is performed. More work will be needed to understand which radiographic measures are most important to normalize to maximize postoperative PROs and return to activities with cervical deformity correction.

Given the high morbidity of cervical deformity surgery, it is certainly important to carefully select patients who truly require aggressive sagittal correction versus those who will benefit from a procedure to simply address the myelopathy and radiculopathy. Here we found that 90% of surgeons in cases of radiculopathy, and 49% of surgeons in cases of myelopathy would not perform an aggressive sagittal realignment procedure beyond what is necessary to treat the neurological issue to correct an asymptomatic radiographic abnormality. If patients have truly symptomatic deformity with symptoms of neck pain associated with difficulty holding one's head upright and with horizontal gaze, along with a clear radiographic deformity, then a sagittal realignment procedure is indicated (Fig. 1E–F). However, if patients simply have radiographic abnormalities (e.g., cervical kyphosis, C2–7 SVA \(>4\) cm, etc.) without a clinically visible or symptomatic deformity (Fig. 1A–D), then in our opinion, and based on these results, a more limited procedure to treat the myelopathy/radiculopathy may be recommended.

There are several limitations associated with this study. The percentage of total respondents was only 50% of those invited. However, this is consistent with previous response rates for other published spine surveys.\(^31–34\) Also, only 20% of the respondents had a neurosurgical training background, and only 15% were from outside North America. Additionally, former/current CSRS
leadership and those who have published extensively in CSD-related topics may not be representative of all cervical spine surgeons. These factors could have led to bias in the results. Despite this, much of the current literature and education related to CSD were developed and provided by those invited for this survey. Lastly, the case descriptions we provided were standardized based on symptom descriptions, and did not include the actual images nor clinical photos for evaluation. We selected this approach in order to increase the generalizability of findings, rather than focusing on the specifics associated with a particular case. Nevertheless, we do recognize that looking at images may certainly impact the decision-making process. Despite these limitations, this is the first survey that seeks to understand when a smaller procedure to treat only the radiculopathy and myelopathy may be sufficient without specifically attempting to correct the radiographic malalignment, and when a more extensive sagittal realignment procedure may be warranted.

**CONCLUSION**

Despite numerous published studies defining CSD by radiographic criteria alone, there is no consensus amongst a diverse group of expert cervical spine surgeons as to what radiographic criteria are necessary to define the presence of cervical defor-
mity in clinical practice. Expert surgeons are more likely to perform CSD realignment procedures in patients with myelopathy versus those with radiculopathy alone, and were also more likely to recommend an extensive deformity correction when clinical symptoms of deformity were present along with the radiologic malalignment. Therefore, based on expert opinion, surgeons should not necessarily recommend extensive CSD realignment operations in all patients with radiologic malalignment alone, but may carefully consider doing so when symptoms of deformity are also present.

Limitations of our report include those inherent to survey studies and the limited numbers of spine surgeons from nonacademic medical centers responding to the survey. However, given the responses from both neurosurgeons and orthopaedic spine surgeons and from both very senior and midcareer surgeons, we believe this provides an accurate representation of expert practice patterns regarding the treatment of CSD. More work is necessary to refine the definition of CSD and what patients will ultimately benefit from a sagittal plane realignment procedure.

NOTES

Supplementary Material: Supplementary Survey Questions can be found via https://doi.org/10.14245/ns.2244924.462.

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Author Contribution: Conceptualization: VMN, PKL, JMR; Data curation: VMN, PKL, CED; Formal analysis: VMN, PKL, CED; Methodology: VMN, PKL, CED, JMR; Visualization: VMN, PKL, JMR; Writing - original draft: VMN, PKL; Writing - review & editing: VMN, PKL, C Drolet, JMR.

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Cervical Inclination Angle: Normative Values in an Adult Multiethnic Asymptomatic Population

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Objective: The role of the craniocervical complex in spinal sagittal alignment has rarely been analyzed but it may play a fundamental role in postoperative mechanical complications. The aim of the study is to analyze the normative value of the cervical inclination angle (CIA) in an adult asymptomatic multiethnic population.

Methods: Standing full-spine EOS of adult asymptomatic volunteers from 5 different countries were analyzed. The CIA was analyzed globally and then in each decade of life. Different ethnicities were compared. Comparisons between different groups was performed using a t-test and statistical significance was considered with a p-value < 0.05.

Results: EOS of 468 volunteers were analyzed. The global mean CIA was 80.2° with a maximum difference of 9° between T1 and T12 (p < 0.001). The CIA remains constant until 60 years old then decreases significantly passing from a mean value before 20 years old of 82.25° to 73.65° after 70 years old. A statistically significant difference was found between the Arabics and other ethnicities with the formers having an inferior CIA: this was related to a mean older age (p < 0.05) and higher body mass index (p < 0.05) in the Arabics.

Conclusion: The CIA remains constant until 60 years old and then reduces slightly but never under 70°. This angle is helpful to evaluate the lever arm at the upper instrumented vertebra after an adult spinal deformity surgery and could predict the occurrence of a proximal junctional kyphosis when its value is lower than normal. Further clinical studies must confirm this theory.

Keywords: Spine deformity, Sagittal imbalance, Mechanical complication, Proximal junctional kyphosis, Cervical inclination angle

INTRODUCTION

With the improvements in health care and life expectancy we witness a raise in adult spinal deformity (ASD) incidence with a reported prevalence up to 68% in patients over 60 years.¹-⁴

When treating ASD, it is mandatory to respect the appropriate sagittal and coronal alignments to have good clinical outcomes and prevent mechanical complications.⁵-⁸ The necessity to keep the head over the pelvis is a fundamental rule firstly supported by Dubousset³⁵: this means that the cervical spine and the head must be included in the balance analysis.

The principal reported mechanical complication in ASD surgery is proximal junctional kyphosis (PJK) that can affect up to 60% of patients undergoing ASD correction with long or short instrumentations with a consequent high rate of reinterventions.⁴¹⁰-¹² This complication was first defined by Glattes et al.¹³
as a kyphotic angle greater than 10° between the upper instrumented vertebra (UIV) and 2 vertebrae above. Several risk factors have been advocated as responsible for the development of PJK and different attempts have been made to classify this complication to reduce its occurrence.4,10,11,14,15

The role of the cranio-cervical complex (CCC) and the upper thoracic spine has rarely been analyzed and only recently Cerpa et al.16 have proposed that the posterior skull plumbline anterior to the UIV on postoperative standing x-rays may be a risk factor for PJK. To analyze the role of the CCC on the global spinal alignment and on the risk of PJK, a new angle was proposed: the cervical inclination angle (CIA), defined as an angle between the center of the odontoid, the mid-point of each thoracic vertebra superior endplate and a horizontal line starting from the center of each thoracic vertebra endplate.17,18 This angle was described to avoid the drawbacks of the C7 sagittal vertical axis which is measured in millimetres and has the inconvenient to be dependant of the length of the spine and the magnification calculation. With the CIA those 2 inconvenient are avoided.

It is known that to maintain an ergonomic sagittal alignment, with less paravertebral muscular effort, the thoracic and cervical spine should be aligned and have small anterior lever arms: each centimetre of anterior displacement of the gravity line results in +3.5 Nm bending moment that raises the risk of vertebral fracture and discal damage.17,18

The aim of this paper is to confirm the reproducibility of the CIA in an adult asymptomatic population and then to analyze its correlation with the other main sagittal parameters.

MATERIALS AND METHODS

1. Study Population

Asymptomatic adult volunteers between the ages of 18–80 years were enrolled prospectively across 5 different countries/centers (France, Japan, Singapore, Tunisia, and United States) forming the MEANS cohort. The study was approved by all local Institutional Ethics Review Boards for each respective center. Volunteers included in the study reported no significant neck or back pain (visual analogue scale ≤ 2), nor any known spinal disorder(s), and had no history of prior surgical or nonsurgical treatment for a spine related disorder. All volunteers underwent a standing full body or full-spine low-dose stereoradiograph (EOS Imaging, part of ATEC Spine, Inc, Carlsbad, CA, USA) for enrolment in the study. Those with an abnormal vertebral count or transitional anatomy were excluded from the analysis. Following exclusion, a total of 468 patients were included in MEANS. Basic demographic data included age, sex, body mass index (BMI), and ethnicity. Oswestry Disability Index (ODI) scores were also obtained.

2. Radiographic Measurements

All radiographic measurements were performed using a 2D/3D sterEOS modelling software (EOS Imaging). The following sagittal parameters were analyzed for the study: pelvic incidence (PI), pelvic tilt (PT), L1–S1 lumbar lordosis (LL), thoracic kyphosis (TK), C7 slope, odontoid-hip axis angle (OD-HA), CIA, and odontoid-thoracic distance (Th-OD) (defined as the distance from the odontoid plumbline and the center of each thoracic vertebra superior endplate). This distance represents the lever arm applied on each vertebral plateau (Fig. 1).

The CIA was first analyzed globally and then in each decade of life (<20 years [n = 12], 21–30 years [n = 143], 31–40 years [n = 108], 41–50 years [n = 94], 51–60 years [n = 58], 61–70 years [n = 40], 71–80 years [n = 19]).

The global population was then divided into 5 different major ethnicities (Caucasian, Japanese, Afro-Americans, Arab-Berber, Asians) and an analysis was performed to identify if the CIA remained constant and reproducible.

The CIA was then analyzed in relation to the BMI and, finally, based on volunteers Roussouly type dividing the population in 3 groups according to the PI value (PI < 45° = Roussouly 1 and 2; PI 45°–60° = Roussouly 3; PI > 60° = Roussouly 4).19

3. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). Categorical variables
were expressed as number of cases and percentage. Continuous variables were reported as mean ± standard deviation; means were compared with the Student t-test. Two-sided p-values and/or 95% confidence interval (CI) were reported, and significance was accepted at p < 0.05.

Comparisons between different age groups and ethnicities was performed using a t-test and statistical significance was considered with a p < 0.05. Correlations between CIA and BMI, and between CIA and Roussouly type, were performed with a Mann-Whitney test and significance was assessed for a p < 0.05.

RESULTS

Four hundred sixty-eight adult asymptomatic volunteers were included in the analysis (176 Caucasians, 119 Japanese,
12 Afro-Americans, 80 Arab-Berber, 81 Asians). The mean age was 40.4 ± 14.8 years (95% CI, 39.1–41.7) and the mean BMI was 24.5 ± 5.3 kg/m² (95% CI, 24.0–25.1). The male to female ratio was 184:284. The mean visual analogue score was 0.3 ± 0.5 (95% CI, 0.2–0.3) and the ODI score was 2.2% ± 4.1% (95% CI, 1.9–2.6).

The global CIA mean value was 80.12° ± 2.8° (95% CI, 78.28–81.96) with a maximal difference of 9° between all thoracic vertebrae (min T5 = 77.05° to max T12 = 86.05°, p < 0.001) (Fig. 2).

Of the included volunteers 12 had ≤ 20 years, 142 had 21 to ≤ 30 years, 107 had 31 to ≤ 40 years, 93 had 41 to ≤ 50 years, 57 had 51 to ≤ 60 years, 39 had 61 to ≤ 70 years, and 18 were older than 70 years old. When analyzing the CIA by different decades of life, we observed a significant decrease of the angle after 60 years old: the CIA remains constant until 60 years old (p > 0.05) and then decreases at all thoracic levels passing from 82.25° to 73.65° of mean value (p < 0.05) (Fig. 3).

Considering the ethnicities, a difference was observed between the Arab-Berbers and the other populations. The Arab-Berber had a statistically lower CIA mean value at each thoracic level (p < 0.05) (Fig. 4). It should be highlighted that the Arab-Berber population had an older age (45.48 ± 14.77 years vs. 39.35 ± 14.58 years).

**Fig. 4.** Graphic of cervical inclination angle (CIA) distribution according to ethnicities.

**Table 1.** CIA correlations with OD-HA, C7 slope, TK, and Th-OD distance

<table>
<thead>
<tr>
<th>Level</th>
<th>OD-HA vs. CIA</th>
<th>C7 slope vs. CIA</th>
<th>TK vs. CIA</th>
<th>Th-OD vs. CIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R coefficient</td>
<td>p-value</td>
<td>R coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td>T1</td>
<td>-0.5252</td>
<td>&lt;2.2°-16</td>
<td>-0.4839</td>
<td>&lt;2.2°-16</td>
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<tr>
<td>T2</td>
<td>-0.5583</td>
<td>&lt;2.2°-16</td>
<td>-0.6117</td>
<td>&lt;2.2°-16</td>
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<tr>
<td>T3</td>
<td>-0.5809</td>
<td>&lt;2.2°-16</td>
<td>-0.6920</td>
<td>&lt;2.2°-16</td>
</tr>
<tr>
<td>T4</td>
<td>-0.5958</td>
<td>&lt;2.2°-16</td>
<td>-0.7325</td>
<td>&lt;2.2°-16</td>
</tr>
<tr>
<td>T5</td>
<td>-0.6052</td>
<td>&lt;2.2°-16</td>
<td>-0.7518</td>
<td>&lt;2.2°-16</td>
</tr>
<tr>
<td>T6</td>
<td>-0.6149</td>
<td>&lt;2.2°-16</td>
<td>-0.7545</td>
<td>&lt;2.2°-16</td>
</tr>
<tr>
<td>T7</td>
<td>-0.6243</td>
<td>&lt;2.2°-16</td>
<td>-0.7491</td>
<td>&lt;2.2°-16</td>
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<tr>
<td>T8</td>
<td>-0.6379</td>
<td>&lt;2.2°-16</td>
<td>-0.7381</td>
<td>&lt;2.2°-16</td>
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<tr>
<td>T9</td>
<td>-0.6521</td>
<td>&lt;2.2°-16</td>
<td>-0.7229</td>
<td>&lt;2.2°-16</td>
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<tr>
<td>T10</td>
<td>-0.6702</td>
<td>&lt;2.2°-16</td>
<td>-0.7011</td>
<td>&lt;2.2°-16</td>
</tr>
<tr>
<td>T11</td>
<td>-0.6918</td>
<td>&lt;2.2°-16</td>
<td>-0.6723</td>
<td>&lt;2.2°-16</td>
</tr>
<tr>
<td>T12</td>
<td>-0.7183</td>
<td>&lt;2.2°-16</td>
<td>-0.6378</td>
<td>&lt;2.2°-16</td>
</tr>
</tbody>
</table>

CIA, cervical inclination angle; OD-HA, odontoid-hip axis angle; TK, thoracic kyphosis; Th-OD, odontoid-thoracic distance.
years, p < 0.05) and a higher BMI (27.13 ± 5.23 kg/m² vs. 23.86 ± 5.15 kg/m², p < 0.001) compared to the other populations.

When analyzing CIA in relation to BMI, no statistically significant correlation was observed between these 2 parameters (p = 0.100). Furthermore, Roussouly type (group 1 = PI < 45°, Roussouly 1 and 2; group 2 = PI 45°–60°, Roussouly 3; group 3 = PI > 60°, Roussouly 4) did not have an influence on CIA values (group 1 vs. group 2, p = 0.748; group 1 vs. group 3, p = 0.446; group 2 vs. group 3, p = 0.578).

The CIA demonstrated good negative correlations with the Th-OD distance (p < 0.001), the OD-HA angle (p < 0.001), the C7 slope (p < 0.001), the TK (p < 0.001) whereas no or little correlations were observed with the LL, lower LL (L4S1), and the PT (p > 0.05) (Table 1).

**DISCUSSION**

The goal of an ASD corrective surgery should be a satisfying global sagittal balance so that the patient may have a horizontal gaze and an upright position with the head over the hips.\(^5\)

Despite all the efforts made to avoid postoperative mechanical complications, the rate of PJK's is still very high.\(^4\) Several factors have been advocated as responsible for this event but rarely the effect of an excessive lever arm on the UIV has been discussed.\(^10,11,14\) To analyze this lever arm, the CIA has been proposed with a mean reported value of 77.7°.\(^17\)

Here we confirm the reproducibility of this angle with a reported mean value of 80.12° ± 2.8° and we were able to confirm that the CIA remains constant through different ages, despite BMI and Roussouly type, until 60 years old. When planning an ASD correction, the surgeon should keep this angle in mind and try to restore the sagittal alignment avoiding an excessive lever force on the UIV (CIA≈80°).

The value of the CIA is confirmed by its correlation to other important sagittal parameters. Here we have observed a strong negative correlation with the C7 slope, TK, OD-HA, and Th-OD: this means that the increasing value of these parameters correspond to a reduction in the CIA. It is well known that with aging the TK raises due to disc degeneration, vertebral body wedging and reduce paravertebral muscle strength.\(^17\) The increase in TK corresponds to a major C7 slope and to a forward displacement of the trunk with a consequent higher OD-HA angle and higher Th-OD distance.\(^10\) The anterior shift of the trunk raises the bending moment and consequently the risk of a vertebral fracture or PJK.\(^17\) In this scenario an excessive reduction of the CIA at the UIV corresponds to an increased risk of mechanical complications.

We have observed a lower normative value of this angle in the Arabo-Berber population, but as reported previously, this might be influenced by the mean older age in this population. The role of the aging process on the CIA has been demonstrated in this study. Concerning the BMI, it is uncertain if this could directly influence the value of the CIA, especially because we did not find significant correlations between higher body weight and CIA, but high BMI has already been reported as a minor risk factor for PJK.\(^4,21,22\)

We are aware that this study has some limitations as it is a descriptive analysis of an adult asymptomatic population and the role of the CIA in prevention of PJK should be confirmed with further clinical investigations. Nevertheless, we have demonstrated the reproducibility of this angle despite age, ethnicities or Roussouly type and its implications in the analysis of the global sagittal balance when planning an ASD correction surgery.

**CONCLUSION**

The CIA remains constant through ages until 60 years old and then reduces slightly but never under 70°. This angle might be a helpful tool to evaluate the lever arm at UIV on the thoracic spine after an ASD surgery and could predict the occurrence of a PJK when its value is lower than normal. Our experience support this feeling but further clinical studies must confirm this theory.

**NOTES**

Conflict of Interest: The authors have nothing to disclose.

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Le Huec JC, et al. Normative Values in an Adult Multiethnic Asymptomatic Population
Measurement of Deformity at the Craniovertebral Junction: Correlation of Triangular Area and Myelopathy

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Objective: Diseases of the craniovertebral junction (CVJ) are commonly associated with deformity, malalignment, and subsequent myelopathy. The misaligned CVJ might cause compression of neuronal tissues and subsequently clinical symptoms. The triangular area (TA), measured by magnetic resonance imaging/images (MRI/s), is a novel measurement for quantification of the severity of compression to the brain stem. This study aimed to assess the normal and pathological values of TA by a comparison of patients with CVJ disease to age- and sex-matched controls. Moreover, postoperative TAs were correlated with outcomes.

Methods: Consecutive patients who underwent surgery for CVJ disease were included for comparison to an age- and sex-matched cohort of normal CVJ persons as controls. The demographics, perioperative information, and pre- and postoperative 2-year cervical MRIs were collected for analysis. Cervical TAs were measured and compared.

Results: A total of 201 patients, all of whom had pre- or postoperative MRI, were analyzed. The TA of the CVJ deformity group was larger than the healthy control group (1.62 ± 0.57 cm² vs. 1.01 ± 0.18 cm², p < 0.001). Moreover, patients who had combined anterior odontoidectomy and posterior laminectomy with fixation had the greatest reduction in the TA (1.18 ± 0.58 cm²).

Conclusion: In CVJ deformity, the measurement of the cervical TA could indicate the severity of brain stem compression. After surgery, the TA had a varying degree of improvement, which could represent the efficacy of surgery.

Keywords: Craniovertebral junction deformity, Atlantoaxial instability, Basilar invagination, Odontoid fracture

INTRODUCTION

The craniovertebral junction (CVJ) resides between the cranium and cervical spine. Its unique structure is responsible for important functions, including head movement and protection of the nervous system.1,2 The CVJ is composed of bony structures, ligaments and joints, including atlas, axis, transverse ligament, cruciate ligament, occipital-atlantal joint and atlantoaxial joint.3,5 Together, these structures not only maintain the stability of the CVJ, but also are involved in the axial rotation and flexion-extension movements.

Although deformity around the CVJ is a rare condition, there are several pathologies that could affect the CVJ, such as congenital anomaly, trauma, autoimmune disease, primary or metastatic bone tumor, and ossification of the posterior longitudinal ligament (OPLL).6-10 These CVJ diseases consequently result in CVJ instability and alignment change. The deformed CVJ could cause significant neck pain due to arthritis or C2 foramininal stenosis and cervicomedullary compressive myelopathy.11-14

There have been numerous diagnostic criteria for CVJ disease. However, most of the current radiographic parameters are...
specific for the diagnosis of certain CVJ diseases. For example, the measurement of the atlanto-dental interval was used for the diagnosis of atlantoaxial subluxation.15,16 Meanwhile, those parameters are based on fluoroscopic examination, such that soft tissue compression cannot be appreciated in those exams. The triangular area (TA) of the CVJ, proposed by Chang et al.17 in 2016, is a novel measurement that can quantify the degree of compression that is applied on patients with basilar invagination. The measurement of the TA is defined by the area determined by 3 points in the midsagittal magnetic resonance T2-weighted image: the lowest point of the clivus, the posterior-inferior point of the C2 vertebral body, and the most dorsal indentation point in the ventral aspect of the brain stem (Fig. 1). The application of TA was further expanded to patients with CVJ trauma and rheumatoid arthritis. Chang et al.18 reported that patients with a TA value greater than 1.36 cm² had high possibility to develop myelopathy that early surgical intervention was highly recommended.

Surgery of CVJ pathology can be difficult and complicated. Several aspects should be of concern before the surgery. First, the anatomy of the CVJ area is usually intricate. Bony or vascular anomalies are not uncommon in patients with CVJ disease.19-21 Second, the alignment correction has a great influence on the surgical outcome. A realigned CVJ indicates the relief of cervicomедullary compressive myelopathy.22 However, alignment correction is not always achievable in every patient with CVJ deformity. Third, a decompression maneuver, either anterior, posterior or combined, should be considered in those patients who had failed realignment of the CVJ23,24 Although there have been several algorithms proposed to treat CVJ deformity, there is still debate on the choice of decompression maneuver in CVJ deformity patients, and there is no definite conclusion till now. In most cases, the choice of decompression method is dependent on the surgeon’s experience. The use of the TA could quantify the degree of ventral compression to the brain stem including medulla. Therefore, it could represent clinical improvement. Using the TA might provide a useful indication to determine the way of decompression in the future. In this study, we aimed to expand the use of TA to various kinds of CVJ pathology. Comparisons were made against age- and sex-matched population-based controls without CVJ deformity. Postoperative TAs were also measured and compared according to different decompression maneuvers.

MATERIALS AND METHODS

1. Study Design and Patient Inclusion
This was a retrospective comparative study that included consecutive patients who had CVJ surgery for instability. Patients who had the diagnosis of CVJ pathologies were extracted from the database for analysis. The other age- and sex-matched cohort members who had a normal CVJ (no structural CVJ anomalies on the MRI, and had an atlantodental interval less than 3 mm on the dynamic lateral radiographs) were extracted from the image database within the same period as the CVJ deformity group. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (No. 2019-12-001AC) and patients’ informed consent was obtained.

Exclusion criteria were prior surgery of the CVJ and those patients who had an unidentified TA due to bony destruction. The TA measurements were performed on the Smart Iris Imaging System (Taiwan Electronic Data Processing Co., Taipei City, Taiwan), and interpreted independently by radiologists and neurosurgeons, who were blinded to the patient information. Data were collected and compared between the groups. Patients of the CVJ deformity group were followed-up regularly and
MRI was arranged at 2-year postoperation. The demographic and perioperative data were also collected for comparison.

2. Radiographical Definition of the TA of the CVJ
A simulated TA ventral to the brain stem was determined in the midsagittal T2-weighted MRIs of each patient on the picture archiving and communication system and calculated by its viewer. The TA was defined by 3 points: the lowest point of the clivus, the posterior-inferior point of the C-2 vertebral body, and the most dorsal indentation point in the ventral aspect of the brain stem. For the surgical cases, the pre- and postoperative 2-year TA was measured and compared.17,18

3. Statistics
Medcalc (Ostend, Belgium) was used for statistical analysis. Descriptive statistics were reported as means and standard deviations, and as frequencies and percentages where appropriate. Continuous variables were compared using an unpaired Student t-test, and categorical variables were compared using Pearson chi-square test. Probability values were 2-tailed and an alpha of 0.05 was considered statistically significant.

RESULTS

1. Demographics
A total of 201 consecutive patients who had CVJ deformity were included in this study. Another 201 age- and sex-matched persons were included as controls. There were 101 male and 100 female patients in both groups. The mean age was, respectively, 59.8 ± 17.2 versus 60.2 ± 13.1, p = 0.78. The body mass index in the CVJ deformity group was smaller (23.5 ± 3.6 vs. 24.7 ± 4.9, p = 0.014). The incidence rate of hypertension was 38.8% versus 30.8%, p = 0.09, type II diabetes mellitus 13.4% versus 15.4%, p = 0.57, and ankylosing spondylitis 1.9% versus 0.9%, p = 0.41. The incidence rate of rheumatoid arthritis was significantly higher in the CVJ deformity group (10.4% vs. 0.9%, p < 0.0001) (Table 1).

2. Type of Pathology and Perioperative Information
The type of pathology and perioperative information were listed in Table 2. There were 10 patients who had C0–2 decompressive laminectomy, 27 patients who had C1 laminectomy, and 39 patients who had C1–2 laminectomy. A total of 8 patients received anterior odontoidectomy, including 6 odontoidectomy before fusion and 2 odontoidectomy after fusion surgery. There were 142 patients who had fusion level within C1–2 and 59 patients who had fusion level spanning C1–2. The average bone density (DEXA T-score) of the CVJ deformity group was -1.39 ± 1.68. There were 12 patients who experienced surgical complication, including 5 cerebrospinal fluid leak, 6 wound infection/poor healing, and 1 postoperative cerebellar infarction. There was no vascular injury among all surgical cases (Table 2).

3. Comparison of the Preoperative TA Between CVJ Deformity Cases and Age-Sex-Matched Controls
The control group had an average TA of 1.01 ± 0.18 cm². The average TA of the CVJ deformity group was 1.62 ± 0.57, which was significantly larger than the control group. The TAs of patients with basilar invagination, odontoid fracture, os odontoideum, stenosis, atlantoaxial subluxation, C2 osteomyelitis, and C2 metastasis were significantly larger than in the control group (Table 3).

4. Comparison of ΔTA Between Different Decompression Maneuvers
The delta TA (ΔTA) was the difference between the preoperative and postoperative 2-year TA. The ΔTA in patients who had combined anterior and posterior decompression surgery was -1.18 ± 0.58. The ΔTA in patients who had no decompression maneuver (fixation-alone) was -0.20 ± 0.37. The ΔTA in patients who had posterior decompression (decompressive laminectomy plus fixation) was -0.21 ± 0.49 (Table 4).

Table 1. Comparison of clinical characteristics between craniovertebral junction (CVJ) deformity cases and age-sex-matched controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CVJ deformity (n = 201)</th>
<th>Controls (n = 201)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>101</td>
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</tr>
<tr>
<td>Female</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.8 ± 17.2</td>
<td>60.2 ± 13.1</td>
<td>0.78</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.5 ± 3.6</td>
<td>24.7 ± 4.9</td>
<td>0.014*</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>78 (38.8)</td>
<td>62 (30.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>27 (13.4)</td>
<td>31 (15.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>21 (10.4)</td>
<td>2 (0.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>4 (1.9)</td>
<td>2 (0.9)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). *p < 0.05, statistically significant differences.
Table 2. Type of pathology and perioperative information

<table>
<thead>
<tr>
<th>Type of CVJ pathology</th>
<th>Value</th>
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<tbody>
<tr>
<td>Neoplasm</td>
<td></td>
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<tr>
<td>Aneurysmal bone cyst</td>
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<tr>
<td>C2 metastasis</td>
<td>12 (6.0)</td>
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<tr>
<td>C2 multiple myeloma</td>
<td>2 (1.0)</td>
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<tr>
<td>Trauma and structural instability</td>
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<tr>
<td>Combined C1 and C2 fracture</td>
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</tr>
<tr>
<td>Jefferson fracture</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Hangman fracture</td>
<td>9 (4.5)</td>
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<td>Odontoid fracture</td>
<td>44 (21.8)</td>
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<td>Os odontoideum</td>
<td>22 (10.9)</td>
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<td>Atlantoaxial subluxation</td>
<td>94 (46.8)</td>
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<td>Congenital anomaly</td>
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<tr>
<td>Basilar invagination</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>OPLL</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Stenosis</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>C2 osteomyelitis</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Surgical detail</td>
<td></td>
</tr>
<tr>
<td>Decompression</td>
<td></td>
</tr>
<tr>
<td>Laminectomy</td>
<td></td>
</tr>
<tr>
<td>C0–2</td>
<td>10 (5.0)</td>
</tr>
<tr>
<td>C1</td>
<td>27 (13.4)</td>
</tr>
<tr>
<td>C1–2</td>
<td>39 (19.4)</td>
</tr>
<tr>
<td>Odontoidectomy</td>
<td></td>
</tr>
<tr>
<td>Before fusion</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>After fusion</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Fusion level</td>
<td></td>
</tr>
<tr>
<td>Within C1–2</td>
<td>142 (70.6)</td>
</tr>
<tr>
<td>Spanning C1–2</td>
<td>59 (29.4)</td>
</tr>
<tr>
<td>Bone density (DEXA T-score)</td>
<td>-1.39 ± 1.68</td>
</tr>
<tr>
<td>Complication</td>
<td></td>
</tr>
<tr>
<td>CSF leak</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Wound infection/poor healing</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Postoperative cerebellar infraction</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

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

Table 3. Comparison of preoperative triangular area between craniovertebral junction (CVJ) deformity cases and normal controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative triangular area (cm²)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.01 ± 0.18</td>
<td></td>
</tr>
<tr>
<td>CVJ deformity</td>
<td>1.62 ± 0.57</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Basilar invagination</td>
<td>1.94 ± 0.48</td>
<td>0.02*</td>
</tr>
<tr>
<td>Combined C1 and C2 fracture</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td>Jefferson fracture</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>Hangman fracture</td>
<td>1.11 ± 0.27</td>
<td>0.13</td>
</tr>
<tr>
<td>Odontoid fracture</td>
<td>1.55 ± 0.56</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Os odontoideum</td>
<td>2.11 ± 0.62</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Stenosis</td>
<td>2.18 ± 0.45</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Atlantoaxial subluxation</td>
<td>1.63 ± 0.52</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>OPLL</td>
<td>0.92 ± 0.12</td>
<td>0.39</td>
</tr>
<tr>
<td>C2 osteomyelitis</td>
<td>1.84 ± 0.68</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>C2 metastasis</td>
<td>1.31 ± 0.41</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>C2 multiple myeloma</td>
<td>1.18</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

Table 4. Comparison of ΔTA between different decompression maneuvers

<table>
<thead>
<tr>
<th>Decompression type</th>
<th>Without decompression</th>
<th>Posterior decompression</th>
<th>Combined anterior and posterior decompression</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTA (cm²)</td>
<td>-0.20 ± 0.37</td>
<td>-0.21 ± 0.49</td>
<td>-1.18 ± 0.58*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

DISCUSSION

The cervical TA of the CVJ deformity group was significantly larger than the age- and sex-matched control group (1.62 ± 0.57 vs. 1.01 ± 0.18, p < 0.001). Furthermore, this study expanded the use of TA to various kinds of CVJ pathology. The TA in most of the CVJ pathology group was significantly larger than the TA in the control group except for several pathologies, such as aneurysmal bone cyst (ABC), combined C1 and C2 fracture, hangman fracture, OPLL and C2 multiple myeloma. Those images were reviewed to discuss why the TA did not increase in those patients. The ABC was a benign, blood-filled vascular lesion in the bone that tends to expand or grow. In our case, the ABC occurred within the C2 laminar, spinous process and bilateral pars interarticularis that caused the destruction of the bilateral atlantoaxial joint. However, the ventral side was totally free of ABC.
Therefore, the TA in our ABC case was normal since it did not have any ventral compression. In combined C1 and C2 fracture and hangman fracture cases, we found the CVJs were reduced during the MRI examination that made the TA value normal. The C2 multiple myeloma was diagnosed at a very early stage, such that the destruction and deformation of the CVJ was not severe. The TA value of 3 OPLL cases were similar to the control group. That was because the OPLL started from the middle of C2, which did not cause a lot of ventral compression.

The measurement of the TA could quantify the degree of cervicomedullary compression in patients with a CVJ deformity. After the surgery, the change of the TA could reflect the efficacy of surgery. The improvement of the TA benefits from 3 factors; the improvement of alignment, the decompression effect, and the resorption of retro-odontoid soft tissue mass. The realignment and decompression immediately influences the TA after surgery. The resorption of retro-odontoid soft tissue mass was a delayed type of TA improvement. It has been well reported by many researchers that the retro-odontoid mass tissue disappeared after fixation of the CVJ.14,17,18,25 Chang et al.17 observed that the TA decreased immediately after the surgery and continued to decrease until 2 years after surgery. In this study, the ΔTA was 1.18 cm² in patients who had combined anterior and posterior decompression surgery. Furthermore, the ΔTA was similar between the posterior decompression group and the group without decompression. This result was quite intuitive that the TA represented the ventral compression to the spinal cord. The measurement of the TA could not depict the outcome of posterior decompression.

The CVJ diseases are usually associated with structural destruction that results in CVJ instability and deformation. The malaligned CVJ causes cervicomedullary compression, so that surgical intervention was necessary to prevent brain stem or spinal cord injury. For optimal treatment, surgeons should consider the etiology, reducibility of bony parts, mechanics of compression, and the presence of an abnormal ossification center. Menezes proposed a treatment algorithm for CVJ abnormality with the primary goal to relieve compression at the CVJ.24 For reducible lesions, the treatment key point is to maintain a neutral position and stabilization, either by external immobilization or internal fixation. Irreducible lesions require decompression at the side at which the compressions occur. The treatment algorithm was straightforward and convincing, which was supported by many published clinical series.2,7,23,26-33 However, the surgical decision was always difficult because the reducibility was difficult to judge, especially for those patients in an acute stage. Most patients in an acute stage were afraid of moving their head and neck due to severe neck pain and muscle spasm. The results of the TA change after surgery in this study might provide a useful information for the surgical planning in the future. As mentioned before, the improvement of the TA benefits from 3 factors: the improvement of alignment (Fig. 2A, B), the decompression effect (Fig. 2C, D), and the resorption of

**Fig. 2.** Pre- and postoperative 2-year (A, B) image of a patient with atlantoaxial subluxation. The TA decreased due to improvement in alignment. Pre- and postoperative 2-year (C, D) image of a patient with os odontoideum. The TA decrease benefitted from the anterior odontoidectomy. Pre- and postoperative 2-year (E, F) image of a patient with rheumatoid arthritis and atlantoaxial subluxation. The TA decrease was due to the disappearance of the retro-odontoid mass.
retro-odontoid soft tissue mass (Fig. 2E, F). In this study, we found the patients who had no decompression maneuver (fixation only) had a decrease of their TA by 0.2 cm$^2$. The decrease of the TA in this patient group was mainly attributed to the improvement of alignment. Otherwise, the combined anterior and posterior decompression group had a decrease of the TA by 1.18 cm$^2$. Our previous study demonstrated that a TA value greater than 1.36 cm$^2$ was highly associated with myelopathy.\textsuperscript{18} The combined conclusions of both studies suggested that anterior odontoidectomy should be highly considered for those patients who had a TA value greater than 2.5 cm$^2$. Once the TA value was larger than 2.5 cm$^2$, it was less likely to have a TA smaller than 1.36 cm$^2$ via the posterior approach only, either with decompression or not. The use of the TA could provide useful information in surgical planning.

There were limitations to this study. This was a single institute, retrospective, nonrandomized, observational study. The age- and sex-matched control cohort was chosen from the patients who had cervical MRI in our image data base with no CVJ abnormality. These patients might not be completely healthy as they could have been slightly symptomatic or had other reasons for MRI examination. There was some heterogeneity in the CVJ deformity cohort; the case numbers of certain pathologies were fewer than others. This reflects the rarity of any particular disease. Otherwise, the TA was designed for quantification of the ventral compression. For the compression from the posterior side, it was unable to be detected. However, the TA is still a very useful measurement for the CVJ, given the reason that most CVJ deformity cases resulted in anterior subluxation. Future investigations should aim to expand its use in more CVJ deformity cases to help in the surgical decision and to evaluate the efficacy of surgery.

**CONCLUSION**

This case-control study has expanded the use of the TA to various kinds of CVJ pathologies. The TA was significantly larger in CVJ deformity cases compared with cases without deformity as controls. After surgery, the change of the TA could reflect the realignment and decompression effect of the CVJ. Therefore, the TA is a valid measurement to quantify compression at the CVJ and to evaluate the efficacy of surgery.

**NOTES**

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**Author Contribution:** Conceptualization: CCC, JCW, THT, WCH; Data curation: CCK, HKC, YHK, CHK, THT; Formal analysis: CCC, CCK, HKC, YHK, CHK; Methodology: CCC, JCW, CCK, THT, WCH; Project administration: JCW, WCH; Writing - original draft: CCC, THT; Writing - review & editing: CCC, JCW.

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Evaluation of Cervicomedullary Compression Around the Craniovertebral Junction: Commentary on “Measurement of Deformity at the Craniovertebral Junction: Correlation of Triangular Area and Myelopathy”

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The craniovertebral junction (CVJ) is the region around the skull base and the upper cervical spine (atlas and axis), along with its neurovascular components, including the brain stem, spinal cord, vertebral artery, and venous plexus.1-6 The stability of CVJ is dependent on a robust ligamentous complex and the shape of the bony structures, which are also responsible for much of the axial rotation (C1–2 joint) and flexion-extension movements (C0–1 and C1–2 joint).7,8 CVJ pathologies are usually rare and can result in progressive deformity, myelopathy, severe neck pain, and functional disability, such as difficulty swallowing.9-12 The most common causes are rheumatoid arthritis, trauma, neoplasm, infection, and congenital bony malformation. These CVJ pathologies may alter the quality of life because of the neck pain, disabling headache, dysphagia, and myelopathy.12,13

In most cases, standard radiographs, computed tomography, and magnetic resonance imaging typically conduct the proper diagnosis of CVJ pathology. However, no one-single method has been recommended to properly diagnose CVJ pathology due to the overlying structures on lateral plain radiographs. Ambiguous landmarks lead to low reliability or consistency for confirming basilar invagination (BI).14-16 Accordingly, we must establish a more reliable and consistent method for diagnosing CVJ pathologies.

Many methods for diagnosing BI and CVJ pathology may imply that choosing just one method in clinical circumstances is complicated. These measurements can show variable results due to multiple reasons. First, anatomical landmarks may be ambiguous, thus leading the interpreter to measure different results. Second, measurement errors can be made by the interpreter himself or on the radiographs. The lack of confidence in anatomic landmarks can cause unreliable results, and it is hard to obtain absolute true-lateral radiographs in every patient.

Variations in measurement may lead to a different type of treatment. Therefore, we need to determine how reliable and reproducible these measurements are.16
In this article, the novel measurement method of the cord compression around CVJ is well described, and the measurement of triangular area (TA) could indicate the severity of cervicomedullary compression.

Cervical TA is a 2-dimensional volumetric measurement of ventral cord compressive lesion. It is possible to evaluate the exact degree of cervicomedullary compression in patients with CVJ deformity compared to the existing 1-dimensional measurement methods.

Moreover, the change of TA could reflect the effect of surgery, such as the improvement of CVJ alignment, cord decompression, and the resorption of retro-odontoid soft tissue mass.

However, there are several limitations of cervical TA evaluation. First, most CVJ pathologies often accompany mechanical instability, and this instability often causes or exacerbates neurological symptoms, but cervical TA measurement does not reflect the dynamic cord compression.

And cervical TA does not show the cord compressive lesions caused by posterior pathologies. And finally, cervical TA cannot reflect the indirect decompression effect of the C1–2 joint distraction technique.

As introduced by Goel, a C1–2 joint distraction technique has been gaining popularity recently as a possible treatment modality for selected CVJ pathologies, especially for BI. C1–2 joint distraction reduces BI and decompresses indirectly by down-migrating the C2 dens and stretching the retro-odontoid pannus in patients with BI and the retro-odontoid pannus. This technique has several advantages over conventional transoral surgery, the most important of which are indirect reduction and fixation are possible posteriorly for the compressive pathology around the cervicomedullary junction.

However, confirming the indirect cord decompression effect by the cervical TA method could be difficult after C1–2 joint distraction surgery because the length between the clivus and the lower C2 endplate increases even though the degree of anterior spinal cord compression decreases after vertical distraction surgery of C1–2 facet joint.

Despite these disadvantages, this cervical TA measurement method can evaluate the degree of ventral compression more accurately in 2 dimensions, which could be helpful for the pre- and postoperative evaluation of many CVJ pathologies. Of course, it will be necessary to evaluate and confirm the efficacy of this new measurement method for the various types of CVJ disease.

Conflict of Interest: The author has nothing to disclose.

REFERENCES


Characteristics and Comparisons of Morphometric Measurements and Computed Tomography Hounsfield Unit Values of C2 Laminae for Translaminar Screw Placement Between Patients With and Without Basilar Invagination

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Objective: Patients with basilar invagination (BI) had high incidences of vertebral variations and high-riding vertebral artery (HRVA) that might restrict the use of pedicle or pars screw and increase the use of translaminar screw on axis. Here, we conducted a radiographic study to investigate the feasibility of translaminar screws and the bone quality of C2 laminae in patients with BI, which were compared with those without BI as control to provide guidelines for safe placement.

Methods: In this study, a total of 410 patients (205 consecutive patients with BI and 205 matched patients without BI) and 820 unilateral laminae of the axis were included at a 1:1 ratio. Comparisons with regard to insertion parameters (laminar length, thickness, angle, and height) for C2 translaminar screw placement and Hounsfield unit (HU) values for the assessment of the appropriate bone mineral density of C2 laminae between BI and control groups were performed. Besides, the subgroup analyses based on the Goel A and B classification of BI, HRVA, atlas occipitalization, and C2/3 assimilation were also carried out. Furthermore, the factors that might affect the insertion parameters and HU values were explored through multiple linear regression analyses.

Results: The BI group showed a significantly smaller laminar length, thickness, height, and HU value than the control group, whereas no significant difference was observed regarding the laminar angle. By contrast, the control group showed significantly higher rates of acceptability for unilateral and bilateral translaminar screw fixations than the BI group. Subgroup analyses showed that the classification of Goel A and B, HRVA, atlas occipitalization, and C2/3 assimilation affected the insertion parameters except the HU values. Multiple linear regression indicated that the laminar length was significantly associated with the male gender (B = 0.190, p < 0.001), diagnoses of HRVA (B = -0.109, p < 0.001), Goel A (B = -0.167, p < 0.001), and C2/3 assimilation (B = -0.079, p = 0.029); the laminar thickness was significantly associated with the male gender (B = 0.353, p < 0.001), diagnoses of HRVA (B = -0.430, p < 0.001), Goel B (B = -0.249, p = 0.026), and distance from the top
INTRODUCTION

Posterior screw placement for C2 vertebrae, including transarticular, pedicle, pars, and translaminar screw fixations, has been used for the treatment of cervical spine pathologies. Among these methods, C2 pedicle and pars screw placements have been frequently applied with high safety of fixation and sufficient biomechanical stability. However, the difficulty of accurate placement for C2 pedicle or pars increases in patients with pedicle anomalies and high-riding vertebral artery (HRVA), and the malposition might contribute to catastrophic outcomes, including injuries of the vertebral artery (VA) and spinal cord. Translaminar screw placement (TSP), which was first introduced by Wright, has been regarded as an alternative strategy for C2 fixation because of its placement under direct visualization, elimination of the need for navigation or fluoroscopy, low risk of critical neurovascular injury, and comparable atlantoaxial stabilization.

For patients with basilar invagination (BI), narrow C2 pedicles and isthmuses of thepars are commonly observed, and the incidence of HRVA is remarkably increased, which reduces the safe zone for the trajectory of pedicle and pars screws. Thus, the TSP is frequently utilized as a salvage method for C2 fixation in BI. Previous research primarily focuses on morphometric measurements, including laminar length, thickness, angle, and height, for translaminar screw insertion on the axis and subaxial cervical segments for people without congenital cervical vertebral anomalies, indicating that TSP can be a reliable and alternative method at these levels. In addition, the acceptability of TSP is analyzed in some studies. Chan et al. performed morphometric analysis of the C1 and C2 laminae and found that 65.5% of C1 and 80.3% of C2 laminae could accept 3.5 mm screws. Ma et al. conducted a cadaveric specimen study to assess the applicability of C2 TSP in adult population and indicated that 5% and 9.2% specimens had a laminar thickness of ≤ 4.0 mm bilaterally and unilaterally. Nevertheless, to our knowledge, no study has been conducted to explore the characteristics of insertion parameters and feasibility of TSP on the C2 vertebrae in BI, and compared these parameters between patients with and without BI.

The Hounsfield unit (HU) obtained from computed tomography (CT) has been widely used for the calculation of bone mineral density (BMD) and the estimation of bone strength. Moreover, HU measured at a region of interest (ROI) of the screw trajectory presents the approximate BMD and correlates strongly with insertion torque and implant stability in vitro and in vivo studies. Furthermore, Han et al. demonstrated that HU values on C2–3 segments indicate a more reliable BMD level than those on C4–7 segments, and HU values of cervical CT provided reliable information regardless of measured sections, age, sex, and degree of degeneration. Therefore, the BMD, insertion torque, and implant stability of translaminar screw can be approximately compared between patients with and without BI using the HU values measured on C2 laminae.

Thus, this study aimed to evaluate the anatomic acceptability and feasibility of TSP with regard to insertion parameters and assess the approximate BMD using HU values on C2 laminae in BI patients, and these parameters were compared with those in patients without BI to provide pertinent clinical data for translaminar screw insertion. Moreover, the factors that might affect the insertion parameters and HU values were explored through multiple linear regression.

MATERIALS AND METHODS

1. Patients and Study Design

Ethical approvals were provided by the ethics committees of the First Affiliated Hospital of Anhui Medical University Ethics Committee and the First Affiliated Hospital of the University of Science and Technology of China Ethics Committee (PJ2022-
Since this is a retrospective study, formal consent is not required. A total of 205 consecutive patients diagnosed with BI according to the Chamberlain line between April 2017 and April 2022 were included. Meanwhile, 205 patients without BI were randomly selected on the basis of the medical records and matched as controls based on age and sex. The inclusion criteria were as follows: (1) ages between 18 and 75 years and (2) patients undergoing 3-dimensional (3D) CT examinations of the head and cervical spine. The exclusion criteria were as follows: (1) postoperative patients whose normal anatomical structures were destroyed, (2) patients with rheumatoid arthritis on many years of steroid treatment, (3) patients with BI secondary to Paget disease, (4) diagnoses of cervical tumor and infection on occipital and cervical regions and fractures violating the pedicles and laminae on the axis, (5) images with unsatisfactory quality or mental artifacts, and (6) incomplete data for review cases.

Various indications for TSP, such as criteria developed by Shin et al., Alvin et al., and Chan et al., have been published for the safety and accuracy of fixation. In this study, the Chan criterion was used for the evaluation of the unilateral and bilateral acceptability of TSP. Subgroup analyses based on the classification of Goel type A and B subtypes in BI (Fig. 1), HRVA (Fig. 2), and the presences of atlas occipitalization and C2/3 assimilation (Fig. 3) were also performed to determine the characteristics of the laminar morphology and feasibility of TSP on the axis.

2. Radiological Measurements
A slice of CT images was 0.625 mm thick, and radiological measurements were performed along multiplanar planes, including axial, coronal, and sagittal sections, after CT reconstructions on the workstation (General Electric Medical Systems, Milwaukee, WI, USA). The measurements were independently and blindly conducted by 2 independent reviewers who were familiar with cervical anatomy. The average values of continuous variables measured by the 2 independent observers were utilized in this research. If divergence occurred during categorical grading, then a third senior independent observer will make the final decision.

3. Morphometric Measurements
The size and morphology of the laminae were measured to determine the feasibility of translaminar fixation on the axis. The following insertion parameters were evaluated on the same para-axial plane correlating with the thinnest part in the midportion of the lamina (Fig. 4A): (1) laminar length refers to the length from the contralateral junction of the lamina and spine.

Fig. 1. (A) The sagittal section of Goel A in basilar invagination. (B) The coronal section of Goel A in basilar invagination. (C) The sagittal section of Goel B in basilar invagination. (D) The coronal section of Goel B in basilar invagination.
Characteristics of C2 Laminae in BI

Zhou LP, et al.

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The characteristics of C2 laminae include:

1. Lamina process to the lateral cortex of the lateral mass;
2. Laminar thickness is the shortest distance portion of the lamina;
3. Laminar angle is the angle from the axis of the lamina to a line passing through the spinous process and vertebral body, which represents the screw trajectory along the longitudinal axis of the lamina using the spinous process as an insertion landmark.

Moreover, laminar height refers to the length from the most rostral point and the most caudal portion of the lamina, which was assessed on the para-sagittal section (Fig. 4B).

Based on the Chan criterion, for laminae undergoing unilateral placement, the minimum laminar thickness and height should not be less than 4.5 mm if a 3.5-mm screw was inserted with a margin of error of 0.5 mm on each side, and the minimum laminar length must be 20 mm; for patients receiving bilateral placement, the bilateral laminar thickness, bilateral length, and bilateral height should be ≥ 4.5, ≥ 20, and ≥ 9 mm, respectively.

Fig. 2. (A) The sagittal section was identified with a line (a) transecting the midportion of the C1–2 facet joint on the coronal section. (B) The high-riding vertebral artery was defined on the sagittal section of the axis as an internal height (b) ≤ 2 mm, isthmus height (c) ≤ 5 mm, or both.

Fig. 3. Presences of atlas occipitalization (blue arrow) and C2/3 assimilation (yellow arrow) in a basilar invagination patient.

Fig. 4. (A) Parameters measured in the para-axial section correlating with the thinnest part in the midportion of lamina. Laminar length (a), the length from the contralateral junction of lamina and spinous process to the lateral cortex of the lateral mass; laminar thickness (b), the shortest distance portion of the lamina; laminar angle (β), the angle from the axis of lamina (a) to a line (c) passing through the spinous process and vertebra body. (B) Parameters measured in the para-sagittal section of C2 lamina. Laminar height (d), the length from the most rostral point and the most caudal portion of lamina.
respectively. In addition, for patients with laminar assimilation of C2/3, the measurement of laminar height was abandoned, and it was assumed that the height of the lamina was large enough to accommodate the safe unilateral placement of the screw. On the contrary, patients with C2/3 assimilation were excluded from the assessment of bilateral placement because of limited data of laminar height.

We reported 2 sets of quantitative data of C2 laminae, namely, measured values for unilateral laminae suitable for screw placement and values for all included unilateral laminae. The former indicated the values of laminae that met the Chan criterion for TSP to provide useful guidelines for their safe placement, whereas the latter showed the demographic characteristics of unilateral laminae between patients with and without BI.

4. CT Hounsfield Unit Values
A ROI was selected using para-axial slices of C2 laminae on the GE workstation for the calculation of an average HU value. The ROI was fixed at 20 mm × 4.5 mm, which represented the Chan criterion for TSP, and all cortical regions (inner and outer walls of the laminae) were avoided during HU attenuation measurement (Fig. 5). In addition, for patients with laminar thickness or length less than the abovementioned ROI (20 mm × 4.5 mm), the ROI was adjusted by reducing the length or width for the accommodation in the laminae and avoidance of overlapping with cortical bone that would falsely elevated HU values.

Fig. 5. Measurement of Hounsfield unit values of C2 lamina via a region of interest (ROI) on the para-axial section. In principle, the ROI was fixed at 20 mm × 4.5 mm (the white linear rectangle).

5. Statistical Analyses
Statistical analyses were completed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). Independent t-test and analysis of variance test were performed to compare 2 sets and multiple sets of quantitative data based on normal distribution. Otherwise, the Wilcoxon test and Kruskal-Wallis test were used for 2 and multiple sets of continuous variables. The nominal p-value was adjusted as 0.05 for multiple comparisons. The categorical variables were compared using the chi-square test. In addition, multiple imputation was performed to obtain missing data. Furthermore, factors that affect the insertion parameters, including sex, age, classification of Goel A and B subtypes, distance from the top of odontoid to the Chamberlain line, diagnosis of HRVA, atlas occipitalization, and C2/3 assimilation, were analyzed using multiple linear regression. By contrast, factors that affect the CT HU values, including the abovementioned possible risk factors, laminar length, laminar thickness, and laminar angle, were explored using multiple linear regression. A p-value of < 0.05 was considered statistically significant.

RESULTS

1. Patient Demographic Data
In this comparative study, a total of 410 patients with and without BI were included at a 1:1 ratio. In the BI group, 59.02% of patients (121 of 205) were diagnosed with Goel A type, and the remaining 40.98% of patients (84 of 205) were diagnosed with Goel B type. No significant differences in mean demographic profiles, including age, body mass index (BMI), and gender, were observed between BI and control groups (p > 0.05) (Table 1) and between Goel A and B groups (p > 0.05) (Supplementary Table 1). A total of 31 (15.1%) and 24 patients (11.7%) in the BI and control group, respectively, lacked the BMI information of medical records and missing data were addressed by using a multiple imputation model. Furthermore, the BI group and Goel A group showed significantly higher rates of atlas occipitalization, C1/2 dislocation, and C2/3 assimilation, and significantly shorter distance from the spinous process to the skin than the control group and Goel B group (p < 0.001) (Table 1, Supplementary Table 1).

2. Acceptability of Unilateral and Bilateral TSPs
The acceptable rates of unilateral and bilateral translaminar fixations using the criteria of Shin, Alvin, and Chan are shown in Supplementary Tables 2 and 3. The results showed that based on the Shin criterion, the con-
control group was associated with a significantly higher rate of acceptability for unilateral translaminar fixation than the BI group (p < 0.001); meanwhile, the Goel A group showed a significantly lower rate of acceptability for unilateral translaminar fixation than the Goel B group (p = 0.010). Based on the Alvin criterion, the control group indicated a significantly higher rate of acceptability for unilateral translaminar fixation than the BI group (p < 0.001), but no significant difference was observed between Goel A and B groups (p = 0.897).

Based on the Chan criterion, the control group showed significantly higher rates of acceptability for unilateral and bilateral translaminar fixations than the BI group (p < 0.001), but such differences were not significant between Goel A and B groups (p > 0.05).

3. Comparative Outcomes Between the Control and BI Groups

For the unilateral C2 laminae suitable for screw placement (Table 2) and the overall unilateral C2 laminae (Supplementary Table 4), the BI group showed significantly smaller laminar length, thickness, height, and HU values than the control group (p < 0.05), whereas no significant difference in laminar angle was observed between the 2 groups.

4. Subgroup Comparisons Based on Goel Classification

For the unilateral C2 laminae suitable for screw placement (Table 3) and the overall unilateral C2 laminae (Supplementary Table 5), the Goel A group showed significantly smaller laminar length, larger laminar angle, and larger laminar height than the Goel B group (p < 0.05), but no significant difference in laminar thickness and HU values was observed between the 2 groups.

5. Subgroup Comparisons Based on the Diagnosis of HRVA

For the unilateral C2 laminae suitable for screw placement...
(Table 4) and the overall unilateral C2 laminae (Supplementary Table 6), the HRVA group had a significantly smaller laminar height than the non-HRVA group in the control cohort (p = 0.028) and a significantly shorter laminar length and thickness in the BI cohort (p < 0.001).

Moreover, we found that for unilateral laminae with HRVA, the BI group had significantly smaller laminar length, height, and HU values than the control group; for unilateral laminae without HRVA, the BI group had significantly smaller laminar height and HU values than the control group (p < 0.05).

6. Subgroup Comparisons Based on Goel Classification and the Diagnosis of HRVA
For the unilateral C2 laminae suitable for screw placement (Table 5) and the overall unilateral C2 laminae (Supplementary Table 7), the HRVA group was significantly associated with shorter laminar length and height compared with the non-HRVA group in Goel A cohorts (p < 0.001). In the Goel B cohort, no significant differences in morphometric measurements and HU values were observed between HRVA and non-HRVA groups (p > 0.05).

However, for the overall unilateral C2 laminae (Supplementary Table 7), the HRVA group was significantly associated with shorter laminar thickness compared with the non-HRVA group in Goel A cohorts (p < 0.001).

7. Subgroup Comparisons Based on the Presence of Atlas Occipitalization
For the unilateral C2 laminae suitable for screw placement (Supplementary Table 8) and the overall unilateral C2 laminae (Supplementary Table 9), the control group without atlas occipitalization had significantly smaller laminar height and HU values than BI groups with and without atlas occipitalization (p < 0.01). In the BI cohort, the atlas occipitalization group was associated with significantly smaller laminar length and angle than the non-atlas occipitalization group (p < 0.001).

8. Subgroup Comparisons Based on the Presence of C2/3 Assimilation
For the unilateral C2 laminae suitable for screw placement (Supplementary Table 10) and the overall unilateral C2 laminae (Supplementary Table 11), the control group without C2/3 assimilation had significantly smaller laminar length and HU values than BI groups with and without C2/3 assimilation (p < 0.05). In the BI cohort, the C2/3 assimilation group was associated with significantly smaller laminar length and angle than the non-C2/3 assimilation group (p < 0.001).

9. Multiple Linear Regressions
Multiple linear regressions were performed on the basis of the overall 820 unilateral C2 laminae, whereas factors affecting laminar height were explored on the basis of the 690 unilateral laminae. The results showed that the laminar length was significantly associated with the male gender (B = 0.190, p < 0.001), diagnoses of HRVA (B = -0.109, p < 0.001), Goel A (B = -0.167, p < 0.001), and C2/3 assimilation (B = -0.079, p = 0.029); the laminar thickness was significantly associated with the male gender (B = 0.353, p < 0.001), diagnoses of HRVA (B = -0.430, p < 0.001), Goel B (B = -0.249, p = 0.026), and distance from the top of odontoid to the Chamberlain line (B = -0.025, p = 0.003); the laminar angle was significantly associated with Goel A (B = 1.841, p < 0.001), C2–3 assimilation (B = 1.461, p = 0.001), and distance from the top of odontoid to the Chamberlain line (B = -0.195, p < 0.001); the laminar height was significantly associated with the male gender (B = 0.068, p < 0.001), diagnoses of HRVA (B = -0.041, p < 0.001), Goel B (B = -0.052, p < 0.001),

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of unilateral laminas (Goel A/Goel B)</th>
<th>Goel A group</th>
<th>Goel B group</th>
<th>t/Z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminar length (cm)</td>
<td>177/124</td>
<td>2.98 ± 0.38</td>
<td>3.15 ± 0.31</td>
<td>-4.876</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>177/124</td>
<td>5.88 ± 1.02</td>
<td>5.83 ± 0.88</td>
<td>-0.003</td>
<td>0.997</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>177/124</td>
<td>50.35 ± 5.28</td>
<td>48.14 ± 4.21</td>
<td>-4.372</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>99/110</td>
<td>1.22 ± 0.15</td>
<td>1.15 ± 0.13</td>
<td>3.392</td>
<td>0.001</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>177/124</td>
<td>205.67 ± 96.67</td>
<td>222.90 ± 116.86</td>
<td>-0.828</td>
<td>0.408</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

HU, Hounsfield unit.

†The t value and Z value were obtained by Student t-test and Mann-Whitney test according to the result of the test for normal distribution.
Table 4. Subgroup comparisons of morphometric measurements and computed tomography HU values for unilateral C2 laminae suitable for screw placement between the control and BI groups based on the diagnosis of HRVA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>BI group</th>
<th>p-value&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of unilateral laminas (A/B)</td>
<td>HRVA (A)</td>
<td>Non-HRVA (B)</td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>108/249</td>
<td>3.13 ± 0.27</td>
<td>3.20 ± 0.27</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>108/249</td>
<td>5.90 ± 0.89</td>
<td>6.15 ± 1.03</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>108/249</td>
<td>49.59 ± 3.01</td>
<td>49.31 ± 2.92</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>108/249</td>
<td>1.22 ± 0.13</td>
<td>1.26 ± 0.13</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>108/249</td>
<td>251.21 ± 92.12</td>
<td>256.66 ± 102.14</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
BI, basilar invagination; HRVA, high-riding vertebral artery; HU, Hounsfield unit.
<sup>†</sup>The p-value were obtained by analysis of variance test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.

Table 5. Subgroup comparisons of morphometric measurements and computed tomography HU values for unilateral C2 laminae suitable for screw placement between Goel A and B groups based on the diagnosis of HRVA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Goel A group</th>
<th>Goel B group</th>
<th>p-value&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of unilateral laminas (A/B)</td>
<td>HRVA (A)</td>
<td>Non-HRVA (B)</td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>103/74</td>
<td>2.89 ± 0.37</td>
<td>3.09 ± 0.37</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>103/74</td>
<td>5.72 ± 0.90</td>
<td>6.11 ± 1.13</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>103/74</td>
<td>50.10 ± 5.73</td>
<td>50.70 ± 4.58</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>44/55</td>
<td>1.17 ± 1.47</td>
<td>1.25 ± 0.15</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>103/74</td>
<td>217.69 ± 106.96</td>
<td>188.93 ± 77.84</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
HRVA, high-riding vertebral artery; HU, Hounsfield unit.
<sup>†</sup>The p-value were obtained by analysis of variance test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.
and distance from the top of odontoid to the Chamberlain line (B = -0.007, p < 0.001); laminar HU values were significantly associated with age (B = -2.517, p < 0.001), Goel A (B = -44.205, p < 0.001), Goel B (B = -25.704, p = 0.014), and laminar thickness (B = -11.706, p = 0.001) (Supplementary Tables 12–16). 

DISCUSSION

As an effective salvage method for axis fixation, translaminar screw might be frequently applied in patients with BI, for whom a high rate of contraindications for C2 pedicle or pars screw placement existed because of morphologic anomalies and the presence of HRV A.14,18,19,32,35-38 However, the malposition of laminar screw can breach the inner cortex of laminae and damage the dura mater and spinal cord.19 In addition, the morphologic variation of C2 lamina in BI and the effect of their morphologic characteristics and bone quality on safe placement and fixation stability of translaminar screw remain unclear.

Our study showed a screw acceptability rate in the control group similar to that of Chan et al.,19 who performed a CT image measurement in an Asian population and reported unilateral screw acceptability of 85.8% and 88.8% in the right and left laminae, respectively, and bilateral screw acceptability of 80.3% for C2. We also revealed that the BI group had subsequently lower rates of unilateral and bilateral screw acceptability than the control cohort. By contrast, no remarkable differences were observed between Goel A and B types in BI. In addition, majority of studies reported the insertion parameters of C2 translaminar screw in patients without congenital cervical vertebral anomalies.14,18,19,32,35-38 The mean laminar length of 3.16 ± 0.27 cm in the control group of our study was similar to that of studies conducted by Wang et al.,14 Kim et al.,15 and Xin-yu et al.17 Meanwhile, the mean laminar thickness of 5.81 ± 1.18 mm, mean laminar angle of 49.51° ± 3.03°, and mean laminar height of 1.24 ± 0.13 cm in the control group were consistent with reports by Dean et al.,32 Ma et al.,19 and Chan et al.18 in adult population. Compared with the control group, we found that the laminar length, thickness, and height in the BI cohort were remarkably smaller. These results might be attributed to craniovertebral anomalies in BI patients who had high incidence of morphological variations, atlas occipitalization, C2/3 assimilation, and pathogenesis of posterior axial elements, including the absence and incompleteness of the isthmus and spinous process, thereby increasing the risk of malposition of translaminar screws.34,39,40 Moreover, except for congenital morphological anomalies, patients with BI likely suffered from developmental central or axial atlantoaxial instability, which further increased the difficulty of accurate screw placement.39,41

The classification of Goel A and B types in BI was based on the abnormal increase in atlantodental or clivodental interval, which represented atlantoaxial instability.42 The atlantoaxial instability was considered abnormally and excessively mobile in Goel A but stable and subtle in Goel B.41 In subgroup analyses of Goel A and B types, the laminar length, angle, and height in the Goel A group were substantially smaller than those in the Goel B group. Thus, the morphological anomaly of Goel B type was found to be more stable than that of Goel A type. Nevertheless, multiple linear regression revealed that the Goel B type independently contributed to smaller laminar thickness and height, whereas the Goel A type was independently associated with a smaller laminar length and larger laminar angle. Therefore, the classification of Goel A and B types was required pre-operatively through 3D CT for the clarification of morphological deformity and personalized treatment to reduce the risk of malposition.

We also investigated the effects of HRVA on the insertion parameters of TSP in control and BI cohorts. In previous studies, the diagnosis of HRVA was remarkably associated with a narrow pedicle and a thin isthmus on the C2 vertebra.3,45 However, whether a narrow and short lamina existed in the presence of HRVA remained unclear. In the current study, we found that the insertion parameters had no substantial differences between unilateral laminae with and without HRVA in the control group. By contrast, for patients with BI, unilateral laminar length and thickness, the critical parameters for TSP, were remarkably smaller in the HRVA group than those in the non-HRVA group. In further subgroup analyses of Goel A and B types, no substantial differences in insertion parameters were found between laminae with and without HRVA in the Goel B group, but the HRVA cohort had remarkably smaller laminar length, thickness, and height than the non-HRVA group for all included laminae in the Goel A group. In addition, multiple linear regression analyses indicated that the presence of HRVA was an independent factor for the smaller laminar length, thickness, and height on the C2 lamina. Thus, the diagnoses of HRVA and Goel A in BI contributed to a narrow lamina, which might increase the risk of malposition, and the preoperative evaluation of VA should be performed to avoid potential neurovascular injuries.

The insertional torque of a screw and the ultimate fixation strength of a device had positive correlations with BMD, which can be approximately assessed on the basis of HU values ob-
tained from CT. We found that a reduced bone quality evaluated by HU values was present in the trajectory of the laminar screw for the BI group compared with that for the control cohort, and no remarkable differences in HU values were found between Goel A and B groups. Meanwhile, subgroup analyses demonstrated that the BMD was not affected by the presence of HRVA, atlas occipitization, and C2/3 assimilation except for the diagnosis of BI. Moreover, the multiple linear regression revealed that older age, smaller laminar thickness, and diagnosis of Goel A or B type independently contributed to low HU values. Elderly patients had a high risk of osteoporosis, an age-related disease, thereby resulting in low bone quality. Besides, Goel A and B types, which were the diagnosis of BI, might be associated with lower BMD. The mean HU value in the BI cohort was 226.21 ± 121.78, which was higher than the determination for osteoporosis, with a HU interval value of 90.9 to 138.7. The low BMD and bone quality in BI might result from the complication of osteogenesis imperfecta and related osteochondrodysplasias, and these so-called “bone softening” disorders further contributed to progressive deformity and neurological dysfunction.

It should be noted that the gold standard for the assessment of BMD is the dual-energy x-ray absorptiometry (DXA). Studies have found a correlation between HU values and BMD based on DXA. Pinto et al. performed a meta-analysis based on 18 studies comparing HU values from spine CT scans to the T scores of gold-standard DXA for the prediction of regional BMD, concluding that the bone quality can be assessed according to HU values obtained from CT. Thus, the HU values in the BI and control groups can approximately show the differences of BMD and bone quality between the 2 groups. Although the HU values have not been widely used for the assessment of BMD in the clinical practice, using HUs values to infer bone quality has a thorough clinical relevance as it could be used for the classification of patients at risk for osteoporotic and fragility fractures.

Inconsistencies in insertion parameters were found in the results of some studies, which might be attributed to the following reasons. First, different methods of measurement were used. For example, a different measurement method for laminar length performed by Cassinelli et al. was performed from the contralateral spinolaminar junction to the lamina/lateral mass junction, which resulted in smaller outcomes compared with the current study. Second, patients with different ethnicities were included. The studies from Korean, Malay, Indian, and American populations conducted by Kim et al., Chan et al., Srivastava et al., and Cassinelli et al., respectively, showed the discrepancies of the same insertion parameters among different ethnicities. Third, different planes were selected for measurement. Ma et al. found a high variability of thickness for the C2 lamina: the thinnest cranial portion, averaging 2.71 mm; the thickness of the caudal edge, averaging 4.46 mm; the thickest portion at the midportion of the lamina, averaging 5.87 mm. Fourth, the included population had different ratios of gender. Cassinelli et al. reported that males had a greater C2 laminar thickness than females. Our study also found that the male gender was independently associated with larger laminar length, thickness, and height. Therefore, the conditions where the parameters were measured should be clarified before utilization in clinical practice.

This study had some limitations. First, given the lack of BMI in medical records for some patients, missing data were obtained by multiple imputation. Thus, the outcomes regarding BMI should be interpreted cautiously. Second, this study was limited to the Eastern Asian population, which has limited generalizability of measured outcomes. Therefore, the morphometric measurements and HU values among different ethnicities must be further investigated. Third, subgroup comparison based on gender, left or right side, were not performed, and biases resulting from 2 factors were reduced by matching gender and the number of included patients between BI and control groups in this study. Fourth, the measurements were performed using 3D CT images without actual clinical application, and the confirmative study concerning the insertion parameters on cadaveric specimens should be carried out.

CONCLUSION

Patients with BI had narrower and smaller laminae with lower HU values and lower unilateral and bilateral acceptability for translaminar screws than patients without BI. The morphometric measurements were affected by gender, classification of Goel A and B types, and the presence of HRVA and C2/3 assimilation, and HU values were affected by age, classification of Goel A and B types, and laminar thickness for C2 laminae.

NOTES

Supplementary Materials: Supplementary Tables 1-16 can be found via https://doi.org/10.14245/ns.2244730.365.
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Characteristics of C2 Laminae in BI

Zhou LP, et al.


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Ren-Jie Zhang: 0000-0002-7203-5769
Cai-Liang Shen: 0000-0002-9835-6384

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malities in osteogenesis imperfecta type V. Osteoporos Int 2022;33:177-83.
**Supplementary Table 1.** Descriptive statistics of the patients in Goel A and B groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with BI</th>
<th>Goel A (n = 121)</th>
<th>Goel B (n = 84)</th>
<th>t/Z/χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td>48.88 ± 10.31</td>
<td>48.99 ± 10.01</td>
<td>-0.114</td>
<td>0.909</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>23.20 ± 3.83</td>
<td>23.90 ± 4.11</td>
<td>-1.247</td>
<td>0.214</td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td>85 (70.2)</td>
<td>55 (65.5)</td>
<td>0.521</td>
<td>0.470</td>
</tr>
<tr>
<td>Atlas occipitalization</td>
<td></td>
<td>116 (95.9)</td>
<td>25 (29.8)</td>
<td>97.847</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C1/2 dislocation</td>
<td></td>
<td>114 (94.2)</td>
<td>6 (7.1)</td>
<td>154.873</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C2/3 assimilation</td>
<td></td>
<td>54 (44.6)</td>
<td>10 (11.9)</td>
<td>24.725</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Distance from spinous process to skin cm</td>
<td></td>
<td>2.70 ± 0.78</td>
<td>3.26 ± 0.86</td>
<td>-4.854</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
BI, basilar invagination; BMI, body mass index.
†The t value and Z value were obtained by Student t-test and Mann-Whitney test according to the result of the test for normal distribution.
‡There were missing data obtained using multiple imputation model.
**Supplementary Table 2. Feasibility and acceptability of laminar screw on unilateral C2 laminae with published criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Acceptability</th>
<th>Acceptability</th>
<th>$\chi^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (n = 410)</td>
<td>BI group (n = 410)</td>
<td>Goel A group (n = 242)</td>
<td>Goel B group (n = 168)</td>
</tr>
<tr>
<td>Criterion of Shin et al. (laminar thickness $\geq 4.0$ mm; screw length $\geq 25$ mm)</td>
<td>388 (94.6)</td>
<td>326 (79.5)</td>
<td>41.648</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Criterion of Alvin et al. (laminar thickness $\geq 4.5$ mm; screw length $\geq 7$ mm)</td>
<td>357 (87.1)</td>
<td>304 (74.1)</td>
<td>21.916</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Criterion of Chan et al. (laminar thickness $\geq 4.5$ mm; screw length $\geq 20$ mm)</td>
<td>357 (87.1)</td>
<td>301 (73.4)</td>
<td>24.124</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
BI, basilar invagination.
### Supplementary Table 3. Feasibility and acceptability of laminar screw on bilateral C2 laminae with published criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Acceptability</th>
<th></th>
<th></th>
<th>Acceptability</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
<td>BI group</td>
<td>(\chi^2)</td>
<td>p-value</td>
<td>Goel A group</td>
<td>Goel B group</td>
</tr>
<tr>
<td></td>
<td>(n = 204)</td>
<td>(n = 141)</td>
<td></td>
<td></td>
<td>(n = 67)</td>
<td>(n = 74)</td>
</tr>
<tr>
<td>Criterion of Alvin et al. (laminar height (\geq 7,\text{mm}))</td>
<td>163 (79.9)</td>
<td>82 (58.2)</td>
<td>19.154</td>
<td>&lt; 0.001</td>
<td>38 (56.7)</td>
<td>44 (59.5)</td>
</tr>
<tr>
<td>Criterion of Chan et al. (laminar height (\geq 9,\text{mm}))</td>
<td>163 (79.9)</td>
<td>81 (57.4)</td>
<td>24.124</td>
<td>&lt; 0.001</td>
<td>37 (55.2)</td>
<td>44 (59.5)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
BI, basilar invagination.
**Supplementary Table 4.** Comparisons of morphometric measurements and computed tomography HU values for overall unilateral C2 laminae between the control and BI groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of unilateral laminas (control/BI)</th>
<th>Control group</th>
<th>BI group</th>
<th>t/Z†</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminar length (cm)</td>
<td>410/410</td>
<td>3.16 ± 0.27</td>
<td>3.00 ± 0.40</td>
<td>-6.383</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>410/410</td>
<td>5.81 ± 1.18</td>
<td>5.36 ± 1.26</td>
<td>5.287</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>410/410</td>
<td>49.51 ± 3.03</td>
<td>49.25 ± 5.10</td>
<td>-1.135</td>
<td>0.256</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>408/282</td>
<td>1.24 ± 0.13</td>
<td>1.15 ± 0.17</td>
<td>-7.762</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>410/410</td>
<td>257.00 ± 100.67</td>
<td>226.21 ± 121.78</td>
<td>-5.331</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

HU, Hounsfield unit; BI, basilar invagination.

†The t-value and Z-value were obtained by Student t-test and Mann-Whitney test according to the result of the test for normal distribution.
### Supplementary Table 5. Comparisons of morphometric measurements and computed tomography HU values for overall unilateral C2 laminae between the Goel A and B groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of unilateral laminae (Goel A/Goel B)</th>
<th>Goel A group</th>
<th>Goel B group</th>
<th>t/Z*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminar length (cm)</td>
<td>242/168</td>
<td>2.91 ± 0.43</td>
<td>3.13 ± 0.32</td>
<td>-6.145</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>242/168</td>
<td>5.38 ± 1.31</td>
<td>5.32 ± 1.18</td>
<td>0.516</td>
<td>0.606</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>242/168</td>
<td>50.07 ± 5.51</td>
<td>48.05 ± 4.18</td>
<td>-4.491</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>134/148</td>
<td>1.16 ± 0.19</td>
<td>1.13 ± 0.14</td>
<td>-2.169</td>
<td>0.030</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>242/168</td>
<td>220.01 ± 120.89</td>
<td>235.15 ± 122.85</td>
<td>-1.125</td>
<td>0.261</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

HU, Hounsfield unit.

\*The t-value and Z-value were obtained by Student t-test and Mann-Whitney test according to the result of the test for normal distribution.
**Supplementary Table 6.** Subgroup comparisons of morphometric measurements and computed tomography HU values for overall unilateral C2 laminae between the control and BI groups based on the diagnosis of HRVA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>BI group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of unilateral laminae (A/B)</td>
<td>No. of unilateral laminae (C/D)</td>
<td>A vs. B</td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>130/280</td>
<td>223/187</td>
<td>0.146</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>130/280</td>
<td>223/187</td>
<td>0.051</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>130/280</td>
<td>223/187</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>130/278</td>
<td>122/160</td>
<td>0.028</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>130/280</td>
<td>223/187</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

BI, basilar invagination; HRVA, high-riding vertebral artery; HU, Hounsfield unit.

*The p value were obtained by ANOVA test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.
### Supplementary Table 7. Subgroup comparisons of morphometric measurements and computed tomography HU values for overall unilateral C2 laminae between Goel A and B groups based on the diagnosis of HRVA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Goel A group</th>
<th>Goel B group</th>
<th>p-value&lt;sup&gt;†&lt;/sup&gt;</th>
<th>p-value&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>No. of</td>
<td>A vs. B</td>
<td>A vs. C</td>
</tr>
<tr>
<td></td>
<td>unilateral</td>
<td>unilateral</td>
<td>A vs. B</td>
<td>A vs. C</td>
</tr>
<tr>
<td></td>
<td>laminas</td>
<td>laminas</td>
<td>C vs. D</td>
<td>B vs. C</td>
</tr>
<tr>
<td></td>
<td>(A/B)</td>
<td>(C/D)</td>
<td></td>
<td>B vs. D</td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>160/82</td>
<td>105/63</td>
<td>0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>2.85 ± 0.43</td>
<td>3.03 ± 0.34</td>
<td>1.000</td>
<td>0.055</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>160/82</td>
<td>105/63</td>
<td>&lt; 0.001</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>5.06 ± 1.19</td>
<td>5.29 ± 1.10</td>
<td>0.001</td>
<td>0.017</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>160/82</td>
<td>105/63</td>
<td>0.118</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>49.81 ± 5.80</td>
<td>48.10 ± 4.32</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>71/63</td>
<td>51/97</td>
<td>0.003</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>1.11 ± 0.19</td>
<td>1.12 ± 0.12</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>160/82</td>
<td>105/63</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>234.50 ± 135.71</td>
<td>235.61 ± 125.38</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
HRVA, high-riding vertebral artery; HU, Hounsfield unit.

<sup>†</sup>The p-value were obtained by analysis of variance test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.
### Supplementary Table 8. Subgroup comparisons of morphometric measurements and computed tomography HU values for unilateral C2 laminae suitable for screw placement between the control and BI groups based on the diagnosis of atlas occipitalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>BI group</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of unilateral laminae</td>
<td></td>
<td>occipitalization</td>
<td>occipitalization</td>
</tr>
<tr>
<td>(A)</td>
<td>353</td>
<td>3.17 ± 0.28</td>
<td>208/93</td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>353</td>
<td>6.07 ± 1.00</td>
<td>208/93</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>353</td>
<td>49.41 ± 2.93</td>
<td>208/93</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>351</td>
<td>1.25 ± 0.13</td>
<td>121/88</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>353</td>
<td>255.55 ± 99.49</td>
<td>208/93</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

HU, Hounsfield unit; BI, basilar invagination.

†The p-value were obtained by analysis of variance test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.
### Supplementary Table 9. Subgroup comparisons of morphometric measurements and computed tomography HU values for overall unilateral C2 laminae between the control and BI groups based on the diagnosis of atlas occipitalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>BI group</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of unilateral laminas (A)</td>
<td>No. of unilateral laminas (B/C)</td>
<td>A vs. B</td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>406</td>
<td>3.16 ± 0.27</td>
<td>282/128</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>406</td>
<td>5.80 ± 1.18</td>
<td>282/128</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>406</td>
<td>49.53 ± 3.01</td>
<td>282/128</td>
</tr>
<tr>
<td>Laminar height (cm)</td>
<td>404</td>
<td>1.24 ± 0.13</td>
<td>162/120</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>406</td>
<td>257.48 ± 100.99</td>
<td>282/128</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
HU, Hounsfield unit; BI, basilar invagination.
†The p-value were obtained by analysis of variance test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.
**Supplementary Table 10.** Subgroup comparisons of morphometric measurements and computed tomography HU values for unilateral C2 laminae suitable for screw placement between the control and BI groups based on the diagnosis of C2-3 assimilation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>BI group</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>No. of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unilateral</td>
<td>C2/3</td>
<td>A vs. B</td>
</tr>
<tr>
<td></td>
<td>laminas</td>
<td>assimilation</td>
<td>A vs. C</td>
</tr>
<tr>
<td></td>
<td>(A)</td>
<td>(B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-C2/3</td>
<td>Non-C2/3 assimilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>assimilation</td>
<td>(A)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(B/C)</td>
<td>(B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(C)</td>
<td>(C)</td>
<td></td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>355</td>
<td>92/209</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>3.17 ± 0.27</td>
<td>2.94 ± 0.46</td>
<td>0.013</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>355</td>
<td>92/209</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>6.08 ± 1.00</td>
<td>5.87 ± 1.08</td>
<td></td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>355</td>
<td>92/209</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>49.39 ± 2.96</td>
<td>51.12 ± 6.09</td>
<td></td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>355</td>
<td>92/209</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>255.92 ± 98.66</td>
<td>212.04 ± 102.38</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>213.09 ± 107.25</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
HU, Hounsfield unit; BI, basilar invagination.
†The p-value were obtained by analysis of variance test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.
## Supplementary Table 11. Subgroup comparisons of morphometric measurements and computed tomography HU values for overall unilateral C2 laminae between the control and BI groups based on the diagnosis of C2–3 assimilation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>BI group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>No. of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unilateral</td>
<td>unilateral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>laminas (A)</td>
<td>laminas (B/C)</td>
<td></td>
</tr>
<tr>
<td>Laminar length (cm)</td>
<td>408</td>
<td>128/282</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>3.16 ± 0.27</td>
<td>2.88 ± 0.50</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.06 ± 0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar thickness (mm)</td>
<td>408</td>
<td>128/282</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>5.81 ± 1.18</td>
<td>5.32 ± 1.30</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.37 ± 1.24</td>
<td>0.719</td>
</tr>
<tr>
<td>Laminar angle (°)</td>
<td>408</td>
<td>128/282</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>49.51 ± 3.04</td>
<td>50.70 ± 5.81</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48.59 ± 4.61</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laminar HU values</td>
<td>408</td>
<td>128/282</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>257.79 ± 100.27</td>
<td>222.40 ± 103.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>227.94 ± 129.40</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

HU, Hounsfield unit; BI, basilar invagination.

*The p-value were obtained by analysis of variance test or Kruskal-Wallis test according to the result of the test for normal distribution. The nominal p-value was adjusted as 0.05 for the multiple comparisons.
**Supplementary Table 12.** Multiple linear regression on laminar length

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Standard β</th>
<th>t</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>3.132</td>
<td>0.017</td>
<td>-</td>
<td>179.465</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.190</td>
<td>0.024</td>
<td>0.252</td>
<td>7.956</td>
<td>&lt; 0.001</td>
<td>1.010</td>
</tr>
<tr>
<td>HRVA</td>
<td>-0.109</td>
<td>0.024</td>
<td>-0.154</td>
<td>-4.563</td>
<td>&lt; 0.001</td>
<td>1.145</td>
</tr>
<tr>
<td>Goel A</td>
<td>-0.167</td>
<td>0.029</td>
<td>-0.216</td>
<td>-5.816</td>
<td>&lt; 0.001</td>
<td>1.398</td>
</tr>
<tr>
<td>C2/3 assimilation</td>
<td>-0.079</td>
<td>0.036</td>
<td>-0.082</td>
<td>-2.191</td>
<td>0.029</td>
<td>1.405</td>
</tr>
</tbody>
</table>

SE, standard error; VIF, variance inflation factor; HRVA, high-riding vertebral artery.
Supplementary Table 13. Multiple linear regression on laminar thickness

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Standard β</th>
<th>t</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>5.823</td>
<td>0.070</td>
<td>-</td>
<td>83.642</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.353</td>
<td>0.090</td>
<td>0.132</td>
<td>3.931</td>
<td>&lt; 0.001</td>
<td>1.008</td>
</tr>
<tr>
<td>HRVA</td>
<td>-0.430</td>
<td>0.088</td>
<td>-0.172</td>
<td>-4.899</td>
<td>&lt; 0.001</td>
<td>1.095</td>
</tr>
<tr>
<td>Goel B</td>
<td>-0.249</td>
<td>0.112</td>
<td>-0.081</td>
<td>-2.225</td>
<td>0.026</td>
<td>1.184</td>
</tr>
<tr>
<td>Distance from the top of odontoid to the Chamberlain line (mm)</td>
<td>-0.025</td>
<td>0.008</td>
<td>-0.111</td>
<td>-2.961</td>
<td>0.003</td>
<td>1.254</td>
</tr>
</tbody>
</table>

SE, standard error; VIF, variance inflation factor; HRVA, high-riding vertebral artery.
**Supplementary Table 14.** Multiple linear regression on laminar angle

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Standard β</th>
<th>t</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>49.529</td>
<td>0.188</td>
<td>-</td>
<td>263.243</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Goel A</td>
<td>1.841</td>
<td>0.426</td>
<td>0.200</td>
<td>4.325</td>
<td>&lt; 0.001</td>
<td>1.866</td>
</tr>
<tr>
<td>C2/3 assimilation</td>
<td>1.461</td>
<td>0.454</td>
<td>0.127</td>
<td>3.219</td>
<td>0.001</td>
<td>1.360</td>
</tr>
<tr>
<td>Distance from the top of odontoid to the Chamberlain line (mm)</td>
<td>-0.195</td>
<td>0.032</td>
<td>-0.260</td>
<td>-6.076</td>
<td>&lt; 0.001</td>
<td>1.593</td>
</tr>
</tbody>
</table>

SE, standard error; VIF, variance inflation factor; HRVA, high-riding vertebral artery.
### Supplementary Table 15. Multiple linear regression on laminar height

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Standard $\beta$</th>
<th>t</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.234</td>
<td>0.009</td>
<td>-</td>
<td>144.243</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.068</td>
<td>0.012</td>
<td>0.206</td>
<td>5.929</td>
<td>&lt; 0.001</td>
<td>1.008</td>
</tr>
<tr>
<td>HRVA</td>
<td>-0.041</td>
<td>0.011</td>
<td>-0.128</td>
<td>-3.646</td>
<td>&lt; 0.001</td>
<td>1.033</td>
</tr>
<tr>
<td>Goel B</td>
<td>-0.052</td>
<td>0.015</td>
<td>-0.138</td>
<td>-3.472</td>
<td>&lt; 0.001</td>
<td>1.316</td>
</tr>
<tr>
<td>Distance from the top of odontoid to the Chamberlain line (mm)</td>
<td>-0.007</td>
<td>0.001</td>
<td>-0.241</td>
<td>-6.022</td>
<td>&lt; 0.001</td>
<td>1.338</td>
</tr>
</tbody>
</table>

SE, standard error; VIF, variance inflation factor; HRVA, high-riding vertebral artery.
### Supplementary Table 16. Multiple linear regression on laminar HU values

<table>
<thead>
<tr>
<th>Valuable</th>
<th>B</th>
<th>SE</th>
<th>Standard $\beta$</th>
<th>t</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>450.263</td>
<td>25.475</td>
<td>-</td>
<td>17.675</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>-2.517</td>
<td>0.321</td>
<td>-0.282</td>
<td>-7.846</td>
<td>&lt; 0.001</td>
<td>1.002</td>
</tr>
<tr>
<td>Goel A</td>
<td>-44.205</td>
<td>10.767</td>
<td>-0.154</td>
<td>-4.105</td>
<td>&lt; 0.001</td>
<td>1.086</td>
</tr>
<tr>
<td>Goel B</td>
<td>-25.704</td>
<td>10.437</td>
<td>-0.093</td>
<td>-2.463</td>
<td>0.014</td>
<td>1.099</td>
</tr>
<tr>
<td>laminar thickness (mm)</td>
<td>-11.706</td>
<td>3.396</td>
<td>-0.126</td>
<td>-3.447</td>
<td>0.001</td>
<td>1.034</td>
</tr>
</tbody>
</table>

HU, Hounsfield unit; SE, standard error; VIF, variance inflation factor.
Clinical Impact and Correlations of Odontoid Parameters Following Multilevel Posterior Cervical Fusion Surgery

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Objective: C2 slope (C2S), a cervical parameter mathematically approximated as T1 slope minus cervical lordosis (T1S–CL), predicts functional improvement in cervical deformity patients. Nonetheless, C2S is a positional parameter based only on the horizontal axis. The current study aims to introduce novel odontoid parameters and establish their relationships with patient-reported health-related quality of life (HRQoL).

Methods: Lateral plain radiographs of 32 adults who underwent multilevel posterior cervical fusion were analyzed. The odontoid parameters included odontoid incidence (OI), C2S, odontoid tilt (OT), and gravity line-C2 distance (GL-C2), while the cervical parameters were the Cobb angle at C0–1, C1–2, C0–2, C2–7, C2–7 sagittal vertical axis (cSVA), T1 slope, and T1S–CL. The range of motion (ROM) of the occipito-atlantoaxial complex was measured in flexion and extension plain radiographs. Scores on the Neck Disability Index (NDI) and visual analogue scale (VAS) for axial neck (VASn) and arm pain were measured.

Results: Compared to asymptomatic subjects, patients had larger C2S, cSVA, and T1S–CL, and smaller OT. Preoperatively, OI was significantly correlated with the ROM of C1–2 (r = 0.37, p < 0.05) and C0–2 (r = 0.46, p < 0.01). OT and C2S had significant correlations with the C0–1, C1–2, and C0–2 angles, GL-C2, and T1S–CL. Postoperative NDI scores were significantly correlated with OI (r = -0.40, p < 0.05) and OT (p = -0.37, p < 0.05). VASn was significantly correlated with GL-C2 (r = -0.35, p < 0.05).

Conclusion: The odontoid parameters were significantly correlated with established cervical parameters and HRQoL measures. OI is a constant parameter representing the individual’s compensatory reservoir at the upper cervical spine.

Keywords: C2 slope, T1 slope minus cervical lordosis, Odontoid, Health-related quality of life, Posterior cervical fusion, Sagittal alignment

INTRODUCTION

Over the last few decades, the concept of sagittal spinal alignment in the thoracolumbar spine has been extensively studied. The idea of optimal alignment of the thoracolumbar spine is well-established, and pelvic parameters are the foundation of sagittal alignment of the spine. A mismatch greater than 9° between pelvic incidence (PI) and lumbar lordosis (LL) is a significant predictor of disability. Accordingly, optimal attempts have been made using various parameters to define optimal cervical alignment. Analogous to the aforementioned PI-LL, a greater mismatch in T1 slope (T1S) minus cervical lordosis (CL; T1S–CL) is associated with a greater degree of cervical malalignment and worse health-related quality of life (HRQoL) outcomes.

To simplify the assessment of cervical malalignment, a novel parameter—C2 slope (C2S), which is mathematically approxi-
mated as T1S–CL—has been proposed. Functional improvement in patients with cervical deformity and the likelihood of achieving optimal outcomes can be predicted with C2S. Nonetheless, unlike the pelvic parameters, C2S is limited in that it is a positional parameter based only on the horizontal axis. The optimal range of C2S may vary among individuals, as the thoracolumbar positional parameters differ between individuals depending on PL. A supplementary parameter based on the vertical axis with a constant value would be essential for a profound assessment of cervical alignment. A recent study proposed a novel concept of odontoid parameters, analogous to the pelvic parameters, as an adjunct to C2S. However, the clinical and prognostic postoperative correlations of these parameters have not been demonstrated.

The current study aims to introduce novel odontoid parameters and investigate their relationship with patient-reported HRQoL outcomes following multilevel posterior cervical fusion. We also sought to explore the relationship between the head position and cervical alignment.

**MATERIALS AND METHODS**

1. Materials

   After obtaining Institutional Review Board approval from Seoul National University Hospital (IRB approval No. B-2208-773-104) a retrospective analysis of clinical and radiographic outcomes was performed for patients who received a single-stage multilevel (3 or more) posterior cervical fusion. The patients were treated for cervical spondylotic myelopathy and/or radiculopathy, ossification of the posterior longitudinal ligament, degenerative disc disorders, and deformities at a single academic center by 5 attending spine surgeons. Standing lateral radiographs of the cervical spine were obtained with patients in a comfortable neutral position. The patients were instructed to look straight ahead, with the upper extremities positioned naturally at the side of the body. The inclusion criteria were patients with more than 1 year of follow-up, an upper instrumented vertebra below C2 to investigate changes in the axial cervical spine, and an acceptable range of the chin-brow vertical angle over -1.5° while maintaining a horizontal gaze in the neutral position in order to minimize the positional deviation in the cervical curvature. Patients with trauma, tumor, or infection of the spine, pseudarthrosis, a misplaced screw, junctional pathologies, or adjacent level disc herniation were excluded in order to verify the impact of the alignment on HRQoL. From 2007 to 2019, 81 patients were treated with multilevel single-stage posterior cervical fusion. After exclusion, a total of 32 patients (male:female, 22:10; age at surgery was 58.72 years) were enrolled in this study. The upper instrumented vertebra was from C2 to C4 and the lowest instrumented vertebra was from C7 to T3. Patient demographics were recorded, including age, sex, body mass index, preoperative diagnosis, and the number of fused levels.

![Fig. 1.](https://doi.org/10.14245/ns.2244604.302)
2. Analysis of Radiographic Images

1) Odontoid parameters

Odontoid incidence (OI) was defined as the angle between the line perpendicular to the C2 endplate (C2EP) at its midpoint and the line connecting this point to the center of the odontoid process (the center of a circle with an anterior/posterior border and the apex of the dens as a tangent). Odontoid tilt (OT) was defined as the angle created by a line running from the C2EP midpoint to the center of the odontoid process and the vertical axis. Negative values indicated that the center of the odontoid process was placed anterior to the C2EP midpoint. C2S was defined as the angle between the C2EP and a horizontal line. A geometric construction using complementary angles showed that OI is the algebraic sum of OT and C2S (Fig. 1A). The distance from the gravity line (GL), defined as the plumb line from the center of the acoustic meatus, to the centroid of C2 (GL-C2) and the posterosuperior aspect of C7 (GL-C7) were measured (Fig. 1B).

2) Cervical spine parameters

The Cobb angle at C0–1, C1–2, C0–2, C2–7, T1S, C2–7 sagittal vertical axis (cSVA), and T1S minus CL (T1S–CL) were measured. For the C0–2 angle, an angle between the C2EP and the McRae line was measured. C0–1 angle was an angle between the McRae line and the line linking the inferior anterior and posterior arch of the atlas; C1–2 angle was defined as an angle between the line linking the inferior anterior and posterior arch of the atlas and the C2EP. T1S was defined as an angle between the T1 upper endplate and the horizontal plane. cSVA was defined as the distance between a plumb line from the centroid of C2 and the posterosuperior aspect of C7 (Fig. 1B). The range of motion (ROM) of occipito-atlanto-axial complex (C0–1, C1–2, C0–2) was calculated by subtracting the extension angle from the flexion angle.

3. Analysis of Patient-Reported Outcomes

Two commonly used self-assessment metrics for HRQoL were employed to measure disability after spine surgery: the Neck Disability Index (NDI) and visual analog pain scale (VAS) for the axial neck (VASn) and arm (VASa) pain.

4. Statistical Analysis

A picture archiving and communication system (p view, Infinitt, Seoul, Korea) was used for measurements. The test for normality was done using the Shapiro-Wilk test. The correlations between the parameters and HRQoL scores were analyzed using Pearson correlation coefficients or Spearman rank-order correlation coefficients for nonparametric variables. Univariable linear regression analysis was performed to determine the possible threshold of radiographic parameters. The statistical analysis was conducted using SPSS software (version 25.0), and a p-value < 0.05 was considered to indicate statistical significance.

RESULTS

1. Demographics and Baseline Cervical Alignment

In total, 32 patients (male, 22; female, 10) met the inclusion criteria for the study, with a mean age of 58.7 ± 14.3 years. The values are presented as mean ± standard deviation or number (%). HRQoL, health-related quality of life; VAS, visual analogue scale.

Table 1. Baseline demographic, radiographic, and surgical parameters (n = 32)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.72 ± 14.34</td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (68.8)</td>
</tr>
<tr>
<td>Heigh (cm)</td>
<td>163.10 ± 7.41</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.75 ± 12.23</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.33 ± 4.23</td>
</tr>
<tr>
<td>Fused level</td>
<td>3.94 ± 1.08</td>
</tr>
<tr>
<td>Baseline HRQoL metrics</td>
<td></td>
</tr>
<tr>
<td>VAS neck</td>
<td>4.63 ± 2.96</td>
</tr>
<tr>
<td>VAS arm</td>
<td>5.87 ± 3.18</td>
</tr>
<tr>
<td>Neck Disability Index</td>
<td>21.44 ± 10.58</td>
</tr>
<tr>
<td>Mean radiographic parameters</td>
<td></td>
</tr>
<tr>
<td>Odontoid incidence</td>
<td>18.22 ± 3.56</td>
</tr>
<tr>
<td>Odontoid tilt</td>
<td>-0.39 ± 12.41</td>
</tr>
<tr>
<td>C2 slope</td>
<td>18.61 ± 12.29</td>
</tr>
<tr>
<td>C0–2 angle</td>
<td>-28.72 ± 9.76</td>
</tr>
<tr>
<td>Extension, C0–1</td>
<td>-9.70 ± 6.08</td>
</tr>
<tr>
<td>Extension, C1–2</td>
<td>-33.67 ± 4.96</td>
</tr>
<tr>
<td>Extension, C0–2</td>
<td>-43.37 ± 8.12</td>
</tr>
<tr>
<td>Range of motion, C0–1</td>
<td>14.79 ± 5.42</td>
</tr>
<tr>
<td>Range of motion, C1–2</td>
<td>8.36 ± 3.62</td>
</tr>
<tr>
<td>Range of motion, C0–2</td>
<td>22.89 ± 6.58</td>
</tr>
<tr>
<td>C2–7 angle</td>
<td>-1.42 ± 20.83</td>
</tr>
<tr>
<td>Gravity line-C2</td>
<td>-1.58 ± 9.11</td>
</tr>
<tr>
<td>Gravity line-C7</td>
<td>23.66 ± 15.74</td>
</tr>
<tr>
<td>C2–7 sagittal vertical axis</td>
<td>25.25 ± 11.56</td>
</tr>
<tr>
<td>T1 slope</td>
<td>23.51 ± 9.23</td>
</tr>
<tr>
<td>T1 slope minus cervical lordosis</td>
<td>22.09 ± 15.61</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
preoperative diagnosis for multilevel fusion included cervical spondylotic myelopathy and/or radiculopathy (n = 9), ossification of the posterior longitudinal ligament (n = 18), ossified ligamentum flavum (n = 1), and cervical deformity (n = 4). The average number of levels fused was 3.94 ± 1.08 (range, 3–6). The number of levels fused did not show a statistically significant correlation with either the radiographic parameters or HRQoL scores. Patient demographics and baseline radiographic parameters can be found in Table 1. Table 2 summarizes the cervical measurements compared with normative data from asymptomatic subjects.† Symptomatic patients had larger C2S, cSVA, and T1S–CL and smaller OT values than asymptomatic subjects.

Preoperatively, the odontoid parameters showed statistically significant correlations with established cervical parameters (Table 3). Both OT and C2S were found to have strong correlations with T1S–CL (r = -0.84 and 0.92, respectively, p < 0.01). C2S was strongly correlated with the C0–1 (r = -0.61, p < 0.01), C1–2 (r = -0.50, p < 0.01), C0–2 (r = -0.68, p < 0.01), and C2–7 Cobb angles (r = 0.55, p < 0.01), GL-C2 (r = 0.71, p < 0.01), and GL-C7 (r = 0.51, p < 0.01). OT also showed similar correlations with the C0–1 (r = 0.58, p < 0.01), C1–2 (r = 0.36, p < 0.01), C0–2 (r = 0.60, p < 0.01), and C2–7 Cobb angles (r = -0.52, p < 0.01), GL-C2 (r = -0.71, p < 0.01), and GL-C7 (r = -0.52, p < 0.01). Dynamic alignment was assessed with ROM, which was calculated by subtracting extension alignment measures from flexion alignment measures. The C1–2 ROM was 8.36° ± 3.62°, and the C0-2 ROM was 22.89° ± 6.58°. OI showed significant correlations with the ROM of C1–2 (r = 0.37, p < 0.05) and C0–2 (r = 0.46, p < 0.01), as well as the C1–2 extension angle (r = -0.40, p < 0.05). OT and C2S showed statistically significant correlations with the C0–1, C1–2, and C0–2 angles, GL-C2, and T1S–CL (Table 3).

### Table 2. Comparison of cervical measurements to normative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asymptomatic</th>
<th>Preoperative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odontoid incidence</td>
<td>17.7 ± 3.7</td>
<td>18.22 ± 3.56</td>
<td>0.570</td>
</tr>
<tr>
<td>Odontoid tilt</td>
<td>6.7 ± 5.3</td>
<td>-0.39 ± 12.41</td>
<td>0.005*</td>
</tr>
<tr>
<td>C2 slope</td>
<td>10.9 ± 6.2</td>
<td>18.61 ± 12.29</td>
<td>0.001*</td>
</tr>
<tr>
<td>C0–2 angle</td>
<td>-25.6 ± 8.8</td>
<td>-28.72 ± 9.76</td>
<td>0.305</td>
</tr>
<tr>
<td>C2–7 angle</td>
<td>-10.4 ± 7.3</td>
<td>-1.41 ± 20.83</td>
<td>0.144</td>
</tr>
<tr>
<td>T1 slope</td>
<td>23.1 ± 6.3</td>
<td>23.51 ± 9.23</td>
<td>0.686</td>
</tr>
<tr>
<td>C2–7 sagittal vertical axis</td>
<td>17.80 ± 6.78</td>
<td>25.25 ± 11.56</td>
<td>0.000*</td>
</tr>
<tr>
<td>T1 slope minus cervical lordosis</td>
<td>12.7 ± 6.5</td>
<td>22.09 ± 15.61</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. *Statistically significant differences (p < 0.05).

### Table 3. Correlation of odontoid parameters with established parameters of the cervical spine at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>OI</th>
<th>OT</th>
<th>C2S</th>
</tr>
</thead>
<tbody>
<tr>
<td>OI</td>
<td>NA</td>
<td>0.30*</td>
<td>0.02*</td>
</tr>
<tr>
<td>OT</td>
<td>0.30*</td>
<td>NA</td>
<td>-0.93***</td>
</tr>
<tr>
<td>C2S</td>
<td>0.02*</td>
<td>-0.93***</td>
<td>NA</td>
</tr>
<tr>
<td>C0–1</td>
<td>-0.07</td>
<td>0.58**</td>
<td>-0.61***</td>
</tr>
<tr>
<td>C1–2</td>
<td>-0.40*</td>
<td>0.36***</td>
<td>-0.50***</td>
</tr>
<tr>
<td>C0–2</td>
<td>-0.27*</td>
<td>0.60**</td>
<td>-0.68***</td>
</tr>
<tr>
<td>GL-C2</td>
<td>-0.13</td>
<td>-0.71***</td>
<td>0.71***</td>
</tr>
<tr>
<td>GL-C7</td>
<td>-0.33</td>
<td>-0.52**</td>
<td>0.51**</td>
</tr>
<tr>
<td>ROM, C1–2</td>
<td>0.37*</td>
<td>0.01*</td>
<td>0.09*</td>
</tr>
<tr>
<td>ROM, C0–2</td>
<td>0.46**</td>
<td>-0.02*</td>
<td>0.18*</td>
</tr>
<tr>
<td>C2–7</td>
<td>0.09*</td>
<td>-0.52**</td>
<td>0.55***</td>
</tr>
<tr>
<td>cSVA</td>
<td>-0.31*</td>
<td>-0.3*</td>
<td>0.29*</td>
</tr>
<tr>
<td>T1S</td>
<td>0.03</td>
<td>0.04*</td>
<td>0.01*</td>
</tr>
<tr>
<td>T1S–CL</td>
<td>0.09*</td>
<td>-0.84***</td>
<td>0.92***</td>
</tr>
</tbody>
</table>

OI, odontoid incidence; OT, odontoid tilt; C2S, C2 slope; GL-C2, gravity line-C2 distance; GL-C7, gravity line-C7 distance; ROM, range of motion; cSVA, C2–7 sagittal vertical axis; CL, cervical lordosis; T1S–CL, T1 slope minus cervical lordosis.

*p < 0.05. **p < 0.01. †Spearman ρ.

2. Associations Between Odontoid Parameters and Postoperative Outcomes

The postoperative NDI scores ranged from 0 to 39, with an average of 12.1 ± 10.9. Table 4 summarizes the postoperative correlations of odontoid parameters and health-related quality of life.

### Table 4. Postoperative correlations of odontoid parameters and health-related quality of life

<table>
<thead>
<tr>
<th>Variable</th>
<th>VAS neck</th>
<th>VAS arm</th>
<th>NDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OI</td>
<td>-0.27</td>
<td>-0.10</td>
<td>-0.40*</td>
</tr>
<tr>
<td>p-value</td>
<td>0.14</td>
<td>0.57</td>
<td>0.02</td>
</tr>
<tr>
<td>OT</td>
<td>-0.13†</td>
<td>-0.26†</td>
<td>-0.37**</td>
</tr>
<tr>
<td>p-value</td>
<td>0.50</td>
<td>0.14</td>
<td>0.03</td>
</tr>
<tr>
<td>C2S</td>
<td>0.08</td>
<td>0.25</td>
<td>0.31</td>
</tr>
<tr>
<td>p-value</td>
<td>0.65</td>
<td>0.18</td>
<td>0.08</td>
</tr>
<tr>
<td>GL-C2</td>
<td>0.35*</td>
<td>0.24</td>
<td>0.32</td>
</tr>
<tr>
<td>p-value</td>
<td>0.04</td>
<td>0.18</td>
<td>0.08</td>
</tr>
<tr>
<td>GL-C7</td>
<td>0.17</td>
<td>0.17</td>
<td>0.27</td>
</tr>
<tr>
<td>p-value</td>
<td>0.34</td>
<td>0.19</td>
<td>0.28</td>
</tr>
</tbody>
</table>

VAS, visual analogue scale; NDI, Neck Disability Index; OI, odontoid incidence; OT, odontoid tilt; C2S, C2 slope; GL-C2, Gravity line-C2 distance; GL-C7, gravity line-C7 distance.

*p < 0.05, statistically significant differences. †Spearman ρ.
Fig. 2. Linear regression analysis of the odontoid parameters and Neck Disability Index (NDI). Positive correlations between odontoid incidence (OI), odontoid tilt (OT), and Neck Disability Index (NDI) scores are noted.

\[ \text{NDI} = -0.419 \times \text{OT} + 11.30 \]
\[ r^2 = 0.178 \]
\[ p = 0.016 \]

Fig. 3. Negative correlation between odontoid tilt (OT) and T1 slope minus cervical lordosis (T1S–CL). The linear regression model indicates that a T1S–CL value of 20° corresponded to an OT value of 0°.

\[ \text{T1S-CL} = -0.760 \times \text{OT} + 20.11 \]
\[ r^2 = 0.702 \]
\[ p < 0.001 \]

average of 12.84 ± 9.12. The VASn scores ranged from 0 to 8, with a mean of 3.06 ± 2.51, and the VASa scores ranged from 0 to 10, with a mean of 3.53 ± 3.04. The correlations between odontoid parameters and HRQoL measures were analyzed (Table 4). The NDI scores were correlated with OI (\( r = -0.40 \), \( p < 0.05 \)) and OT (\( r = -0.37 \), \( p < 0.05 \)) after surgery (Fig. 2). VASn showed a significant correlation with GL-C2 (\( r = -0.35 \), \( p < 0.05 \)). Using linear regression, OT was also found to be a key factor for predicting NDI: \( \text{NDI} = -0.42 \times \text{OT} + 11.3 \) (\( r^2 = 0.1776 \), \( p < 0.01 \)). The OT was matched to cervical malalignment, as determined by T1S–CL, in the entire cohort. An OT of 0° matched a T1-CL of 20° (\( r^2 = 0.760 \), \( p < 0.001 \)) (Fig. 3).

DISCUSSION

T1S–CL is a global assessment of sagittal alignment, detecting mismatches between the cervical and remaining thoracolumbar spine. T1S–CL depicts the harmony of a patient’s cervical alignment with the thoracic alignment that T1S describes. T1S is a vital factor influencing overall cervical sagittal alignment, and an increase in T1S is significantly correlated with more significant sagittal malalignment of the dens. C2S is mathematically approximated as T1S–CL. Accordingly, C2S has been suggested as a key to understanding cervical deformity relative to the thoracic alignment, combined with its clear visibility on radiographs compared to the C7-slope or T1S and its correlation with T1S–CL. If a patient has insufficient CL in a given T1S, anterior tilting of the dens occurs, leading to an increase in the C2S and inversely a decrease in OT (Fig. 4). The extent of the T1S–CL mismatch can be represented by the sagittal malalignment of the dens, which can be meticulously described with odontoid parameters, as OI is an anatomical feature unique to each individual, regardless of its position, and C2S and OT are inversely related.
Recent studies have reported multiple cutoff values for the optimal T1S–CL. In one study, a cutoff value of 20° for the T1S–CL predicted moderate clinical disability according to the NDI score following multilevel cervical fusion, and another demonstrated that moderate NDI could be predicted if the C2S exceeds 17°. The average reported OI is approximately 17°, and if we subtract the C2S presented above from the OI, we obtain an OT of 0°. An OT of approximately 0° also corresponds to a T1S–CL mismatch of 20°, as shown through the current study’s linear regression model (Fig. 3). It can be assumed that anterior tilting of the dens axis (a line running from the C2EP midpoint to the center of the odontoid process) beyond the vertical line illustrates the dissonance of a patient’s cervical alignment. Understanding the spatial orientation of the dens is essential. However, each individual has a unique morphology of the dens. PI reflects the relative position of the pelvis. Subsequently, patients with low PI have a low sacral slope and a low reservoir of pelvic retroversion or PT. Likewise, the morphology of the dens differs among individuals, and the clinical impact of the C2S may differ. At a given C2S, patients with a larger OI have a smaller clinical impact than patients with a smaller OI (Fig. 5). As a result, at a given C2S, a patient with a larger OI can maintain a more neutral cervical alignment.
larger OT than a patient with a smaller OI (Fig. 6A). A patient with a smaller OI is unable to maintain a positive value of OT as C2S increases, which results in a poorer NDI outcome. The correlation of exacerbating NDI with decreasing OT (r = -0.37, p < 0.05) was well demonstrated in the current study. When cervical malalignment is corrected, anterior inclination of the dens resolves, which is associated with an improved NDI score (Fig. 6B).

In cervical malalignment, subsequent forward-shifting of the head results in chronic neck pain and leads to a downward gaze. Subsequently, the upper cervical spine extends to maintain a horizontal gaze (Fig. 4).21-23 Through reciprocal changes, the thoracolumbar spine can compensate for malalignment, but it leads to further pain and disability.24-27 Similar results were obtained in the current study. The forward-shifting of the head correlates with anterior-shifting of the GL (GL-C2, r = -0.71, p < 0.01 and GL-C7, r = -0.52, p < 0.01), and the correlation between VASt score and GL-C2 (r = 0.35, p < 0.05) indicates increasing neck pain as the head shifts forward. A decrease in OT indicates the shifting of the GL away from the center of the body, resulting in imbalance and disability. OT was found to be correlated with the NDI score (r = -0.37, p < 0.05) in the current study. Regarding the cone of economy, the cervical spine shows a larger stable zone, indicating a larger compensatory reservoir. In the setting of malalignment, the cervical spine may easily adapt to remain in balance. Thus, other factors may contribute to the overall disability of the cervical spine, which resulted in small correlation coefficients regarding HRQoL measures. Nevertheless, from a statistical perspective, OT showed a more significant correlation—in terms of correlation coefficient value (-0.37 vs. 0.19)—than the previous study related to the tilt angle of C2.15 It can be assumed that the amount of tilt of C2 is related to HRQoL measured and it differs between each individual.

The patient’s compensation to maintain a horizontal gaze may be represented by C2S.11 Incremental inclination is represented by C2S, which reflects the need for more extension of the upper cervical spine. Thus, the capacity to extend the upper cervical spine is related to a patient’s ability to maintain the horizontal gaze during cervical malalignment. Recently, the reserve of extension (ROE) of C0–2 has been reported to be associated with improved clinical outcomes. The correction of cervical alignment is proportional to the relaxation of cervical hyperextension, which increases the upper cervical ROE.25 In the current study, we found that a larger OI leads to a larger C1–2 extension angle, C1–2 ROM, and C0–2 ROM, as shown in a previous biomechanical study.28 The potential to extend the upper cervical spine relates to the anatomical characteristics of the dens. A dens demonstrating greater posterior inclination, or a larger OI, leads to an increased ROM of C1 relative to C2. A patient with a larger OI can be assumed to have a larger compensatory reservoir or ROE. As a result, a patient with a larger OI can maintain a positive OT, which is significantly correlated with an improved NDI score (r = -0.40, p < 0.05) (Fig. 2).

In this study, we sought to elucidate the relationships of the odontoid parameters with clinical outcomes and radiographic cervical alignment in patients following multilevel posterior cervical fusion. This study bridges the gap between the conventional cervical parameters and explains the clinical improvement observed after cervical realignment surgery. C2S presents a simplified understanding of cervical alignment and is suggested as a unified key to understanding cervical alignment relative to the thoracic spine.21 OT, like PT, denotes the spatial orientation of the dens, which may vary according to the balance of the cranium and horizontal gaze. OI, like PI, is related to the compensatory reservoir of cervical extension. A profound analysis of the cervical alignment and the patient’s compensatory status is possible using the odontoid parameters. The utilization of the odontoid parameters has some advantages. OI is an independent and individually specific parameter not affected by external factors.15 Furthermore, C2S is able to distill the concept of cervical and thoracic harmony into a single measurement, enabling a simplified analysis.10 Complementing C2S with other odontoid parameters may provide a more profound and individualized understanding of cervical alignment in both the horizontal and vertical axes. Lastly, the dens is more visible on plain radiographs than on either C7 or T1; thus, observing the alignment of the dens enhances the reliability of the analysis.13,29

This study has certain limitations. First, it is a retrospective study with a small number of patients who had not been randomized. As a result, a detailed analysis was not possible, and we could not provide a valid cutoff value regarding NDI and OT. However, the study demonstrated significant correlations between the odontoid parameters and T1S–CL, allowing a simplified multiaxial assessment of cervical alignment harmony using the dens. In addition, the study was done with a heterogeneous cohort of patients. The majority of the patients in the present study underwent surgery not for cervical deformity, but for degenerative cervical disorders. Nonetheless, solid fusion was demonstrated to determine the true cause of disability, and we excluded patients with a misplaced screw, pseudarthrosis, facet arthrosis, or adjacent level disc herniation. After excluding other common causes of pain, we were able to assume that poor
HRQoL was due to malalignment. The results from the current study revealed that odontoid parameters are valuable in assessing the relationship between cervical alignment and HRQoL. In the future, larger series of homogeneous populations undergoing cervical deformity corrective surgery can validate the results of our study.

Our study examined the novel odontoid parameters as an adjunct to the widely used C2S. Our findings demonstrate that similar to pelvic parameters, the severity of cervical malalignment differs due to the anatomical characteristics of each individual. The spatial orientation of the dens can be different between patients with identical C2S, since the angulation of the dens may vary. As OI represents the patient’s compensatory reservoir, it is possible to assess the compensatory status of a patient and meticulously plan the optimal cervical alignment correction.

CONCLUSION

OI is the algebraic sum of OT and C2S. The odontoid parameters were significantly correlated with established cervical parameters and HRQoL measures following multilevel posterior cervical fusion. While C2S has shown utility in describing cervical deformities simply and effectively, it is limited in that it is a positional parameter, and its normal range may vary in each individual. In contrast, OI is a constant parameter and can represent the individual’s compensatory reservoir at the upper cervical spine, like PI. Odontoid parameters can provide an effective tool for surgeons in assessing cervical malalignment. Based on the results of this study, in a given C2S, postoperative HRQoL scores showed better results in patients with larger OI. A larger OI resulted in larger cervical ROM, allowing more upper cervical spine extension, indicating a larger ROE. Therefore, it is essential to consider not only C2S, but all odontoid parameters, as an adjunct to C2S to assess the cervical alignment thoroughly.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES


It is phenomenal to overview development of studies on spinal balance from the first study on lumbopelvic balance and the concept of pelvic incidence (PI) in 1992 to modern upper cervical parameters. Studies on spinal sagittal balance have been conducted to understand the physiologic balance of normal spinal column and predict ideal alignment for the treatment of spinal pathologies. The initial studies to understand spinal balance started from the lumbopelvic alignment, PI and the relation with sacral slope and pelvic tilt. The research on lumbopelvic balance has extended to thoracic spine alignment, and their reciprocal correlations in surgical treatment cohorts as well as normative data. The early studies on cervical spine alignment were on the correlation with outcome of local cervical pathologies including cervical myelopathy and cervical disc arthroplasty. But cervical spine alignment has gained great interest in the field of spinal deformity research over the last decade since the concept of T1 slope (T1S) has been published in early 2010’s. Extensive studies have been performed to understand physiologic cervical alignment, reciprocal influence between cervical radiographic parameters, outcomes related to alignment, and prediction of ideal cervical alignment. Many innovative cervical parameters have been proposed to understand correlations of cervical radiographic parameters. After numerous studies, T1S, T1S-cervical lordosis (CL) were thought to be key parameters to understand cervical alignment. Most recently, upper cervical spine parameters were presented including C2 slope (C2S) and odontoid parameters.

The study, "Clinical impact and correlations of odontoid parameters following multilevel posterior cervical fusion surgery" is a sequel of the authors’ first published study on an innovative odontoid parameter, "Odontoid incidence: a novel cervical parameter influencing cervical alignment from top to bottom." In the first study, the authors have analyzed 42 asymptomatic adults and presented odontoid incidence (OI), odontoid tilt (OT) and C2S demonstrated significant correlation with cervical alignment including C0–2 angle and C2–7 angle. In the current follow up study, the authors have analyzed 32 patients who underwent posterior cervical fusion. After comparison with the normal data in the first study, they concluded those odontoid parameters were correlated with patient-reported related quality of life (QoL) as well as radiographic outcomes.

Although numerous cervical parameters have been proposed, reported, and published,
they demonstrated radiographic correlations, but no parameters showed significant correlations with clinical outcome parameters except T1S and T1S-CL. The one of the impressive points of this study is that the authors have found the correlation between the odontoid parameters and QoL.

Like most studies with radiographic analysis, the results presented with regression equation models, the conclusion could be deductive, not always inductive to estimate actual clinical significance. The static parameter in this study; OI had a narrow standard deviation, 3.56°. OI in this study is a constant parameter like PI or thoracic inlet angle in the literature, but it may change according to the degeneration of C2/3 intervertebral disc and deformation. How the narrow-ranged parameter and possible changes act on the overall alignment and clinical outcomes will need more investigations in the future.

Also, a C2S is a part of C2–7 angle and closely related to T1S–CL with statistical significance. Prior alignment studies have been based on influence of the distal segments on the proximal part of the spine, like pelvis on lumbar spine, T1S on cervical spine etc. The influence from the cranial part; OI and OT on the distal part of cervical segments and reciprocal reaction with the subaxial cervical spine could be the next point to study.

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

**REFERENCES**

Commentary on Odontoid Parameters

Title: Girl Before a Mirror
Year: 1932
Artist: Pablo Picasso
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Significance of Atlantoaxial and Subaxial Spinal Instability in Cervical Spinal Spondylosis: Commentary on “Clinical Impact and Correlations of Odontoid Parameters Following Multilevel Posterior Cervical Fusion Surgery”

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Standing posture has unique implications for human spine. Facetal articulation forms the fulcrum of activity for a large part of muscle bulk of the nape of neck and back that maintains the erect spinal posture. On the other hand, only a relatively few strands of muscles are associated with the vertebral body and intervertebral disc. Our articles discuss that the disc (and the odontoid process) is the brain of spinal movements, whilst the brawn of the movements are the muscles.¹ Intervertebral disc regulates spinal movements and mimic in actions an opera conductor who plays all music without holding any instruments in hand.

The conductor of an orchestra (the disc) doesn’t make a sound. He depends, for his power on his ability to make other people (muscles) powerful – Benjamin Zander

For several decades ‘old’ age or injury related affection of the disc, reduction in its water content and its herniation has been incriminated as the nodal point of genesis of cascade of secondary events that are grouped under the term spinal degeneration. ‘Pathological’ issues related to spinal degeneration include bulging of the disc into the spinal canal, osteophyte formation, ligamentum flavum hypertrophy, bone fusion, and listhesis of the facets. The eventual outcome is reduction in the spinal canal and neural foraminal dimensions that results in neural compression and related symptoms of radiculopathy and/or myelopathy.

In 2010, we proposed that muscle weakness related to their injury, disuse or abuse results in telescoping or listhesis of the facets or in ‘vertical’ spinal instability and forms the point of genesis of spinal spondylosis.²³ Identification of instability of the facets on dynamic imaging is difficult if not impossible. Our studies conclude that all the so-called ‘pathological alterations’ in spinal degeneration are secondary, naturally protective, indicators of segmental instability and are potentially reversible following spinal stabilization.

Atlantoaxial joint is the most mobile joint of the spine. Its flat and round surface makes it prone to develop instability. It appears that atlantoaxial instability is ‘frequently’ associated
with multisegmental cervical spinal degeneration. Such atlantoaxial instability is more often associated in patients presenting with symptoms related to severe myelopathy. As the instability is more often of central or axial variety, there may not be compression of the dura or neural structures by the odontoid process. Craniovertebral junction degenerative alterations secondary to atlantoaxial instability are relatively common and probably a neglected clinical entity.\\n
Essentially, instability is the issue in spinal degeneration and stabilization is the treatment. ‘Decompression’ by resection of bone, soft tissue, osteophytes or intervertebral disc may not be necessary. In selected cases, inclusion of the atlantoaxial joint in the fixation construct is critical for success of surgery.\\n
Our articles suggest that ossification of posterior longitudinal ligament is a consequence of longstanding spinal instability that more often includes atlantoaxial instability. Spinal deformities are secondary events that originate from multisegmental spinal instability. Hirayama disease is also probably an outcome of multisegmental cervical spinal instability.\n
Craniovertebral junction has been essentially ignored in the management of degenerative spinal disease. The authors of this article have identified alterations in the angulation of the odontoid process and in the C2 slope in cases with multisegmental cervical spondylotic myelopathy. These parameters indicate alterations in alignment and spinal balance and are additional evidences that indicate atlantoaxial instability. The authors have performed spinal stabilization from C3 below. It is unclear if they performed simultaneous decompression or not.\\n
As our experience in the field is growing, we realize that inclusion of atlantoaxial joint in the fixation construct is essential in a large majority of these cases where there is multisegmental spinal instability related spinal degeneration. We have recently advocated an alternative technique of atlantoaxial stabilization that involves C2–3 transarticular fixation and sectioning of the muscles attached to the C2 spinous process. This technique stabilizes the C2 bone and the odontoid process, avoids direct insertion of the screw in the facet of atlas and retains the rotatory movement initiated by the muscles attached to the large transverse process of the atlas bone. Inclusion of C2 spinal vertebra in the fixation construct appears to be essential in a majority of cases of multisegmental spinal degeneration.\\n
Understanding that instability is the issue and stabilization is the treatment can greatly influence the treatment for spinal degeneration. Atlantoaxial segmental degeneration is a relatively common clinical event and is often associated with subaxial spinal instability. Identification of unstable spinal segments on the basis of clinical and radiological parameters and direct observations during surgery can indicate the levels of spinal segments that need stabilization.\\n
**Conflict of Interest:** The author has nothing to disclose.

**REFERENCES**

spinal instability is the cause of cervical spinal degeneration and spinal stabilization is the treatment: an experience with 215 cases surgically treated over 7 years. World Neurosurg 2020;140:614-21.


Title: Mother and Child
Year: 1921
Artist: Pablo Picasso
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The Effect of Subsidence on Segmental and Global Lordosis at Long-term Follow-up After Anterior Cervical Discectomy and Fusion


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Objective: Subsidence following anterior cervical discectomy and fusion (ACDF) may lead to disruptions of cervical alignment and lordosis. The purpose of this study was to evaluate the effect of subsidence on segmental, regional, and global lordosis.

Methods: This was a retrospective cohort study performed between 2016–2021 at a single institution. All measurements were performed using lateral cervical radiographs at the immediate postoperative period and at final follow-up greater than 6 months after surgery. Associations between subsidence and segmental lordosis, total fused lordosis, and cervical sagittal vertical alignment change were determined using Pearson correlation and multivariate logistic regression analyses.

Results: One hundred thirty-one patients and 244 levels were included in the study. There were 41 one-level fusions, 67 two-level fusions, and 23 three-level fusions. The median follow-up time was 366 days (interquartile range, 239–566 days). Segmental subsidence was significantly negatively associated with segmental lordosis change in the Pearson (r = -0.154, p = 0.016) and multivariate analyses (beta = -3.78; 95% confidence interval, -7.15 to -0.42; p = 0.028) but no associations between segmental or total fused subsidence and any other measures of cervical alignment were observed.

Conclusion: We found that subsidence is associated with segmental lordosis loss 6 months following ACDF. Surgeons should minimize subsidence to prevent long-term clinical symptoms associated with poor cervical alignment.

Keywords: Cervical vertebrae, Intervertebral disc, Vertebral body, Spinal fusion, Discectomy, Lordosis

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) is a standard operative treatment for degenerative conditions of the cervical spine. Historically, spine surgeons have used allograft or autograft bone to fill the interbody space after discectomy. More recently, synthetic cages have been used with the most common being carbon fiber, titanium, and polyetheretherketone (PEEK). In comparison to autologous bone, synthetic cages have the added benefit of avoiding iliac crest harvesting which increases operative time, patient discomfort, and risk of donor-site morbidity. Synthetic cages may provide a stronger support to help maintain disc height and promote fusion. Despite the use of interbody devices, alterations in spinal geometry, such as subsidence, are still relatively common.

Subsidence is generally defined as a reduction in the anterior or posterior disc height of greater than 2 or 3 mm during the postoperative period following ACDF. According to one system-
atic review of 35 articles, subsidence is a common occurrence with an incidence of approximately 19.3% to 42.5%. Thus, some loss of disc height may be expected following ACDF, but the amount of subsidence that becomes clinically significant remains unclear. Evidence of adverse clinical outcomes associated with subsidence has been mixed. Some studies suggest no impact on outcomes, whereas others have found associations with worse pain and clinical outcomes when subsidence occurs. Differing results may be due to heterogeneity in radiographic measurements, interbody cages, and length of follow-up.

Although the clinical impact of subsidence remains equivocal, it can have a substantial impact on cervical sagittal alignment. Normal sagittal alignment of the cervical spine is highly variable in contrast to the lumbar or thoracic regions, and the clinical implications of these alignment variations remains uncertain. Consequently, the optimal sagittal alignment to target after cervical surgery is unclear. Some studies suggest a loss of cervical lordosis to be pathological and advocate for restoration of cervical lordosis, although some patients with neutral or kyphotic alignment are entirely asymptomatic. To achieve the best ACDF outcomes, it is critical for spine surgeons to better understand the impact of subsidence on sagittal alignment. Therefore, the purpose of this study was to assess the effect of subsidence on segmental and global lordosis following ACDF.

2. Demographics and Outcome Measurements

Demographic information, including age at the time of surgery, sex, smoking status, and osteopenia were collected from the electronic medical record. Smoking status was confirmed as positive if the patient was a current or former smoker. Osteopenia included both osteopenia and osteoporosis and was identified based on prior diagnosis or dual-energy x-ray absorption bone density scan results. T-scores less than -1.5 were defined as osteopenic.

Fig. 1. Measurement of anterior disc height (ADH, A), total fused height (TFH, B), segmental lordosis angle (SLA, C), total fused lordosis (TFL, D), C2–7 lordosis (E), and cervical sagittal vertical alignment (cSVA, F).

MATERIALS AND METHODS

1. Study Design

This retrospective study was approved the Institutional Review Board of Icahn School of Medicine at Mount Sinai (STUDY-21-01028). Consecutive patients who underwent ACDF between 2016 and 2021 were included. Patients undergoing ACDF were identified using Current Procedural Terminology codes 22551, 22552, and 22554. Exclusion criteria included patients under 18 years of age at the time of surgery, revision surgery, surgery in the setting of trauma, those undergoing cervical fusion via a posterior approach, and those requiring a corpectomy. All data for this study was collected using the electronic medical record at our institution.

Eligibility criteria included patients who had both immediate postoperative and final follow-up radiographs. Final follow-up radiographs were defined as the final radiograph where the intervertebral disc spaces in the fused segments were distinguishable. Patients were excluded from the study if they did not have both an immediate postoperative radiograph within 6 weeks of surgery and a final follow-up radiograph greater than 6 months from the date of surgery. Additionally, radiographs with significant shoulder shadow at C7 or poor image quality were excluded from the study to preserve measurement accuracy.
Plain radiographs were evaluated for segmental and total subsidence of the intervertebral cage. Segmental subsidence was determined by taking the difference of the anterior disc heights between the final follow-up and immediate postoperative radiographs. Total subsidence was determined by taking the difference of the total height of the fused segments between the final follow-up and immediate postoperative radiographs (Fig. 1). A decrease in disc height or total fused height was defined as positive subsidence. All radiographic measurements were collected by trained researchers and were verified by a senior author with high interobserver reliability.

Intervertebral cage type was determined by assessing the shape and density of the cages on radiographs and by confirming with operative notes when possible. Intervertebral cage types included structural allograft, titanium, PEEK, ceramic, and zero-profile. With the exception of patients receiving a zero-profile implant with integrated screws, all patients underwent plating with interbody fusion. The cage-to-vertebral body ratio was also collected by measuring both the intervertebral cage length and vertebral body length below each level of the fusion. The ratio was calculated by dividing the cage length by the vertebral body length for each level. All radiographic measurements were performed on lateral cervical radiographs using the PACS (picture archiving and communications system) imaging software within the electronic record system at our institution.

The outcome variables of this study were radiographic measures of lordosis and vertebral alignment including segmental lordosis, total fused lordosis, C2–7 lordosis, and sagittal cervical vertical alignment. The segmental lordosis was defined as the angle between the inferior and superior end plates of each level of the fusion. The total fused lordosis was defined as the angle between the superior aspect of the superior most vertebrae and the inferior aspect of the inferior most vertebrae. C2–7 lordosis was defined as the angle between the inferior endplate of C2 and the inferior endplate of C7. If the inferior endplate of C7 was not visible, the angle was estimated using the superior endplate of C7 or inferior endplate of C6. Cervical sagittal vertical alignment (cSVA) was defined as the horizontal distance between the superior posterior corner of C7 and a vertical plumb line from the centroid of C2.

### 3. Statistical Analysis
Continuous data is presented as mean and standard deviation or median and interquartile range. For categorical variables, counts with percentage of the total sample are provided. To determine the relationship between subsidence and lordosis, Pearson correlation coefficients were calculated and are presented in the results section with p-values. The results are divided based on segmental and total fused subsidence correlations.

Multivariate linear regression models were constructed to examine the relationship between subsidence and lordosis while controlling for other variables. The main predictor in the regression models was subsidence. Separate regression models were created with segmental or total fused subsidence as the predictor. The outcome variables of each regression model were various measures of lordosis and cervical alignment as defined previously. The regression models controlled for age, sex, smoking status, osteopenia, cage-to-body ratio, level of fusion, number of fused segments, and cage type. All statistical analyses were performed in Python version 3.8.8. Alpha less than 0.05 was defined as the level of significance for all statistical testing.

### RESULTS
In total, 131 patients and 244 fused levels (1.86 ± 0.69 mean levels per patient) were included in the study. The mean age of the patients was 53.6 ± 10.9 years. The median follow-up time for immediate postoperative radiographs was 11 days (interquartile range [IQR], 1–14 days), and median follow-up for final radiographs was 366 days (IQR, 239–566 days). There were 56 males (42.7%) and 75 females (57.3%). Sixty-two patients

<table>
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<td>Total patients</td>
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<tr>
<td>Total levels</td>
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<tr>
<td>Age (yr)</td>
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<tr>
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<tr>
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Values are presented as mean ± standard deviation or number (%). ACDF, anterior cervical discectomy and fusion; PEEK, polyetheretherketone.
(47.3%) had a history of smoking, and 27 patients (20.6%) had a diagnosis of osteopenia. There were 41 one-level fusions (31.3%), 67 two-level fusions (51.1%), and 23 three-level fusions (17.6%). The majority of fusions (n = 68, 51.9%) were performed with a structural allograft. There were also 27 PEEK cages (20.6%), 22 titanium cages (16.8%), 11 ceramic cages (8.4%), and 3 zero-profile spacers (2.3%; 2 PEEK and 1 allograft) which were considered separately (Table 1, Supplementary Tables 1 and 2).

Pearson correlation testing showed that segmental subsidence was significantly negatively correlated with segmental lordosis change (r = -0.154, p = 0.016) (Fig. 2). Segmental subsidence was also positively correlated with C2–7 lordosis change (r = 0.015, p = 0.811) and cSV A change (r = 0.057, p = 0.376) and negatively correlated with total fused lordosis change (r = -0.055, p = 0.393) but these correlations were not significant. No significant correlations were found between total fused subsidence and C2–7 lordosis change (r = 0.026, p = 0.767) (Fig. 3), cSV A change (r = 0.019, p = 0.832), or total fused lordosis change (r = 0.066, p = 0.456) (Table 2, Supplementary Table 3).

After controlling for characteristics of the patient and fusion, multivariate analysis found that segmental subsidence was significantly negatively associated with segmental lordosis change (beta = -3.78; 95% CI, -7.15 to -0.42; p = 0.028). Although not significant, segmental subsidence was positively associated with cSV A change (beta = 0.45; 95% CI, -0.52 to 1.43; p = 0.358) and C2–7 lordosis change (beta = 0.91; 95% CI, -4.58 to 6.41; p = 0.743) and negatively associated with total fused lordosis change (beta = -3.30; 95% CI, -8.19 to 1.59; p = 0.185). The multivariate model Table 2. Pearson correlation matrix with segmental and total fused subsidence from immediate postoperative radiograph to final follow-up radiograph

<table>
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<tr>
<td>Segmental lordosis change</td>
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<td>0.016*</td>
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<td>C2–7 lordosis change</td>
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<tr>
<td>cSV A change</td>
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<tr>
<td>Total fused lordosis change</td>
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<td>0.393</td>
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<td>Total fused subsidence (n = 131)</td>
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<tr>
<td>C2–7 lordosis change</td>
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<td>cSV A change</td>
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<tr>
<td>Total fused lordosis change</td>
<td>-0.066</td>
<td>0.456</td>
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cSV A, cervical sagittal vertical alignment.
*p < 0.05, statistically significant differences.

Table 3. Linear regression results with segmental and total fused subsidence as the predictor variables

<table>
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<th>95% CI</th>
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<tr>
<td>Segmental lordosis change</td>
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<td>-7.15 to -0.42</td>
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<tr>
<td>C2–7 lordosis change</td>
<td>0.91</td>
<td>-4.58 to 6.41</td>
<td>0.743</td>
</tr>
<tr>
<td>cSV A change</td>
<td>0.45</td>
<td>-0.52 to 1.43</td>
<td>0.358</td>
</tr>
<tr>
<td>Total fused lordosis change</td>
<td>-3.30</td>
<td>-8.19 to 1.59</td>
<td>0.185</td>
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<tr>
<td>Total fused subsidence (n = 131)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C2–7 lordosis change</td>
<td>2.99</td>
<td>-0.47 to 6.45</td>
<td>0.089</td>
</tr>
<tr>
<td>cSV A change</td>
<td>-0.21</td>
<td>-0.82 to 0.39</td>
<td>0.485</td>
</tr>
<tr>
<td>Total fused lordosis change</td>
<td>-0.28</td>
<td>-3.14 to 2.58</td>
<td>0.847</td>
</tr>
</tbody>
</table>

The segmental subsidence model controls for cage-to-body ratio, the level of the fusion, the position of the level with respect to the fusion, cage type, age, sex, smoking, and osteopenia. The total fused subsidence model controls for the number of levels, cage type, sex, age, smoking status, and osteopenia.

CI, confidence interval; cSV A, cervical sagittal vertical alignment.
*p < 0.05, statistically significant differences.
for fused subsidence did not show any significant associations. However, there was a nonsignificant positive association with C2–7 lordosis change (beta = 2.99; 95% CI, -0.47 to 6.45; p = 0.89) and negative association with both cSVA change (beta = -0.21; 95% CI, -0.82 to 0.39; p = 0.485) and total fused lordosis change (beta = -0.28; 95% CI, -3.14 to 2.58; p = 0.847) (Table 3).

**DISCUSSION**

Subsidence of intervertebral cages in the cervical spine have been associated with increased pain, worse clinical outcomes based on Odom's criteria, and higher nonunion rates in some studies while others show no correlation. However, postoperative cervical sagittal alignment has been shown to lead to worse clinical outcomes after ACDF. One study by Iyer et al. found that preoperative C2–7 cSVA was an independent predictor of preoperative Neck Disability Index (NDI). Poor cervical alignment has also been associated with increased risk for adjacent segment disease. Although the relationship between subsidence and clinical outcomes is unclear, further exploration of the relationship between subsidence and cervical sagittal alignment is necessary. In this study, our aim was to assess the effect of subsidence on cervical sagittal alignment after ACDF using lateral cervical radiographic measurements at the immediate postoperative and final follow-up time periods.

Although segmental lordosis measurements are specific to a single level in the cervical spine, some studies suggest that segmental kyphosis may correlate with cervical disc herniation and worse clinical outcomes. Yang et al. in their retrospective study of ACDF with allograft found that decreased segmental height was associated with decreased segmental lordosis. Another retrospective study published by Pinter et al. found that segmental subsidence was associated with greater segmental lordosis loss in ACDF with allograft. Similarly, Lee et al. found in their retrospective analysis of single-level ACDF that segmental kyphosis was greater in levels with significant cage subsidence. Our findings mirror the results of the aforementioned studies as we found that segmental subsidence was significantly correlated with decreased segmental lordosis. Therefore, there is growing evidence that cage subsidence leads to decreased segmental lordosis. While segmental subsidence leads to kyphotic changes at the segmental level, total subsidence may have a larger effect on global cervical alignment, especially for patients undergoing multilevel fusion procedures.

Previous studies have shown conflicting results regarding the impact of subsidence on regional and global lordosis. In their retrospective study, Yang et al. found that segmental subsidence after ACDF was associated with decreased C2–7 lordosis. Segmental lordosis in their study was measured between the upper endplate of the superior vertebrae and lower endplate of the inferior vertebrae. Additionally, measurements were performed using computed tomography scans of the cervical spine. Conversely, Pinter et al. reported that subsidence did not correlate with global cervical alignment as measured by C2–7 lordosis. In our study, neither segmental subsidence nor total subsidence was significantly correlated with any measures of regional or global cervical alignment. Differences between our study and others are likely due to variations in measurement methods, choice of imaging modality, patient population, and surgical technique.

We found a nonsignificant trend of total subsidence being correlated with C2–7 lordosis loss during the postoperative period which suggests that there may be compensatory mechanisms which allow the vertebral segments above and below the subsided levels to counteract segmental kyphotic changes. While such adjustments may maintain global lordosis in the short term, long-term global lordosis maintenance is still unknown. As our sample of segmental subsidence measurements was greater than our sample of total subsidence measurements, a larger sample size may show an association between total fused subsidence and C2–7 lordosis. Overall, our findings generally agree with previously published results that segmental subsidence does not affect total fused lordosis change, cSVA change, or C2–7 lordosis change at short-term follow-up after ACDF.

The effect of subsidence on lordosis may depend on variations of ACDF surgery including but not limited to cervical plating, revision following cervical disc arthroplasty, and multilevel fusion. Recent studies have compared clinical outcomes and subsidence rates between ACDF with and without cervical plating. Lee et al. found that subsidence rates were higher when cervical fusions were performed without plating. In our study, all fusions were performed with plating or with a zero-profile cage with integrated screws. It is important to consider that plating may affect both subsidence and changes to lordosis of the cervical spine. Furthermore, with the increasing use of cervical disc arthroplasty, revision ACDF procedures may show differing subsidence and lordosis restoration outcomes than index procedures. Finally, although multilevel cervical fusion may increase the amount of subsidence, 3-level cervical fusion with plating has been shown to restore cervical lordosis in patients with degenerative spine diseases.

While ACDF generally provides excellent fusion rates and
patient outcomes, the effect of subsidence on nonunion and poor clinical outcomes is debated. Nonunion is a known complication of ACDF with a reported rate of about 5 percent.\textsuperscript{24,29} A systematic review by Karikari et al.\textsuperscript{3} found no significant differences in fusion rates based on cage subsidence. Since subsidence causes a compounding effect in multilevel cervical fusions, it is possible that cage subsidence in multilevel fusions increases the risk of nonunion.\textsuperscript{30} However, further research is needed on this topic. Furthermore, while studies have found no correlation between subsidence of intervertebral cages and clinical outcomes,\textsuperscript{15,27,28} one prospective randomized controlled trial performed by Kast et al.\textsuperscript{9} in 2009 concluded that subsidence of PEEK cages significantly correlated with poorer patient outcomes as measured by Odom’s criteria.

The current literature may not fully encompass the true effect of subsidence on clinical symptoms due to many studies reporting short-term follow-up less than 2 years. Some research suggests that segmental kyphosis allows for increased posterior disc space and opening of the intervertebral foraminal space which may explain why subsidence has not been correlated with clinical symptoms such as return or persistence of radiculopathy.\textsuperscript{4} Since segmental kyphosis may increase stress on musculoskeletal segments adjacent to the fusion, clinical symptoms as a result of this additional stress could take longer to manifest. As more long-term studies are reported, it is possible that a relationship between cage subsidence and clinical symptoms will become clearer.

There are several limitations of this study that the authors would like to acknowledge. This is a retrospective study performed using data from a single institution, and as such there may be variations in patient population and surgical techniques that do not generalize to other populations. Although we attempted to control for variations in patient and surgery characteristics in our multivariate analysis, there may be additional variations in surgical techniques that we were unable to account for. Additionally, radiographic techniques are not standardized across clinics which introduces variability in posture and rotation of the patient with respect to the x-ray detector. Furthermore, there may be some “settling” of the cage immediately following surgery which we were unable to control for in this radiographic study. Finally, our radiographic findings may not extrapolate to clinical outcomes. In spite of these limitations, the strengths of our study examining the effect of subsidence on lordosis include using a large, heterogeneous database of ACDF patients with average follow-up greater than 1 year.

CONCLUSION

Herein we present our results which show a relationship between segmental cage subsidence following ACDF and segmental lordosis of the cervical spine after controlling for patient and surgical characteristics. Neither segmental subsidence nor total fused subsidence was significantly associated with changes in global lordosis or cervical sagittal alignment at a mean follow-up greater than 1 year. Radiographic analysis does provide some strengths in that it allows an objective assessment of alignment and morphological changes in the cervical spine. While a correlation between subsidence and clinical outcomes has not been proven, surgeons should attempt to minimize cage subsidence when possible as changes in segmental lordosis due to subsidence of cervical cages may lead to adjacent segment disease and long-term cervical misalignment.

NOTES

Supplementary Materials: Supplementary Tables 1-3 can be found via https://doi.org/10.14245/ns.2244750.375

Supplementary Table 1. Pearson correlation analysis with segmental and total fused subsidence excluding zero-profile cages

Supplementary Table 2. Pearson correlation analysis with segmental and total fused subsidence for zero profile cages only

Supplementary Table 3. Pearson correlation analysis with cage height and subsidence (n = 244)

Conflict of Interest: SKC: IP royalties from Globus Medical and paid consultant from Stryker; JSK: paid consultant from Stryker. Other authors have nothing to disclose.

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Author Contribution: Conceptualization: AD, UNI, JSK, SKC; Data curation: AD, CG, EAG, PJF Jr, AMR, UNI, BZ, JSK, SKC; Formal analysis: AD, CG; Methodology AD, CG, EAG, PJF Jr, AMR, UNI, BZ, PMAA, JM, JSK, SKC; Project administration: UNI, JSK, SKC; Visualization: AD, CG; Writing - original draft: AD, CG, EAG; Writing - review & editing: PJF Jr, AMR, UNI, BZ, PMAA, JM, JSK, SKC.

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<https://doi.org/10.14245/ns.2244750.375>
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23. Pinter ZW, Mikula A, Shirley M, et al. Allograft subsidence decreases postoperative segmental lordosis with minimal
effect on global alignment following ACDF. Global Spine J 2022;12:1723-30.


**Supplementary Table 1.** Pearson correlation analysis with segmental and total fused subsidence excluding zero-profile cages

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<th>Variable</th>
<th>Pearson r</th>
<th>p-value</th>
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<td><strong>Segmental subsidence (n = 239)</strong></td>
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<td>Segmental lordosis change</td>
<td>-0.158</td>
<td>0.015*</td>
</tr>
<tr>
<td>C2–7 lordosis change</td>
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<td>cSVA change</td>
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<td>Total fused lordosis change</td>
<td>-0.068</td>
<td>0.448</td>
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cSVA, cervical sagittal vertical alignment.
*p < 0.05, statistically significant differences.
**Supplementary Table 2.** Pearson correlation analysis with segmental and total fused subsidence for zero profile cages only

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<td>Segmental lordosis change</td>
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<td>C2–7 lordosis change</td>
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<td>cSVA change</td>
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<td>Total fused lordosis change</td>
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<tr>
<td><strong>Total fused subsidence (n = 3)</strong></td>
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<tr>
<td>C2–7 lordosis change</td>
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<td>cSVA change</td>
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<td>Total fused lordosis change</td>
<td>0.149</td>
<td>0.905</td>
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cSVA, cervical sagittal vertical alignment.
**Supplementary Table 3.** Pearson correlation analysis with cage height and subsidence (n = 244)

<table>
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<tr>
<th></th>
<th>Pearson r</th>
<th>p-value</th>
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<tr>
<td>Cage height × segmental subsidence</td>
<td>0.329</td>
<td>&lt; 0.001*</td>
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A Narrative Review of Advances in Neural Precursor Cell Transplantation Therapies for Spinal Cord Injury

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A spinal cord injury (SCI) is a destructive event that causes a permanent deficit in neurological function because of poor regenerative potential. Transplantation therapies have attracted attention for restoration of the injured spinal cord, and transplantation of neural precursor cells (NPCs) has been studied worldwide. Several groups have demonstrated functional recovery via this therapeutic intervention due to the multiple beneficial effects of NPC transplantation, such as reconstruction of neuronal circuits, remyelination of axons, and neuroprotection by trophic factors. Our group developed a method to induce NPCs from human induced pluripotent stem cells (hiPSCs) and established a transplantation strategy for SCI. Functional improvement in SCI animals treated with hiPSC-NPCs was observed, and the safety of transplanting these cells was evaluated from multiple perspectives. With selection of a safe cell line and pretreatment of the cells to encourage maturation and differentiation, hiPSC-NPC transplantation therapy is now in the clinical phase of testing for subacute SCI. In addition, a research challenge will be to expand the efficacy of transplantation therapy for chronic SCI. More comprehensive strategies involving combination treatments are required to treat this problematic situation.

Keywords: Spinal cord injury, Transplantation, Neural precursor cells, Induced pluripotent stem cell

INTRODUCTION

Spinal cord injury (SCI) occurs upon sudden high-energy impact such as that in vehicular or contact sports accidents. In recent years, cervical SCI caused by minor traumas among the elderly has been raised as an additional issue for the aging society. In clinical stage, SCI is classified to complete injury, which is defined as no preservation of motor and/or sensory function, and incomplete injury which remains any neurological function below the injured site.¹ More than 70% of patients with complete SCI progress without functional improvement.² As a result, 3 million people are estimated to suffer from SCI worldwide, with 180,000 new cases each year.³

Since Cajal proposed the difficulty of regenerating the central nervous system, numerous researchers have struggled to develop treatments for SCI.¹ However, the effects of conventional treatments, including methylprednisolone sodium succinate infusion, are modest,⁴ and surgical decompression of the injured spinal cord is still the only gold standard therapy for this injury.⁷,⁸

The lack of regenerative capacity in the injured spinal cord is related to many factors, such as characteristics that inhibit axonal regeneration, poor regenerative ability of endogenous neural precursor cells (NPCs), and insufficient support by trophic factors.⁵ Particularly in complete transection model, which well reproduces the complete injury in human, there are no spared axons in the injured site and exogenous replacements are essential. Cell transplantation therapies have attracted attention as possible methods to overcome these disadvantages due to their multiple types of therapeutic potentials.⁶ We aim to develop a human induced pluripotent stem cell (hiPSC)-derived NPC transplantation therapy to treat this challenging pathology and...
NPC Transplantation to Spinal Cord Injury

NPC TRANSLANTATION FOR SCI

Transplantation therapy for SCI has been researched worldwide over a few decades. Several types of cells, such as Schwann cells, 
mesenchymal stem cells, 
olfactory ensheathing cells, 
and NPCs 
have been attempted to be used as candidate cell sources. The diverse characteristics of each cell have been found to promote unique beneficial effects for the injured spinal cord and to lead to functional recovery in a SCI animal model. The main concept for NPC transplantation is to replace lost neural cells by compensating for the poor regenerative ability of endogenous NPCs.

Approximately 20 years ago, embryonic cells or tissues were transplanted into SCI animals. Transplantation of these heterogeneous cells resulted in functional recovery of the animals along with histological reorganization, and the findings implied the efficacy of cell restoration via transplantation of fetal cells. However, a large number of fetuses are required to obtain enough tissue to apply to humans. Therefore, this treatment has not advanced to clinical use. In addition, advances in biological techniques have led to the routine dissociation and expansion of NPCs from fetal tissues. Collaboration of these culture methods and research to treat SCI have enabled great progress in knowledge to be made in the field of NPC transplantation therapy.

Vacanti et al. transplanted spinal cord progenitor cells isolated from the spinal tissue of adult rats into SCI model animals. Even though engraftment of transplanted cells and functional improvement were observed, the transplanted cells in that study included differentiated neurons. The authors did not fully prove the efficacy of NPCs in transplanting cells. In addition, Ogawa et al. performed transplantation of NPCs derived from the rat embryonic spinal cord. The transplanted cells differentiated into neural cells, and the donor-derived neurons integrated into host tissue. Behavioral improvement was also observed, which was presumed to be caused by the regenerated axons and oligodendrocytes derived from graft cells. Moreover, this study was demonstrated in a contusive injury model animal, which closely mimics the pathology of incomplete injury in clinical study compared with incomplete transection models.

Following these results, the multipotency of NPCs is expected to produce various beneficial effects for the injured spinal cord and attracted researchers wishing to treat SCI.

TRANSPLANTATION OF NPCs IN THE SUBACUTE PHASE

The timing of transplantation is a critical factor in SCI treatment. Treating acute and chronic SCI is considered difficult due to environmental changes, such as the formation of a cavity surrounded by a glial scar. Parr et al. reported a poor survival rate of transplanted cells in the acute and chronic phases compared with the subacute phase. A similar result was revealed from the group of Fehlings. That group observed dead grafted cells in the center area when the cells were transplanted in the chronic phase and failed to treat the injury. Nishimura et al. clarified the underlying difficult conditions of chronic SCI and reported that glial scar formation and inflammation were the most remarkable differences in the injured spinal cord microenvironment between the subacute and chronic phases.

Including the aforementioned reports, subacute phase in rodents are defined as 7-14 days after injury. In contrast, analyzes of gene expression revealed that the inflammatory response is significantly prolonged and the onset of glial scar formation is temporally delayed in nonhuman primates. Thus, the time window for cell transplantation to nonhuman primates are thought to be 14-28 days after injury.

All in all, the subacute phase is considered to be the optimal time for NPC transplantation, and various reports have demonstrated the therapeutic effect of transplanting NPCs at this phase. To understand the pathology of injured spinal cord is extremely important to achieve sufficient improvement by transplantation therapy. Further research must be conducted to define and evaluate the timing of transplantation to human.

THERAPEUTIC MECHANISMS OF NPC TRANSPLANTATION

Although NPC transplantation improves functional outcomes in SCI animals, the detailed underlying mechanisms of this treatment remain unclear. In recent years, several studies have focused on the mechanisms of recovery mediated by NPC transplantation. Several approaches have been utilized to demonstrate how transplanted cells contribute to the improvement of motor function. Administration of diphtheria toxin to ablate engrafted human cells is frequently used to evaluate the therapeutic potential of the transplanted cells. Elimination of whole trans-
NPC Transplantation to Spinal Cord Injury

Kitagawa T, et al.

https://doi.org/10.14245/ns.2244628.314

www.e-neurospine.org 937

planted cells leads to the functional deterioration of host animals, indicating that engrafted NPCs somehow contribute to the recovery of host motor function. Regarding the favorable effects, 3 main mechanisms have been proposed as therapeutic factors for NPC transplantation: reconstruction of the neuronal circuits, remyelination of axons, and neuroprotection by trophic factors (Fig. 1).

1. Reconstruction of Neuronal Circuits

The strategy for reconstruction of neuronal circuits can be divided into 2 models: (1) regrowth of an injured axon back to the original target and (2) relay formation, in which a new neuron is inserted between the injured axon and the target neuron. The advantage of NPC transplantation is that it can provide neurons that may be capable of extending axons in the injured spinal cord and achieve new neuronal circuits by relay formation.

In the early days, axon tracing techniques or immunohistochemical staining of neurons was used to annotate the connections between host neurons and graft neurons. Lu et al. demonstrated a large number of grafted axons extending over the injury site even in severe SCI model animals. Immunohistological synaptic markers also show synapse formation between the graft and host neurons, and immunoelectron microscopy analysis has confirmed the detailed formation of each synapse.

The latest technologies of neuroscience have also attracted attention in this spinal cord area. A previous study by Tuszynski’s group combined the optogenetic stimulation method and a genetically encoded calcium indicator to reveal the relay mechanisms of host neurons and graft neurons. Stimulation of host corticospinal tract axons elicited neuronal network responses throughout the grafted neurons. Moreover, optogenetic stimulation of graft neurons triggered the neuronal activity of host neurons in the causal area of injury, which implies the existence of an electrophysiological connection in the relay-formed neuronal network.

Another strategy is to visualize neuronal activity using a luminescent protein. The AkaBLI system, which is a newly developed redshifted bioluminescence imaging system, has been used to demonstrate in vivo imaging of graft neuronal activity. Upon transduction of the AkaLuc enzyme under the control of a potent neuronal activity-dependent synthetic promoter in transplanted NPCs, engrafted cells show enhanced luminescence upon stimulation of the CST tract. This also indicates the neuronal connections of host neurons and graft neurons.

Our group and others have focused on the relationship between graft neurons and host motor functions. Designer Receptor Exclusively Activated by Designer Drugs (DREADD), which is a chemogenetically engineered protein that permits control of neuronal activity via administration of the ligand clozapine N-oxide (CNO), has been applied to verify the therapeutic effect on neuronal activity in graft-derived cells. By inhibiting the activity of the graft-derived neurons with inhibitory DREADD receptor, the locomotor function of host animals temporarily declined after CNO administration, which directly suggested the contribution of graft neuronal activity to the recovery of locomotor function. On top of that, activation of graft neuronal activity by excitatory DREADD results in increased connectivity with host neurons and additional functional recovery. This also shows the connectivity of host and graft neurons and indicates the possibility of improving this therapy by enhancing the neuronal connections.

Accordingly, neurons derived from grafted NPCs have been successfully integrated into host neuronal circuits and play a role in functional recovery with transplantation therapy.

Fig. 1. Three main mechanisms have been proposed to repair the injured spinal cord. (A) Reconstruction of the neuronal circuits by relay formation of engrafted cells. (B) Remyelination of graft axons and host axons by graft-derived oligodendrocytes. (C) Neuroprotection by trophic factors secreted from the transplanted cells.
2. Remyelination of Axons

The beneficial effect of remyelination after SCI is still controversial. Duncan et al.\(^9\) inhibited remyelination by deleting *Myrf*, a gene that plays a crucial role in remyelination. As the deletion of *Myrf* did not correlate with the motor function of the host animals, the results implied that there is no relationship between functional outcome and remyelination due to endogenous oligodendrocyte precursor cells (OPCs). On the other hand, Yagura et al.\(^{59}\) reported the importance of remyelination by graft-derived cells for functional recovery after the transplantation of NPCs. In that report, transplantation of NPCs isolated from myelin-deficient shiverer mutant mice resulted in a lower rate of functional recovery than transplantation of NPCs isolated from wild-type mice.

Similarly, a study by Salewski et al.\(^{60}\) demonstrated a practical difference upon transplantation of iPSC-NPCs derived from shiverer mutant mice and wild-type mice, which also implies the importance of remyelination due to transplanted cells. Despite these controversial results, myelinating injured axons is recognized as a critical process after SCI. Several studies have aimed to increase the myelinating potential of transplanting cells. The use of OPC-enriched NPCs for transplantation is a representative example of such a strategy.\(^{61-64}\) Kawabata et al.\(^{65}\) and Kamata et al.\(^{66}\) transplanted gliogenic NPCs generated by a culture protocol modified from one previously reported. Remyelination by graft-derived oligodendrocytes was confirmed by immunoelectron microscopy analysis after OPC-enriched NPCs were transplanted into SCI animals. Similarly, Fehlings’ group observed remyelination of axons and functional recovery after transplanting oligodendrogenic NPCs directly reprogrammed from somatic bone marrow cells.\(^{67}\) Overall, animals treated with OPC-enriched NPC exhibit functional improvement. Thus, remyelination by transplanted cells is considered to exert a beneficial effect on the injured spinal cord.\(^{61-64}\)

3. Neuroprotection by Trophic Factors

After the primary mechanical trauma to the spinal cord, secondary injury, which causes progressive damage through complex biochemical factors, begins and continues for weeks or months.\(^{65}\) Neuroprotection by trophic factors secreted from transplanted NPCs is presumed to mediate secondary injury and support the regeneration of neural cells. Hawryluk et al.\(^{66}\) reported elevated expression levels of glial-derived neurotrophic factor (GDNF), leukemia inhibitory factor, and basic fibroblast growth factor (bFGF). Another previous study has identified 49 neurotrophic factors expressed by transplanted cells, including insulin-like growth factor 1 (IGF-1), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and transforming growth factor 1.\(^{67}\) Similarly, we have previously demonstrated the secretion of nerve growth factor, BDNF, vascular endothelial growth factor (VEGF), NT3, NT4, ciliary neurotrophic factor (CNTF), and hepatocyte growth factor (HGF) from hNPCs, and these factors exerted favorable effects on behavior soon after transplantation.\(^{68,69}\) NT3, NT4, and CNTF encourage axonal sparing after injury, and VEGF enhances angiogenesis at the lesion site by promoting cell survival pathways.\(^{43}\) HGF is known to promote NPC proliferation and neuronal differentiation, thereby playing a key role in the enhancement of functional recovery.\(^{69}\) Because of these favorable effects of trophic factors, delivering growth factors is thought to promote therapeutic effects. Karimi-Abdolrezaee et al.\(^{28}\) combined NPC transplantation with the delivery of growth factors such as platelet-derived growth factor (PDGF-AA), bFGF, and epidermal growth factor (EGF) to promote cell survival in the environment of the injured spinal cord. Lu et al.\(^{29}\) achieved long-distance growth of grafted neurons by supporting graft survival with BDNF, NT-3, PDGF-AA, IGF-1, EGF, bFGF, acidic FGF, GDNF, HGF, and a calpain inhibitor.

In recent years, microRNA (miRNA), such as miRNA-210 and miRNA 126, has also been reported to mediate the environment of injured spinal cord via angiogenesis or attenuation of inflammation.\(^{56,60}\) In case of NPC transplantation, Yang et al.\(^{71}\) showed upregulation of miRNA-375-3p and miRNA-1-3p, and downregulation of miRNA-363-3p, miRNA-449a-5p, and miRNA-3074 in mice treated with oligodendrogenic NPCs. As bioinformatics analysis of these miRNA indicates the relation with cell proliferation and neuronal differentiation, these results suggest the possibility that miRNA promoted functional recovery in oligodendrogenic NPC transplantation.

Despite this evidence, the detailed effects of each factor are still being investigated, and further studies are needed.

CELL SOURCES FOR GENERATING NPCs

In basic research, NPCs are generated from several cell sources. In the early era, somatic stem cells were used to prepare NPCs, as described above.\(^{28,29}\) Similarly, Lu et al.\(^{29}\) demonstrated the neuronal connections of host and graft cells by transplanting NPCs dissected from the embryonic rat spinal cord in a recent study. In the same way, NPCs have been generated from fetal spinal cells of rodents or humans in several studies.\(^{77,28,31,72}\) Reprogramming from somatic cells has also been performed in
recent studies, Fehling’s group transplanted OPC-enriched NPCs, which were directly reprogrammed from bone marrow somatic cells and demonstrated functional recovery.\textsuperscript{62,63}

In the past few decades, methods to induce NPCs from pluripotent cells have been investigated.\textsuperscript{77} Kumagai et al.\textsuperscript{74} promoted functional recovery by transplanting NPCs generated from embryonic stem cells (ESCs). However, using somatic stem cells or ESCs for the clinical phase is associated with ethical and immunological concerns and therefore casts a shadow over the advancement of this transplantation therapy. iPSCs were invented by Yamanaka’s group, and the use of these new pluripotent stem cells as a source of NPCs resolves these problems.\textsuperscript{75} In addition to this ethical problem, iPSCs raised a possibility of autologous transplantation. This was an obvious advantage to allogenic transplantations, such as NPCs derived from somatic stem cells or ESCs, which requires immunosuppression when transplanting to human spinal cord. Tsuji et al.\textsuperscript{76} transplanted NPCs derived from murine iPSC, followed by a report from Nori et al.\textsuperscript{8} which transplanted human iPSC. Lu et al.\textsuperscript{80} transplanted NPCs derived from iPSCs that were harvested from a healthy 86-year-old male and induced to differentiate. Salewski et al.\textsuperscript{81} transplanted NPCs derived from iPSCs generated by a nonviral piggyBac transposon approach.

According to these reports from several groups, iPSC-NPC transplantation shows favorable results. Moreover, using hiPSCs as a cell source for NPCs enables the transplanted cells to successfully survive the injured spinal cord and differentiate into neural cells.\textsuperscript{84,83} Similar to NPCs derived from other cell sources, neurons differentiated from hiPSC-NPCs integrate into host neuronal circuits and alter the motor activity of host animals.\textsuperscript{8,49,57} hiPSC-NPCs also secrete nerve growth factor, BDNF, and HGF, which exert favorable effects on behavior soon after transplantation.\textsuperscript{8} Additionally, remyelination of axons by graft oligodendrocytes has been observed after enrichment of OPCs in transplanted cells.\textsuperscript{84,84} Overall, the multiple beneficial factors clearly improve the locomotor function of host animals, and hiPSC-NPCs have become a leading candidate cell type for transplantation for SCI treatment.

**SAFETY OF hiPSC-NPC TRANSPLANTATION**

Although hiPSC-NPC transplantation leads to a favorable result for SCI animals, transplantation of immature cells has a risk of tumorigenicity. The potency of tumorigenic change differs by hiPS cell line.\textsuperscript{77,78} Even if safe iPSC cell line-derived NPCs are transplanted, tumor-like growth occasionally occurs.\textsuperscript{79} For clinical application, establishing a safe transplantation therapy is indispensable, and we have handled this problem from multiple perspectives.

1. Prediction and Detection of Tumorigenic Change

The ideal strategy to avoid tumorigenicity after transplantation is to predict the risk of tumorigenic change before transplantation and to select safe cell lines. To achieve selection accuracy, we compared the gene expression profiles of tumorigenic and nontumorigenic hiPSC-NPCs by comprehensive DNA methylation analysis.\textsuperscript{80} The genomic regions surrounding the transcriptional start sites of the tumor suppressor genes were hypermethylated in tumorigenic NPCs but not in nontumorigenic NPCs. Interestingly, the aberrant DNA methylation profile was more pronounced when the number of passages increased, even for the cell lines that were initially nontumorigenic. The methylation profiles and the passage number limits should be included in the criteria for clinical settings.

Detecting tumorigenic formation at the early stage will also be required to guarantee the safety of this therapy. In tumorigenic hiPSC-NPCs, the differentiation-resistant properties of abnormal cells cause the continuous growth of transplanted cells. Tanimoto et al.\textsuperscript{86} reported a method to detect these proliferating cells using positron emission tomography (PET). The immature NPCs showed a high expression level of the 19 kDa translocator protein (TSPO), also known as the peripheral-type benzodiazepine receptor. PET with \textsuperscript{18}F FEDAC (a TSPO radioligand) succeeded in visualizing the remaining undifferentiated hiPSC-NPC derived cells, which were TSPO and Nestin cells, by histological analysis. This technique could also play a key role in the clinical stage.

2. Prevention of Tumorigenic Overgrowth by Pretreatment With a Notch Signaling Inhibitor

Despite the careful selection of cell lines for transplantation, the infrequent occurrence of tumorigenic changes remains a concern for this therapy. To address this problem, we investigated pretreatment with a gamma secretase inhibitor (GSI), which inhibits Notch signaling that controls the induction of NPCs.\textsuperscript{50,51} Pretreatment of GSI promoted neuronal differentiation and maturation of hiPSC-NPCs in vitro. By this pretreatment, transplantation of tumorigenic hiPSC-NPCs resulted without any tumor formation. Thus, this study indicates the effectiveness of GSI pretreatment in preventing cell overgrowth. Moreover, pretreatment with GSI before transplantation of nontumorigenic hiPSC-NPCs leads to further functional recovery of host.
animals according to the maturation and neuronal differentiation induced by Notch signal inhibition. Therefore, GSI pretreatment is considered a critical process in hiPSC-NPC transplantation treatment to prevent tumorigenic changes and enhance therapeutic efficacy.

3. Usage of Suicide Genes to Eliminate Tumorigenic hiPSC-NPCs

Even though selection of cell lines and pretreatment to prevent overgrowth decreases the risk of tumorigenesis, measures should be taken to eliminate proliferating cells. In order to solve this issue, we have proposed several methods to ablate tumorigenic transplanted cells by using a suicide gene system, which is also applied to transplantation therapy in other diseases. In the first method, induced caspase-9, which is a member of the caspase family of cysteine proteases that have been implicated in apoptosis and cytokine processing, was transduced into tumorigenic hiPSC-NPCs and transplanted into SCI animals. As expected, the transplanted cells formed tumor-like growths. When the apoptosis inducer was injected, the transplanted cells were completely ablated, indicating this system’s effectiveness in salvaging from undesired overgrowth. However, this system ablated all transplanted cells, including the differentiated cells that were contributing to the functional recovery. Eventually, the improved motor function achieved by the transplantation deteriorated after the suicide gene system was triggered.

To overcome this disadvantage, we next chose the herpes simplex virus type 1 thymidine kinase (HSVtk) gene as a candidate suicide gene. Via HSVtk, ganciclovir (GCV), the prodrug, can be converted to cytotoxic GCV-triphosphate. Thus, HSVtk-expressing cells can be eliminated by GCV induction. This system kills the cell by causing a delay in the S and G2 phases, resulting in apoptosis of only proliferating cells. Upon transplanting HSVtk-transduced tumorigenic hiPSC-NPCs and stimulating the suicide by GCV, only proliferative cells were ablated, and the improved locomotor function was sustained. Therefore, this new approach enables treatment of tumorigenesis without sacrifice of the improved motor function.

CLINICAL APPLICATION OF hiPSC-NPC TRANSPLANTATION

Given the considerable evidence from basic and preclinical studies revealing the effectiveness and safety of hiPSC-NPC transplantation, our transplantation therapy for SCI has reached the clinical application stage.

Similar to other transplantation therapies for SCI, the treatments in our previous studies have mainly treated SCI at the subacute phase, which is considered an optimal time for treatment due to the neural plasticity and reactivity at this stage.

Since autologous transplantation is unrealistic for the subacute phase because of the lack of a generation period for transplanted iPSCs, allograft transplantation of NPCs derived from an hiPSC stock at the Center for iPS Cell Research and Application (CiRA) is being applied in this clinical trial. The hiPSC stocks were generated from human leukocyte antigen (HLA) superdonors who are homozygous at the 3 major HLA gene loci to maintain a pool of immunologically safe iPSC clones corresponding to various HLA types. The quality of the generated cells has been thoroughly checked based on general characteristics, marker

![Fig. 2. Schematic illustration of iPSC-NPC transplantation therapy in the clinical trial. iPSC, induced pluripotent stem cell; NPC, neural precursor cell; HLA, human leukocyte antigen; SCI, spinal cord injury; CiRA, Center for iPS Cell Research and Application.](https://doi.org/10.14245/ns.2244628.314)
expression of differentiated cells, and genomic factors to ensure safety after transplantation (Fig. 2).10

Beginning in 2021, we began recruiting complete SCI patients (American Spinal Cord Injury Association Impairment Scale A) within 14–28 days of injury. hiPSC-NPCs pretreated with GSI are being transplanted, and patients will be followed up for one year with proper neurologic evaluations.

### TRANSPLANTATION THERAPY FOR THE CHRONIC PHASE

The next mission for this treatment is to expand toward the chronic phase after injury. More than 90% of patients still suffer from their impairments and disabilities in the chronic phase; therefore, this phase is the most significant stage for related research.93 However, as Nishimura et al. proved the difficulty of treating chronic SCI by only NPC transplantation, several studies have failed to recover motor functions in the chronic phase, and only a few reports have shed light on this challenging situation.84–86 Additionally, the timing of chronic phase in the studies of rodent model lay from 28 days to 91 days after injury.28,37,38,87

The underlying environment in chronic phase will not be in a homogeneous pathology following the progression after injury, thus, the wide range of this phase results in confusion and difficulty for treating.

Since NPC transplantation alone is insufficient for treating chronic SCI, combination with other therapeutic factors is required to overcome this difficult situation. Okubo et al.37 reported functional recovery upon transplantation of GSI-pretreated hiPSC-NPCs into chronic SCI model mice. Notch signaling inhibition promoted the maturation of transplanted cells and resulted in significantly enhanced axonal regrowth, remyelination, and inhibitory synapse formation with host neurons. Additionally, GSI pretreatment caused phosphorylation of p38 mitogen-activated protein kinases, which are also key molecules required to promote axonal regeneration. Through these favorable factors, we succeeded in improving locomotor function in the chronic phase.

Another promising therapy involves concomitant rehabilitation. Rehabilitation is known to be an effective treatment for SCI, even in the clinical stage.85–92 In our previous report, combining rehabilitative treatment with transplantation of NPCs harvested from embryonic mouse spinal cords enhanced the independent therapeutic effects of each single therapy.93 The synergistic effects of this combination therapy facilitated neuronal differentiation of transplanted cells and maturation of the central pattern generator. Since hiPSC-derived cells were not used in this study, the synergistic effects of hiPSC-NPCs and rehabilitation need to be confirmed in the near future.

The use of chondroitinase ABC (ChABC) to degrade chondroitin sulfate proteoglycans, which form a potent barrier for axon regeneration, is also a promising strategy to treat chronic SCI.94 Upon delivery of ChABC, transplanted iPSC-NPCs can survive and differentiate into neural cells. Furthermore, the differentiated neurons form functional synapses and improve the motor function of host animals.

Finally, the Marsala group transplanted human spinal cord-derived neural stem cells into 4 humans with chronic SCI.95 By using a cell line authorized by U.S. Food and Drug Administration, the safety of the transplantation was implied, although it did not have the statistical power to evaluate functional changes.

### CONCLUSION

Due to the numerous efforts and evidence accumulated to date, hiPSC-NPC transplantation therapy has advanced to the clinical application stage. Nevertheless, several aspects remain to be investigated, such as the detailed therapeutic mechanisms and strategies to enhance the therapeutic effects. Although numerous studies have significantly succeeded to improve functional outcomes, no one has fully recovered the injured spinal cord and behaviors, especially in severe injury models. The pathophysiological knowledge of injured spinal cord and mechanisms to treat this injury must lead to an optimal strategy for complete improvement from SCI. Additionally, the permanent effect of transplantation has not been proven in animal models because of the short lifespan compared with human. To secure safety and confirm the persistent functional enhancement, long-term studies using primate models are required. Lastly, to establish and enable this transplantation therapy to proceed to the treatment of chronic SCI, further basic researches are required.

### NOTES

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

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NPC Transplantation to Spinal Cord Injury

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Advances in Neural Stem Cell Therapy for Spinal Cord Injury: Safety, Efficacy, and Future Perspectives

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Spinal cord injury (SCI) is a devastating central nervous system injury that leads to severe disabilities in motor and sensory functions, causing significant deterioration in patients' quality of life. Owing to the complexity of SCI pathophysiology, there has been no effective treatment for reversing neural tissue damage and recovering neurological functions. Several novel therapies targeting different stages of pathophysiological mechanisms of SCI have been developed. Among these, treatments using stem cells have great potential for the regeneration of damaged neural tissues. In this review, we have summarized recent preclinical and clinical studies focusing on neural stem cells (NSCs). NSCs are multipotent cells with specific differentiation capabilities for neural lineage. Several preclinical studies have demonstrated the regenerative effects of transplanted NSCs in SCI animal models through both paracrine effects and direct neuronal differentiation, restoring synaptic connectivity and neural networks. Based on the positive results of several preclinical studies, phase I and II clinical trials using NSCs have been performed. Despite several hurdles and issues that need to be addressed in the clinical use of NSCs in patients with SCI, gradual progress in the technical development and therapeutic efficacy of NSCs treatments has enhanced the prospects for cell-based treatments in SCI.

Keywords: Spinal cord injury, Neural stem cells, Clinical trials, Cell-based therapies, Transplantation, Regenerative medicine

INTRODUCTION

Traumatic spinal cord injury (SCI) is a catastrophic event with a high mortality rate and causes physical and emotional difficulties in patients. It is defined as injury to the spinal cord, nerve roots, osseous structures, and disco-ligamentous components. The subsequent formation of reactive tissue scarring and cystic cavitation results in the development of molecular and physical barriers to regenerative axonal growth and long-term neurological deficits in SCI. The prevalence and incidence of SCI vary according to geopolitical and economic conditions, and approximately 1,000 new cord injury cases occur every year in South Korea. Although the global incidence is similar between sexes, men have a higher incidence than women aged 20–40 years. Moreover, as the global population tends to grow and health care systems improve, an increase in the absolute number of people living with SCI is expected. Anti-inflammatory methylprednisolone sodium succinate is the first-line drug treatment for patients with SCI. After initial management, clinicians surgically decompress the spinal cord and control the lesion site if needed. Many studies have been conducted to prevent or reduce the effects of secondary injury;
among them, research on steroids and neuroprotective alternatives has been discussed for a long time. For the regeneration of damaged neural cells in SCI, various types of stem cells including Schwann cells, olfactory ensheathing cells, embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs), have been examined preclinically and in animal models of SCI.

Recently, transplantation of NSCs has been shown to promote the repair or regeneration of damaged spinal cords. In this review article, we have discussed the characteristics, origin, and recent developments of NSCs in clinical trials of SCI.

**BASIC CHARACTERISTIC OF STEM CELLS**

Stem cells exhibit 2 characteristics: self-renewal and multipotency. ESCs that are established from fertilized eggs can satisfy the definition of stem cells because ESCs can proliferate indefinitely and differentiate into whole body.11 Recently, induced pluripotent stem cells (iPSCs) have been suggested to exhibit characteristics similar to those of ESCs.12 These 2 types of stem cells are called pluripotent stem cells (PSCs). In contrast, adult stem cells (ASCs) reside in organs and regenerate their tissues when damaged.13 Therefore, ASCs usually have limited lifespan and differentiation potential. In clinical trials to regenerate the damaged central nervous system (CNS), 2 types of ASCs have been used: MSCs and NSCs. The key feature of MSCs is their differentiation potential into mesodermal tissues, such as osteoblasts, adipocytes, chondrocytes, and even other lineages.14 Moreover, MSCs produce various paracrine factors that have beneficial effects on regeneration and immune modulation.15 However, several studies have concluded that their beneficial effects are due to functional modulation, and not by direct neuronal regeneration and integration into the injured CNS.16,17 NSCs are characterized by the expression of typical markers, such as Nestin or Sox2.18 Generally, they reside in the subventricular zone and the subgranular zone,19,20 which are specialized niches where young neurons for the olfactory bulb and hippocampus, respectively, are generated.21 NSCs can self-renew and play a role in neurogenesis in the adult brain.22,23 NSCs preferentially differentiate into neural lineages such as neurons, astrocytes, and oligodendrocytes, which are attractive for clinical use in CNS diseases.24 NSCs also secrete beneficial paracrine factors that can help regenerate the damaged CNSs.25-27 Such characters make NSCs a potent and versatile cellular drug candidate for the treatment of the CNS injuries.

**ESTABLISHMENT OF NSCs**

NSCs have been established from several sources.28 Among them, the conventional source of NSCs is the fetal CNS.8,26,29 Fetal NSCs (fNSCs) have self-renewal potential and neural differentiation capacity.30 The therapeutic potential of fNSCs has been demonstrated in a model of SCI,8,29,31 and interestingly, human fNSCs showed neurogenesis after injection into immunodeficient mice in vivo.32 fNSCs can differentiate into neurons, which can connect with surrounding neurons.8,29,31 With promising data from several preclinical studies, most clinical trials have used NSCs derived from the human fetal CNS, including the brain and spinal cord.13 However, unavoidable ethical issues using fetal CNS are critical for commercial development, and they provide a strong motivation for other cellular sources.

One candidate is the adult NSCs (aNSCs), which can be isolated from the adult CNS. The adult olfactory bulb is the source of NSCs. The olfactory bulb core is an extension of the rostral migratory stream and is thus a potential source of neural progenitors and NSCs.34 Human spine is another option for aNSCs transplantation.35-37 Through several preclinical studies, the beneficial effects of aNSCs have been proven in SCI models.32,38-43 These studies suggested that the beneficial effects of aNSCs come not only from their paracrine effects in neural tissue repair and regeneration, but also from their direct differentiation into various neuronal lineage cells that are integrated and form neuronal networks with the host CNS. This multiple recovery mechanism implies that aNSCs could be an optimal choice in the treatment of SCI.

Despite these advantages, technical difficulties remain to be solved in order to utilize these cells in real-world clinical practice. For the appropriate use of aNSCs, they must be properly isolated and effectively increased in number. Compared with other stem cells, aNSCs reside in relatively restricted areas of the adult CNS.44 In addition, they have limited and different proliferation capacities according to the lesion type and location.45 To address the technical difficulties in primary isolation and stable in vitro expansion of aNSCs, several research teams have suggested various scientific and technical approaches.46 Surgical samples from adult CNS are usually very small (1–2 mL) and the number of resident aNSCs within the tissue is also very small. Therefore, aNSCs isolation techniques have been optimized to increase the success rate of primary isolation. First, CNS tissues were physically minced and enzymatically digested into single cells. Enzymatic digestion is a critical step because it
directly affects NSC survival. Papain, trypsin, and collagenase have been commonly used, and in some reports, papain dissociation was suggested to be optimal for the primary isolation of aNSCs. After mechanical and enzymatic dissociation of CNS tissues, isolated single cells expand in number. There are 2 alternative culture methods in use: the neurosphere and adherent culture methods. Conventionally, the neurosphere culture method has been used for in vitro culture of NSCs. However, difficulties in stable in vitro expansion of aNSCs using suspension culture methods require the development of other culture methods. Moreover, a single neurosphere may not be derived from a single NSC. The possible heterogenic origin of neurospheres could not guarantee the homogeneity of in vitro-expanded aNSCs in suspension culture conditions. To overcome the limitations of the neurosphere culture method, an alternative adherent culture methods for NSCs, was developed. In this method, each group used its coating plates to attach NSCs to the plates and various culture medium compositions. Lam inin and poly-L-ornithine (PLO) have been used to coat plate frequently, which increase the adherent efficiency of NSCs. To maintain stemness and proliferation of NSCs, the amount of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) have been optimized. For example, we expanded aNSCs from temporal lobectomy samples of epilepsy patients without any neoplastic diseases on PLO-coated dishes in a DMEM/F12 media supplemented with 1% B27, 1% penicillin/streptomycin cocktail, EGF (50 ng/mL), bFGF (50 ng/mL), and 0.5% fetal bovine serum. Using the adherent culture method, aNSCs were expanded in vitro from 10 to 10 cells within 8 subcultures for 2 months. Moreover, expression of NSC markers such as nestin and SOX2 maintained stably. If the number of aNSCs required for transplantation is 10 per patient, at least one hundred thousand patients could be treated with a primary culture of aNSCs.

Recently, technical developments have resulted in the establishment of NSCs from ESCs or iPSCs. When ESCs and iPSCs are induced to differentiate into NSCs by several inducers, such as growth factors and cytokines, these NSCs have similar characteristics to NSCs, which can induce neurogenesis in the CNS of immunodeficient mice. In several preclinical studies, the therapeutic potential of NSCs derived from ESCs or iPSCs has been demonstrated in animal models of SCI. To date, human clinical data using ESCs or iPSCs for SCI treatment are scarce. Only 2 clinical trials (one in each ESCs and iPSCs) are ongoing right now. Compared to the other cellular sources, iPSCs have great advantages in ethical issues and immune rejection. Therefore, interests in NSCs from iPSCs will continuously increase with the advances with iPSCs technology.

### PRECLINICAL STUDY OF NSC FOR SCI

Preclinical studies should be designed to address the activity and safety of stem cell-based products for clinical use. Information about the potential mechanism of action of stem cells in the disease indication, the timing of intervention with respect to disease course, and the mode of delivery to the site of action must be investigated in preclinical models. Many preclinical studies using NSCs in animal models of SCI have been reported in the literature and the therapeutic potential, safety, and several technical aspects of NSCs transplantation have been tested under various conditions.

The characteristics of experimental studies using NSCs are summarized in Table 1. NSCs treatments have been tested at various stages of SCI: acute, subacute and chronic. Mice and rats are the most used animals. In a few studies, human NSCs have been tested in non-human primates. The thoracic spinal cord has been the most frequently studied region, where the injury is made by mechanical trauma, such as dropping weight or clip compression. As sudden contusive injury to the cervical spinal cord can be life-threatening, hemitranssection is the preferred model for models of cervical SCI. Functional testing scales are somewhat standardized according to animal model species. In mice and rats, the Basso mouse scale or Basso-Beattie-Bresnahan test and CatWalk gait analysis are the most frequently used scales. In addition, many studies have used the von Frey test to evaluate the sensory function. Several studies have also reported functional recovery after transplantation of NSCs as well as graft survival, differentiation and axonal regeneration.

Although a number of studies have reported promising results of NSCs treatment in SCI, we still have a long way to go to use NSCs in real-world clinical practice. To move from bench to bedside, determining the differences between the animal model and human SCI and closing the gap caused by inherent limitations of the model should be the first step. In general, there are no reliable animal models that can predict human diseases. Under such circumstances, using a model that most closely represents the critical features of the intended indication is the best alternative. Most human SCI cases are caused by mechanical injury. Consequently, we have developed several animal models of SCI using mechanical trauma to the spinal cord. However, the regenerative potential and physical size of the spinal cord...
Table 1. Summary of preclinical studies using neural stem cells/neural progenitor cells in animal spinal cord injury models in literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Injury location</th>
<th>SCI model</th>
<th>Transplantation time after SCI</th>
<th>Cell type</th>
<th>Cell source</th>
<th>Route and dose</th>
<th>Combination</th>
<th>Functional evaluation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeifer et al.24 2006</td>
<td>Rat</td>
<td>Cervical</td>
<td>Transection</td>
<td>8 Weeks</td>
<td>Auto/allogenic NPCs</td>
<td>Rat brain</td>
<td>Intralesional injection, 2.4 × 10^5 cells</td>
<td>Fibroblasts</td>
<td>N/A</td>
<td>Showed substantial axonal regeneration</td>
</tr>
<tr>
<td>Nomura et al.104 2008</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Transection</td>
<td>0 Day</td>
<td>NSCs</td>
<td>Rat brain, spinal cord</td>
<td>Intralesional grafts, N/A for cell dose</td>
<td>Chitosan channel</td>
<td>BBB test</td>
<td>Astrocytic, oligodendrocytic differentiation observed in the channels No functional improvements</td>
</tr>
<tr>
<td>Olson et al.84 2009</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Transection</td>
<td>0 Day</td>
<td>NSCs</td>
<td>Rat brain</td>
<td>Intralesional grafts, 4.76 × 10^6 cells</td>
<td>PLGA polymer scaffold</td>
<td>BBB test</td>
<td>Facilitated axonal regeneration No functional recovery</td>
</tr>
<tr>
<td>Bozkurt et al.103 2010</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Clip compression injury</td>
<td>3 Weeks</td>
<td>NSCs</td>
<td>SC of transgenic rats</td>
<td>Intralesional, 1 × 10^6 cells</td>
<td>Chitosan channel</td>
<td>BBB test</td>
<td>No functional improvements</td>
</tr>
<tr>
<td>Karimi-Abdolrez et al.41 2010</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Clip compression injury</td>
<td>6 Weeks</td>
<td>NSCs/NPCs</td>
<td>Mouse fetal brain</td>
<td>Intralesional, 4 × 10^5 cells</td>
<td>ISD Chondroitinase ABC, EGF, bFGF, PDGF-AA</td>
<td>BBB test Grid walking test Von Frey test</td>
<td>Promoted axonal integrity, plasticity of the corticospinal tract Enhanced the plasticity of descending serotonergic pathways</td>
</tr>
<tr>
<td>Kusano et al.76 2010</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Clip compression injury</td>
<td>6 Weeks</td>
<td>NPCs</td>
<td>Rat fetal brain</td>
<td>Perilesional injections (4 points around lesion cavity), 2.5 × 10^5 cells, each</td>
<td>NT-3</td>
<td>BBB test</td>
<td>Enhanced myelin formation Partial improvements of hindlimb motor</td>
</tr>
<tr>
<td>Pritchard et al.69 2010</td>
<td>Monkey</td>
<td>Thoracic</td>
<td>Hemisection</td>
<td>0 Day</td>
<td>Human NSCs</td>
<td>N/A</td>
<td>Intralesional grafts, 1 × 10^5 cells</td>
<td>PLGA polymer scaffold ISD</td>
<td>Ambulation chamber video observational neuromotor score</td>
<td>Improvements in postures and movements of leg, foot and toe</td>
</tr>
<tr>
<td>Salazar et al.43 2010</td>
<td>Mouse</td>
<td>Thoracic</td>
<td>Drop weight Contusion injury</td>
<td>1 Month</td>
<td>Human NSCs</td>
<td>Human fetal brain</td>
<td>Perilesional injections, 5 × cells</td>
<td>None</td>
<td>BMS score, Cat-Walk test, von Frey test</td>
<td>Differentiation into oligodendrocytes and neurons as well as astrocytes Showed locomotor recovery</td>
</tr>
<tr>
<td>Yamane et al.70 2010</td>
<td>Monkey</td>
<td>Cervical</td>
<td>Drop weight Contusion injury</td>
<td>9 Days</td>
<td>Human NSCs</td>
<td>Human fetal brain</td>
<td>Perilesional injection, 1 × 10^4 cells</td>
<td>ISD Galectin-1</td>
<td>Spontaneous movements, Bar grip strength, treadmill test</td>
<td>Motor function improvements</td>
</tr>
<tr>
<td>Du et al.72 2011</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Transection</td>
<td>0 Day</td>
<td>NSCs</td>
<td>Hippocampus of rat pups</td>
<td>Cord lesion site, cell dose not specified</td>
<td>PLGA scaffold LacZ, NT-3, TrkC gene modification</td>
<td>BBB test Indined-grid climbing test</td>
<td>Transfected NSCs, co-cultured with scaffold showed the smallest tissue defects at the injury site. Functional improvements observed. Limited ability of corticospinal tract axonal regeneration</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
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<th>Injury location</th>
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<th>Route and dose</th>
<th>Combination</th>
<th>Functional evaluation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng et al.²⁷</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>0 Day</td>
<td>Human NSCs</td>
<td>Human fetal NSCs</td>
<td>Either intrathecal or perilesional SC lesion, 5 × 10⁵ cells</td>
<td>None</td>
<td>BBB test</td>
<td>Functional improvements in both intrathecal and perilesional injections</td>
</tr>
<tr>
<td>Lu et al.²⁰</td>
<td>Rat</td>
<td>Cervical Thoracic</td>
<td>Hemisection Transection</td>
<td>2 Weeks</td>
<td>Rat and human NSCs</td>
<td>Rat fetal SC Human fetal SC</td>
<td>Intralesoinal grafts, N/A for cell dose</td>
<td>Fibrin matrices with growth factor cocktail</td>
<td>BBB test</td>
<td>Grafted cells differentiated into multiple cellular phenotypes. Long axon growths with abundant synapses with host cells. Improved motor functions</td>
</tr>
<tr>
<td>Amemori et al.²⁰</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Balloon-induced compression injury</td>
<td>1 Week</td>
<td>Human NSCs</td>
<td>Human fetal spinal cord</td>
<td>Intralesoional, 5 × 10⁴ cells</td>
<td>ISD</td>
<td>BBB, Plantar, walking-beam test</td>
<td>Significant motor, sensory function recovery. Showed robust cell survival and partial lesion filling</td>
</tr>
<tr>
<td>Kumamaru et al.³¹</td>
<td>Mouse</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>12 Weeks</td>
<td>NSCs/ NPCs</td>
<td>Mouse fetal brain</td>
<td>Perilesional injections (both rostral and caudal side), 5 × 10⁵ cells, each</td>
<td>None</td>
<td>Grip walk test, Footprint analysis</td>
<td>No improvement in motor function</td>
</tr>
<tr>
<td>Nemati et al.³⁰</td>
<td>Monkey</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>10 Days</td>
<td>NSCs</td>
<td>Monkey brain</td>
<td>Intralesoional injection, 1 × 10⁷ cells/kg</td>
<td>None</td>
<td>Tarlov scale and tail movements Limb and tail pinch test</td>
<td>In all scales, transplanted group was faster in recovery.</td>
</tr>
<tr>
<td>Salewski et al.³¹</td>
<td>Mouse</td>
<td>Thoracic</td>
<td>Clip compression injury</td>
<td>1 Week</td>
<td>NSCs</td>
<td>Murine embryonal stem cell</td>
<td>Perilesional injections, 5 × 10⁴ cells</td>
<td>ISD</td>
<td>BMS score, Cat-Walk test, von Frey test</td>
<td>Differentiation to oligodendrocytes. Promote remyelination and axonal function. Motor function improvements.</td>
</tr>
<tr>
<td>Cheng et al.³⁰</td>
<td>Mouse</td>
<td>N/A</td>
<td>N/A</td>
<td>1 Week</td>
<td>NSCs</td>
<td>Mouse fetal brain</td>
<td>N/A</td>
<td>None</td>
<td>BMS score</td>
<td>Improvements in BMS scores. NSC transplantation may modulate SCI-induced inflammatory responses.</td>
</tr>
<tr>
<td>Cheng et al.³⁰</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>4 Weeks</td>
<td>Human NSCs</td>
<td>Human fetal NSCs</td>
<td>Either intrathecal or perilesional SC lesion, 5 × 10⁵ cells</td>
<td>None</td>
<td>BBB test</td>
<td>Functional improvement in intrathecal group. No functional improvements in perilesional injection group</td>
</tr>
<tr>
<td>Jin et al.³¹</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>13 Weeks</td>
<td>NPCs</td>
<td>SC of transgenic rats</td>
<td>Intralesoional &amp; rostral and caudal perilesional injections, 1 × 10⁷ cells each</td>
<td>ISD Chondroitinase Neurotrophic factors</td>
<td>BBB test Grid test, Von Frey test, Bladder function test</td>
<td>Similar functional improvements between the treatment groups. Rats treated with NPC with chondroitinase and neurotrophins showed the most significant improvements in bladder function.</td>
</tr>
</tbody>
</table>

Table 1. Summary of preclinical studies using neural stem cells/neural progenitor cells in animal spinal cord injury models in literature (Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Injury location</th>
<th>SCI model</th>
<th>Transplantation time after SCI</th>
<th>Cell type</th>
<th>Cell source</th>
<th>Route and dose</th>
<th>Combination</th>
<th>Functional evaluation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kadoya et al.</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Transection</td>
<td>2 Weeks</td>
<td>NPCs</td>
<td>SC of rat and mouse</td>
<td>1–2 × 10⁶ cells</td>
<td>None</td>
<td>Staircase task</td>
<td>Cell graft survived Plus survival Positive axonal corticospinal tract regeneration and functional synaptic formation Improved forelimb function</td>
</tr>
<tr>
<td>Tashiro et al.</td>
<td>Mouse</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>7 Weeks</td>
<td>NSCs/ NPCs</td>
<td>Mouse fetal brain</td>
<td>5 × 10⁵ cells</td>
<td>Treadmill training</td>
<td>BMS score, von Frey test, Hargreaves plantar test</td>
<td>Improved motor and sensory functions</td>
</tr>
<tr>
<td>Lu et al. 2017</td>
<td>Rat</td>
<td>Cervical</td>
<td>Hemisection</td>
<td>2 Weeks</td>
<td>Human NSCs</td>
<td>Human ESCs</td>
<td>Growth factor cocktail</td>
<td>Forepaw placements on gridwalk task</td>
<td>More than a year later, forelimb motor function improved and astrocytes migrated to host tissue.</td>
<td></td>
</tr>
<tr>
<td>Nguyen et al.</td>
<td>Mouse</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>0 Day</td>
<td>Human NSCs</td>
<td>Human fetal brain</td>
<td>Perilesional injections (6 points around lesion cavity), 2.5 × 10⁵ cells, each</td>
<td>Anti-Ly6G IgG2a</td>
<td>CatWalk behavior test</td>
<td>Showed astroglial differentiation No locomotor improvements</td>
</tr>
<tr>
<td>Robinson et al.</td>
<td>Rat</td>
<td>Cervical</td>
<td>Hemisection</td>
<td>2 Weeks</td>
<td>NPCs</td>
<td>Rat spinal cord</td>
<td>Intralesional injection, 6.25 × 10⁵ cells</td>
<td>N/A</td>
<td>BBB test</td>
<td>Enhanced graft survival, neuronal differentiation Reduction of the lesion sites</td>
</tr>
<tr>
<td>Hosseini et al.</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Clip compression injury</td>
<td>3 Days</td>
<td>MSCs/ NSCs</td>
<td>Rat bone marrow/rat fetal brain</td>
<td>Perilesional injection (both rostral and caudal side)</td>
<td>MSCs</td>
<td>BBB test</td>
<td>Most functional improvement in MSCs/NSCs combined treatment group</td>
</tr>
<tr>
<td>Nori et al. 2018</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Clip compression injury</td>
<td>7 Weeks</td>
<td>Human NPCs</td>
<td>Human bone marrow somatic cells</td>
<td>Intralesional injection, 4 × 10⁵ cells</td>
<td>Chondroitinase ABC</td>
<td>BBB test, CatWalk behavioral test, von Frey test</td>
<td>Enhanced NPC survival, migration and oligodendrogenic differentiation Promoted synapse preservation, and enhanced myelination of axons Showed functional improvements</td>
</tr>
<tr>
<td>Riemann et al. 2018</td>
<td>Rat</td>
<td>Cervical</td>
<td>Clip compression injury</td>
<td>10 Days</td>
<td>NPCs</td>
<td>Rat fetal brain</td>
<td>Perilesional injection, 4 points 1 × 10³ cells each</td>
<td>None</td>
<td>BBB test, CatWalk test, Gridwalk test</td>
<td>Showed differentiation along the oligodendroglial lineage and long-term survival Reduction in inflammatory cells and markers, apoptosis Showed functional improvements</td>
</tr>
</tbody>
</table>

(Continued)
### Table 1. Summary of preclinical studies using neural stem cells/neural progenitor cells in animal spinal cord injury models in literature (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Injury location</th>
<th>SCI model</th>
<th>Transplantation time after SCI</th>
<th>Cell type</th>
<th>Cell source</th>
<th>Route and dose</th>
<th>Combination</th>
<th>Functional evaluation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenzweig et al.19 2018</td>
<td>Monkey</td>
<td>Cervical</td>
<td>Hemisection</td>
<td>2 Weeks</td>
<td>Human NSCs</td>
<td>Human embryonic spinal cord</td>
<td>Intralesional injection, 2 x 10^7 cells</td>
<td>ISD</td>
<td>Object manipulation, dimpling, and over ground manipulation</td>
<td>Graft survival over 9 months. Showed axon regeneration with synapse formation. Improved forelimb function.</td>
</tr>
<tr>
<td>Karova et al.101 2019</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Balloon-induced compression injury</td>
<td>1 Week</td>
<td>NPCs</td>
<td>Human fetal spinal cord</td>
<td>Intralesional, 5 x 10^5 cells</td>
<td>ISD</td>
<td>None</td>
<td>TNF-α downregulation, p65 NF-κB inhibition. Reduction of glial scar and cavity size.</td>
</tr>
<tr>
<td>Lien et al.80 2019</td>
<td>Rat</td>
<td>Cervical</td>
<td>Hemisection</td>
<td>2 Weeks</td>
<td>Human NSCs</td>
<td>Human ESCs</td>
<td>Perilesional injections (4 points around lesion cavity), 2.5 x 10^5 cells, each</td>
<td>Growth factor cocktail</td>
<td>None</td>
<td>No neuron migration</td>
</tr>
<tr>
<td>Li et al.109 2020</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Transection</td>
<td>0 Days</td>
<td>NSCs</td>
<td>Rat fetal brain</td>
<td>Perilesional injections (2 points rostral, caudal to lesion), 5 x 10^6 cells</td>
<td>Wnt5a stimulation</td>
<td>BBB test</td>
<td>Wnt5a-induced NSC differentiate into neurons and promote motor functional and histological recovery.</td>
</tr>
<tr>
<td>Jevans et al.90 2021</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Drop weight contusion injury</td>
<td>3 Days</td>
<td>NSCs</td>
<td>Rat enteric nervous system</td>
<td>Perilesional injection, 1 x 10^6 cells</td>
<td>Chondrotinase ABC</td>
<td>Horizontal ladder test</td>
<td>Gastrointestinal tract could be a viable option for cell source. Cotreated with Chondrotinase ABC showed highest regenerative effect with modest functional improvement.</td>
</tr>
<tr>
<td>Xue et al.110 2021</td>
<td>Mouse</td>
<td>Thoracic</td>
<td>Transection</td>
<td>0 Day</td>
<td>NSCs</td>
<td>Mouse spinal cord</td>
<td>Cord lesion site</td>
<td>Collagen nerve regeneration scaffolds</td>
<td>BMS score</td>
<td>Promotion of neuronal differentiation, synapse formation. Improved hindlimb motor function.</td>
</tr>
<tr>
<td>Liu et al.111 2022</td>
<td>Rat</td>
<td>Thoracic</td>
<td>Transection</td>
<td>0 Day</td>
<td>NSCs</td>
<td>Rat fetal brain</td>
<td>Cord lesion site</td>
<td>3D bioprinting sodium in-nateate/gelatin scaffold OLGs</td>
<td>BBB test</td>
<td>Improved hindlimb motor function. Promoted neural regeneration.</td>
</tr>
</tbody>
</table>

SCI, spinal cord injury; NPC, neural progenitor cell; N/A, not available; BBB test, Basso-Beattie-Bresnahan test; NSCs, neural stem cells; PLGA, poly-lactico-glycolic acid; SC, spinal cord; BMS, Basso mouse scale; ISD, immunosuppressant drugs; EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; ESC, embryonal stem cell; PDGF-AA, platelet-derived growth factor; MSC, mesenchymal stem cell; NT-3, neurotrophin-3; 3D, 3-dimensional; OLG, oligodentrocyte; iPSC-NP, induced pluripotent stem cell derived neural precursor cell.
differs among species. Considering that our knowledge regarding the pathophysiological mechanism of SCI is limited, there is a need for multiple animal models to properly address the delivery, efficacy, toxicity and tumorigenicity of NSCs in SCI treatments.

**STRATEGIES FOR CLINICAL TRANSITION OF NSCs**

In addition to the general consideration of clinical transition from preclinical studies, more knowledge of NSCs needs to be elucidated. The key questions that remain unanswered are as follows: (1) What is the optimal timing for treatment? (2) What are the optimal combinatory or supplementary measures for successful treatment? (3) What is the optimal route of administration? (4) How many cells should be transplanted? (5) Which cellular source should be used, with regard to efficacy, utility, and safety?

1. **Optimal Timing for NSC Treatment**

Since glial scarring is one of the major barriers to axonal growth and reintegration into neural circuits at the lesion site, cell grafting in the acute phase of SCI might be more beneficial than treatment in chronic-phase SCI. Cheng et al. tested 3 different timings of human NSCs injection (acute, subacute, and chronic) in a T10 contusion injury rat model. The subacute group showed more prominent functional improvements than the chronic group, which supports the idea of the early treatment of SCIs. Furthermore, several studies have suggested that NSCs exert beneficial effects by suppressing neuroinflammation. These findings imply that NSC transplantation may benefit the acute to subacute phase of SCI, the period during which the most active inflammatory process takes place. However, several studies have reported contradictory findings. Nguyen et al. injected human NSCs into mice immediately after T9 contusive SCI, and the donor cells showed astrogial differentiation near the lesion but failed to produce functional improvements. In contrast, Salazar et al. transplanted human NSCs into mice 1 month after T9 spinal cord contusive injury, and NSC transplanted mice demonstrated significantly improved locomotor recovery. Therefore, it is difficult to determine that which time window would be the most beneficial for transplanting NSCs after SCI, and we need more data for validation. Many preclinical studies have shown that grafted NSCs survive, migrate and integrate into the injured spinal cord, and differentiate into 3 CNS cell lineages. This suggests that data is insufficient to set specific time window for successful NSCs treatment, and more studies are required to verify the effective treatment timing for NSCs therapy.

2. **Considered Combinatory or Supplementary Measures for Successful NSC Treatment**

Since SCI is a complicated process with multiphasic cellular and molecular responses that vary over time, testing various strategies in patients with different injury time windows and situations is important along with efforts to find the best time window for the treatment of SCI patients. It is clear that a single treatment modality is not effective in SCI treatment. Several combinatory treatments to enhance grafted cell survival, migration, differentiation and axonal regeneration along with functional recovery have been studied. Synergic treatments with neurotrophic factors such as EGF, bFGF, platelet-derived growth factor, and neurotrophin-3 by implanting genes in NSCs. In addition, mixing other cells such as fibroblasts or neuroepithelial-like stem cells with transplanted NSCs to enhance structural repair, cotreatment with growth factor cocktail, and adding rehabilitation exercise also showed promising results. In chronic-phase SCI, pretreatment with chondroitinase ABC (ChABC) before transplantation of NSCs seemed to unlock scar tissue around the injury sites and produce a microenvironment conducive for NSCs regeneration. Several preclinical studies have tested the efficacy of ChABC pretreatment in chronic SCI have also shown locomotor improvements. These studies are in progress. In the future, there is a need to develop a comprehensive protocol by combining effective strategies according to the injury timeline.

One of the most promising combinatory treatments for NSCs is the use of tissue-engineered scaffolds. The use of scaffolds may act as a bridge that fills the lesion gap and helps reconnect and recover neural networks. Several scaffold types have been developed and tested in preclinical studies. Günther et al. reported that anisotropic alginate hydrogel scaffolds promote axonal regrowth and guided regenerated axons. Huang et al. had used similar scaffolds and demonstrated axonal regrowth through these scaffolds in chronic SCI after the lesion scar was removed. In addition, they have shown significant improvements in functional outcomes and electrophysiological conductivity. Nguyen et al. reported 3-dimensional aligned nanofiber-hydrogel scaffolds could be effective. Furthermore, several other types of scaffolds, such as taxol-modified collagen scaffolds, graphene oxide scaffolds, nanostructured composite scaffolds, have shown efficacy in axonal regeneration. Several studies have tested combinatory treatment with NSCs, and several types of scaffolds have reported reductions in lesion cavities, enhanced grafted

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cell survival and axonal regeneration, and functional improvements. However, the results have not been consistent in other studies. Clearly, various types of scaffolds have shown their efficacy in providing anatomical, structural, and histological framework which can guide and promote axonal regeneration. These scaffolds can replace the injured tissue gap, which would not be possible for regenerating axons to pass through and may help the axons to overpass the lesion site. Future studies are required to verify the role of scaffolds in combination with stem cell-based treatments for SCI.

3. Administration Routes

The issue of NSCs administration routes is also a complicated question that needs to be addressed. Three injection routes are possible for SCI treatment and have been tested: intrathecal, intraspinal, and intravenous. As shown in Table 1, most preclinical studies using NSCs used the intraspinal route for cell transplantation. Amemori et al. compared the intrathecal and intraspinal administration routes in an acute contusive SCI model. Both the methods facilitated functional locomotor recovery; however, cell graft survival at the lesion site was better in the intraspinal injection group, and they concluded that intraspinal transplantation would be more helpful for long-term spinal cord tissue regeneration. Nevertheless, evidence favoring intrathecal injection as an administration route is also available. Cheng et al. transplanted human NSCs into a contusive rat model of SCI both locally and distally, and significant functional recovery was observed in the distally injected group. Most researchers agree that these beneficial effects arise mainly from the paracrine effects of NSCs. Although these administration routes are clearly disadvantageous in terms of direct neuronal differentiation and tissue regeneration, the intrathecal or intravenous route is a more minimally invasive approach than intraspinal injection, and it can be performed much easier in real-world clinical settings, especially for treating patients in the acute stage of SCI. In summary, the most effective administration route for NSCs transplantation seems to be intraspinal injection. More studies to standardize intraspinal injection procedure and verify its efficacy. In addition, there is also a need for seeking the potential utility of intrathecal or intravenous cell injection in SCI treatment.

4. Number of Cells Needed for Transplantation

The number of cells that should be transplanted to obtain a positive result is another unanswered question. Preclinical studies typically provide the basis for determining the starting human dose. The dose of stem cells is dependent on their stability because effective number of stem cells should be maintained before administration. The number of transplanted cells in preclinical studies presented in the literature ranged between 1 × 10^5 and 4 × 10^6 cells per kilogram of animal body weight. Referring to Table 1, most preclinical studies NSCs have used approximately 5 × 10^6 to 1 × 10^7 cells for intraspinal cell transplantation. Yousefifard et al. suggested that higher cell doses (> 3 × 10^6 cells/kg) are optimal for transplantation. However, a few studies suggest that there is a certain threshold for the number of transplanted stem cells to survive, and there is no correlation between the number of transplanted cells and functional recovery. Further studies are needed to determine the optimal range of transplanted cell numbers, not only in animal models but also in humans.

5. Issues in Cellular Sources of NSCs

Finally, the cellular source that should be used to obtain NSCs is also an important question in stem cell treatment in SCI. Various cellular sources have been tested. Graft survival, neuronal differentiation and functional recovery have been demonstrated in most preclinical studies where allogeneic NSCs from the fetal brain and spinal cord, as well as human NSCs were transplanted in mouse and rat models. No specific NSC line showed significant comparative advantage over others. This means that all of NSCs from different cellular sources and lineages should be explored further for their efficacy and safety.

Tumorigenicity and immune rejection are the 2 most important concerns regarding cellular sources. In terms of tumorigenicity, there are numerous experimental design parameters to consider, including the choice of animal model, study duration, route of administration, number of cells tested, positive control selection, and the definition of a positive result. The selected animal model should allow sufficient survival of the stem cell product to enable the assessment of potential tumorigenicity. Therefore, immunocompromised rodents are frequently used for this purpose. Likewise, the study duration should be sufficient to permit the detection of potential tumors. Tumorigenicity studies lasting 9–12 months have been requested by regulatory agencies. To date, reports of tumor formation in NSCs treatments in animal models of SCI are scarce. However, Salewski et al. reported that primitive NSCs derived from ESCs could be transformed into teratomas. Tumorigenicity potential may also reside in NSC lineages and should be closely monitored in future studies.

Ready-made NSCs, which are usually obtained from allogene-
neic brains or spinal cords, have been used in most preclinical studies.40,41,72,74-78,102-104 This may be due to limitations in time and autologous source tissue to obtain a sufficient number of NSCs for transplantation. Human NSCs were tested in several animal models with promising results.39,70,71,77,80,83,86,98,101 Long-term survival of grafted cells is necessary for locomotor functional recovery.22 For graft survival, either immunosuppressants were administered after transplantation or nude mice and nude rats were used. Such conditioning for experimental purposes is possible at a preclinical level. However, the use of immunosuppressants in human patients with acute or subacute stage SCI might be risky. SCIs are usually combined with severe multiple traumatic injuries affecting multiple organs and musculoskeletal regions and using immunosuppressants in such conditions poses high risk for sepsis. Transplanted NSCs have paracrine effects which help SCI recovery, even in the absence of graft survival.25 Nonetheless, considering that grafted cell survival with neuronal differentiation and integration into the host neuronal network would be a favorable long-term outcome, issues regarding immune rejection should be thoroughly studied. The immune rejection issue has brought iPSCs into the spotlight. With the advantage of avoiding ethical issues, autologous iPSCs have become one of the most attractive cell sources for human NSCs. However, a vast number of studies are required to ensure the efficacy, feasibility, and safety of iPSCs in SCI treatment.

CLINICAL TRIALS USING NSCs

In contrast to the relative abundance of preclinical studies on NSCs transplantation in animal models of SCI, clinical trials of NSCs treatment in patients with SCI, which have been published in the literature have been scarce (Table 2). It is encouraging that several studies reported its procedural safety as well as partial success in functional recovery after NSCs transplantation in patients with SCI.105-108 However, since the number of enrolled patients was small, and only patients in the subacute (within 1 week to 6 months from the injury) and chronic (over 6 months from the injury) phases of SCI were included in most trials, it is quite difficult to conclude therapeutic efficacy of NSCs, especially in acute phase SCI.

The paucity of clinical trials implies difficulty in translation from bench to bedside in SCI research. The fundamental limitation of translational research is the anatomical difference between experimental animal models and humans. In addition, stem cell therapy in animal models had shown inconsistent results regarding functional recovery. The therapeutic potential of NSCs in SCI treatment was observed, but the absence of a certain, reliable modality resulted in numerous exploratory studies that were far from standardization. Consequently, practical questions such as the location and route of cell transplantation, adequate number of transplanted cells, assessment tools and protocols and variability in NSCs generation are still unknown. Furthermore, real-world problems, such as setting a reliable and safe logistic to obtain, store and deliver NSCs for clinical use,

Table 2. Summary of published clinical trials using neural stem cells in spinal cord injury patients in literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Clinical phase</th>
<th>Injury location</th>
<th>Treatment timing</th>
<th>Cell type</th>
<th>Cell source</th>
<th>Administration route</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moviglia et al.107 2009</td>
<td>Argentina</td>
<td>Phase I</td>
<td>Cervical/thoracic</td>
<td>Chronic*</td>
<td>Autologous NSCs</td>
<td>Human fetal brain</td>
<td>Feeding artery infusion</td>
<td>Functional recovery was shown in 5/8 patients.</td>
</tr>
<tr>
<td>Shin et al.111 2015</td>
<td>South Korea</td>
<td>Phase I/II</td>
<td>Cervical</td>
<td>22–213 days after SCI</td>
<td>hNSPCs</td>
<td>Human fetal brain</td>
<td>Intralesional injection</td>
<td>Partial improvements in sensorimotor function</td>
</tr>
<tr>
<td>Ghabrial et al.115 2017</td>
<td>USA</td>
<td>Phase II</td>
<td>Cervical/thoracic</td>
<td>At least 4 months after SCI</td>
<td>NSCs (HuCNS-SC)</td>
<td>Human fetal brain</td>
<td>Intralesional injection</td>
<td>Improvements in overall mean functional outcomes measures</td>
</tr>
<tr>
<td>Levi et al.112 2018</td>
<td>USA</td>
<td>Phase I</td>
<td>Cervical/thoracic</td>
<td>4–24 months after SCI</td>
<td>NSCs (HuCNS-SC)</td>
<td>Human fetal brain</td>
<td>Intralesional injection</td>
<td>A manual injection technique are safe and feasible</td>
</tr>
<tr>
<td>Curtis et al.113 2018</td>
<td>USA</td>
<td>Phase I</td>
<td>Thoracic</td>
<td>1–2 years after SCI</td>
<td>NSCs (NSI-566)</td>
<td>Human fetal spinal cord</td>
<td>Intralesional injection</td>
<td>Can be transplanted safely</td>
</tr>
<tr>
<td>Levi et al.116 2019</td>
<td>USA</td>
<td>Phase II</td>
<td>Cervical</td>
<td>4–24 months after SCI</td>
<td>NSCs (HuCNS-SC)</td>
<td>Human fetal brain</td>
<td>Intralesional injection</td>
<td>Motor functional gains in the treated participants</td>
</tr>
</tbody>
</table>

HuCNS-SC, human fetal-derived central nervous system neural stem cell; NSCs, neural stem cells; NSI-566, NSI-566 cell line human spinal-cord-derived neural stem cell; hNSPCs, human neural stem/progenitor cells; SCI, spinal cord injury; USA, United States of America.

*Specific treatment timing after spinal cord injury was not described.
recruiting patients, and running clinical trials, would be expensive. Several ongoing clinical trials have been attempted despite of hurdles mentioned above. However, extensive efforts to find major breakthroughs in SCI treatment are still needed.

CONCLUSION

NSCs are self-renewing and multipotent stem cells that can differentiate into neural lineage cells. For the past 2 decades, many preclinical studies have tested efficacy and safety of NSCs in several animal models of SCI. Successful neuronal differentiation, replacing damaged neural tissue, and functional improvement were observed in several studies. In addition, NSCs secrete neurotropic factors that help protect or regenerate injured spinal cord. In preclinical level, transplantation of NSCs has been proved as a promising therapeutic approach for SCI treatment. However, some of clinical trials of NSCs did not show enough efficacy as expected. These results suggest that a need for further assessment, and the exact mechanism by which NSCs transplantation improves outcomes after SCI should be explored further.

For future perspective, further data such as treatment benefits in terms of neuronal regeneration and functional recovery, adjustments in dose and administration period, optimal injection route, safety, and the most promising cell source for obtaining NSCs should be acquired and verified through future studies. Moreover, matching preclinical animal models and human SCI is another major hurdle to overcome. Finally, it is also important to highlight that a single treatment modality alone may not be sufficient to treat SCI. In addition to cellular transplantation, combinatory therapies such as neurotrophic and growth factors, the use of scaffolds, and neurorehabilitation may be necessary. Their optimal combination and efficacy should also be verified in future studies. Despite these uncertainties, numerous preclinical studies and clinical trials have reported promising results with NSCs treatment for SCI. We are convinced that NSCs have a potential to make a major breakthrough in SCI treatment in the near future.

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REFERENCES


Therapeutic Approaches Targeting Vascular Repair After Experimental Spinal Cord Injury: A Systematic Review of the Literature

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Traumatic spinal cord injury (SCI) disrupts the spinal cord vasculature resulting in ischemia, amplification of the secondary injury cascade and exacerbation of neural tissue loss. Restoring functional integrity of the microvasculature to prevent neural loss and to promote neural repair is an important challenge and opportunity in SCI research. Herein, we summarize the course of vascular injury and repair following SCI and give a comprehensive overview of current experimental therapeutic approaches targeting spinal cord microvasculature to diminish ischemia and thereby facilitate neural repair and regeneration. A systematic review of the published literature on therapeutic approaches to promote vascular repair after experimental SCI was performed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards. The MEDLINE databases PubMed, Embase, and OVID MEDLINE were searched using the keywords "spinal cord injury," "angiogenesis," "angiogenesis inducing agents," "tissue engineering," and "rodent subjects." A total of 111 studies were identified through the search. Five main therapeutic approaches to diminish hypoxia-ischemia and promote vascular repair were identified as (1) the application of angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery. There are different therapeutic approaches with the potential to diminish hypoxia-ischemia and promote vascular repair after experimental SCI. Of note, combinatorial approaches using implanted biomaterials and angiogenic factor delivery appear promising for clinical translation.

Keywords: Spinal cord injury, Blood-spinal cord barrier, Vascular injury, Spinal cord regeneration, Biocompatible materials, Therapeutics

INTRODUCTION

Traumatic spinal cord injury (SCI) is one of the leading causes of disability and a major burden for healthcare systems. Current therapeutic strategies are limited to acute medical and surgical management and rehabilitation, as there are no therapies available to promote spinal cord regeneration.1

SCI results from a primary mechanical injury which is amplified by a secondary injury cascade to result in loss or disruption of neural elements and vascular structures. The traumatic vascular disruption in the injured spinal cord plays a key role in modulating secondary injury development by promoting local blood-spinal cord barrier (BSCB) breakdown, inflammation, and neuronal cell death as well as creating a hypoxic-ischemic
environment which can spread to initially intact regions. The characterization of endogenous vascular regeneration following SCI-induced vascular injury has been the goal of some recent experimental studies, conducted mostly in rodents. Results show that vascular regeneration occurs spontaneously after SCI, following a definite time schedule – this regeneration process is however deficient and, due to an increased BSCB-permeability, even potentially detrimental to preserved neural tissue. But even if this new vasculature is only partially functional, it provides guidance for regenerating axons and is thereby crucial for neural regeneration. To find a way to improve vascular repair after SCI and restore a functional blood supply, thereby supporting neural regeneration, is one of the major challenges in experimental SCI research.

A multitude of experimental therapeutic approaches have been applied to restore functional vascularization, consisting of (1) the application of angiogenic factors, (2) genetic engineering therapy, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery.

The aim of this systematic review is to rigorously summarize and evaluate the present state of research in this emerging field. We first outline a focused overview of SCI pathophysiology with an emphasis on vascular injury and endogenous vascular repair and then shift to an examination of current experimental therapeutic approaches to promote vascular repair with the prospect of future translation of innovations into clinical patient care.

MATERIALS AND METHODS

1. Approach to the Systematic Literature Review

We performed a systematic, qualitative review of the literature, by screening the established MEDLINE databases PubMed, Embase, and OVID MEDLINE. The main search terms included “spinal cord injury,” angiogenesis,” “angiogenesis inducing agents,” and “tissue engineering,” in combination with “rodent subjects.” The search included no time limit. Articles in English were included, meeting the following criteria: experimental research, original studies, rodent subjects, therapeutic intervention, and focus on vascular injury and repair. The systematic literature search was conducted by one researcher from June 2021 to July 2021 and from May 2022 to June 2022. Data analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A total of 614 articles were selected for review, of which 475 were excluded after screening as a result of not meeting the inclusion criteria. An additional 30 articles were excluded due to not meeting the inclusion criteria after full-text assessment for eligibility. For qualitative synthesis 111 articles were assessed in detail and included in this publication (Fig. 1).

2. Relevant Experimental Therapeutic Approaches According to the Literature Search

According to the systematic literature search, 5 main categories of therapeutic approaches to promote vascular repair in experimental SCI research were identified: (1) angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery (Table 1).

RESULTS

1. PART 1: Pathophysiology of Traumatic SCI With Emphasis on Vascular Injury And Repair

1) Pathophysiology and its progression following SCI

SCI is characterized as a sudden mechanical force impacting the spinal cord, e.g., following a fall, vehicle accident, or sports-related injury. It is commonly comprised of both contusion and compression injury causing direct cell death, axonal shearing, and disruption of the microvasculature with traumatic bleeding. This primary injury is not accessible to treatment and is immediately followed by a sustained secondary injury cascade. This secondary injury spreads to formerly unaffected regions, leading to further spinal cord damage with the consequences of demyelination and axonal dieback. The developing secondary injury can be divided into acute (first 48 hours), subacute (48 hours–14 days), intermediate (14 days to 6 months) and chronic phases (> 6 months) (Fig. 2).

2) Time course of BSCB disruption and restitution following SCI

The BSCB protects the spinal cord, as part of the central nervous system (CNS), from the periphery and maintains a homeostatic environment. The BSCB, formed by endothelial cells (ECs), astrocytic foot processes and pericytes as well as a basal lamina together with adjoining neurons comprise the neurovascular unit (NVU) (Fig. 2A). The unique cell-cell-contacts between ECs containing CNS-specific tight junctions (TJs) provide an immune privilege to the spinal cord compared to the periphery, restricting the passage of neurotoxic molecules and inflammatory cells.

Following the primary injury, a localized direct disruption of the NVU damages the microvasculature directly surrounding...
the injury site: Disruption of the protective cell-cell-contacts leads to altered cell permeabilization and consequent oedema formation, causing increased apoptotic and necrotic cell death\textsuperscript{14,16,17} (Fig. 2B). These permeability changes not only lead to electrolyte influx and oedema, but to an influx of inflammatory cells (lymphocytes, macrophages, and neutrophils), as well as cytokines (tumor necrosis factor-\(\alpha\), interleukin [IL]-1\(\beta\), IL-5) and vasoactive peptides. This immune response, commencing within the first minutes postinjury, leads to further oedema formation and thus tissue compression, resulting in further injury development spreading farther from the primary injury site\textsuperscript{2,15,18}.

These events further destabilize the BSCB and lead to a release of reactive oxygen species, resulting in the dysfunction of the NVU in formerly unharmed regions\textsuperscript{2,3,14}. Correlating with these mechanisms, the first peak in BSCB-permeability in the penumbra zone is reached 24-hour postinjury, followed by a smaller peak after 3–5 days\textsuperscript{4,5}.

Most of the BSCB function is believed to be reinstated after 14 days\textsuperscript{4,19} (Fig. 2C). However, experimental studies show that the permeability for small molecules is increased up to the chronic phase of SCI, for as long as 56-day postinjury\textsuperscript{6}.

3) Endogenous revascularization after SCI

The major form of vascular regeneration in the spinal cord is known to be angiogenesis, with a smaller part displayed by postnatal vasculogenesis. Angiogenesis is defined by the formation of blood vessels out of pre-existing vessels, whilst vasculogenesis describes the formation of new vessels\textsuperscript{20}. The hypoxic milieu after SCI results in the release of angiogenic factors from the injury site. Endogenous revascularization following SCI is
Fig. 2. (A-C) Pathophysiology of spinal cord injury and the neurovascular unit in health and its disruption. SC, spinal cord; BSCB, blood – spinal cord barrier; EC, endothelial cells; AC, astrocytic foot processes; PC, pericyte; BL, basal lamina; TJ, tight junction; ROS, reactive oxygen species; h, hours; d, days; w, weeks; m, months.
4) Regenerative potential facilitated by vascular repair after SCI

As the spinal cord remains in a state of chronic hypoxia and ischemia postinjury, reinstatement of a steady tissue perfusion would be desirable. This was shown by previous research indicating that neovascularization is crucial for axon regeneration, as these were shown to grow along blood vessels. This suggests that the developing vasculature guides axonal sprouting after injury. However, the increased permeability for molecules otherwise excluded from the selective CNS environment might provide a unique chance for therapeutic intervention, with a potential window of opportunity displayed over the first days postinjury.

To address this multifaceted pathophysiology, several aspects of SCI must be taken into account to allow for tissue regeneration: Inhibition of the inflammatory response and sufficient perfusion might limit the secondary injury, while prevention of the glial scar formation could enable neural regeneration. Therefore, combinatorial approaches accounting for these mechanisms together in the adequate timespan might be promising for spinal cord repair.

2. PART 2: Experimental Therapeutic Approaches To Promote Vascular Repair

According to the systematic literature search, several experimental therapeutic approaches promising to diminish hypoxia and improve spinal cord microvasculature after SCI exist. In summary, 5 categories of experimental therapy were identified: (1) delivery of angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery. In the following section of this study, we aim to provide a comprehensive overview of the literature in this field, comparing and discussing the most promising approaches for clinical translation.

Fig. 3. Therapeutic approaches for vascular repair after experimental spinal cord injury: (1) angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery.
1) Angiogenic factors

Many different therapeutic agents evoking an angiogenic answer, either directly or indirectly, have been investigated in experimental SCI models, often in combination with the implantation of biomaterials. In the following, we give an overview of different angiogenic factors and their previous experimental use in SCI research (Fig. 4A).

The therapeutic effects of vascular endothelial growth factor (VEGF) in SCI have been variable. VEGF-A is used in many studies and is a promising growth factor that binds to the tyrosine kinase receptors (VEGFRs) 1 and 2, resulting in the proliferation of ECs and angiogenesis. VEGF-A may also have neurotrophic, neuroprotective, and neuroproliferative effects. A common application of VEGF-A in experimental SCI is the direct injection into the lesion site which results in increased blood vessel density and blood vessel diameter. This effect has been confirmed in studies of controlled release of VEGF from biomaterials, such as gel foam. On the downside, increased BSCB-permeability was observed after application of VEGF-A indicating the growth of non- or only partially functional blood vessels. Changes in vessel architecture, resulting in tumor-like blood vessels, were described in human studies.

To improve the angiogenic and neurotrophic effect through the application of VEGF, a release from biomaterials in combination with other growth factors such as fibroblast growth factor-2 (FGF2), angiopoietin 1 and FGF2 or brain-derived
neurotrophic factor\(^{34}\) was explored, also resulting in increased blood vessel density and associated localization of mature oligodendrocytes and axons.

FGF2 has also been frequently applied in experimental SCI. FGF2 was found to be highly overexpressed after SCI\(^ {35}\) and FGF2 is known to play a role in proliferation, differentiation and BSCB-integrity.\(^ {36,37}\) The application of FGF2 via biomaterials has been shown to increase the number of blood vessels,\(^ {38-40}\) whereas no significant vascular changes were observed when FGF2 was infused at the injury site.\(^ {41}\)

Further angiogenic factors that were previously tested for application in experimental SCI are hepatocyte growth factor (HGF) and the whole blood concentrates platelet-rich plasma (PRP) and platelet-derived wound healing formula (PDWHF). The number of blood vessels has been shown to increase after the application of activated PRP,\(^ {42}\) PDWHF alone, or PDWHF in combination with nerve growth factor and of HGF.\(^ {43-44}\)

Apart from these often-applied factors, other factors such as hormones, especially oestrogen,\(^ {45}\) enzymes,\(^ {46}\) and a multitude of anti-inflammatory substances\(^ {47}\) listed in (Fig. 4A) also showed potential to induce angiogenesis or to increase BSCB-integrity following SCI.

2) Genetic engineering

Genetic engineering is not widely used in experimental SCI but was shown to hold the potential to increase vascular repair and functional outcome after SCI.\(^ {48-51}\) (Fig. 4B). Proofs-of-concept were brought forward in experiments using RNAs like micro-RNA-210,\(^ {49}\) micro-RNA-126 contained in exosomes\(^ {49}\) and X-inactive specific transcript-RNA.\(^ {50}\) The endogenous overexpression of VEGF using viral vectors also increased the number of blood vessels at the injury site.\(^ {51,52}\) The combination of VEGF165 and Ang-1 using an adeno-associated viral vector furthermore decreased the BSCB-permeability at the injury site.\(^ {53}\) Therefore, genetic engineering could become a promising approach to support vascular repair after experimental SCI.\(^ {54}\)

3) Physical stimulation

As the only noninvasive therapeutic approach, physical stimulation was also shown to increase angiogenesis and functional outcome after experimental SCI. Methods under investigation include water treadmill training,\(^ {52}\) low-energy extracorporeal shock wave therapy,\(^ {53}\) whole-body vibration,\(^ {54}\) chronic mild hypoxia,\(^ {55}\) and electric stimulation (Fig. 4C). Especially water treadmill training seems to improve the regeneration of functional blood vessels and improve functional outcome after SCI.\(^ {52}\) Using low-energy extracorporeal shock wave therapy, not only increased vessel density but also enhanced functional outcomes suggesting that the regenerative potential is higher than the risk of further damage to the spinal cord. Electrical stimulation has made tremendous progress as experimental therapy in both preclinical and clinical studies, although only few studies focus on the evaluation of angiogenic effects. The application of transspinal direct current stimulation increases the blood temporarily and is able to stimulate cell proliferation and migration.\(^ {56}\) Another experimental therapeutic approach is the induction of chronic mild hypoxia after SCI. The induction of mild hypoxia results in vascular remodelling, with endothelial proliferation and vascular expansion being more pronounced in the white matter. Interestingly, newly formed blood vessels grow towards neurons and show the upregulation of TJ proteins, indicating the enhanced formation of functional blood vessels.\(^ {57}\) These results are promising to increase angiogenic repair after SCI, but further research needs to address the effect of these approaches in the intermediate and chronic injury phase.

4) Cell transplantation

Cell transplantation is widely used after experimental SCI. Stem cells of different origins can result in a significant increase in angiogenesis and have previously been injected, infused, or implanted following SCI with the result of potently increasing the angiogenic response and improving functional outcome (Fig. 4D). Endothelial progenitor cells (EPCs),\(^ {57}\) bone marrow mesenchymal stem cells,\(^ {58}\) bone marrow adipose-derived stem cells,\(^ {59}\) human umbilical cord blood stem cells,\(^ {60}\) neural stem cells (NSCs),\(^ {61}\) amniotic mesenchymal stem cells,\(^ {62,63}\) human-induced pluripotent stem cells,\(^ {64,65}\) peripheral blood stem cells,\(^ {66}\) lamina propria-derived olfactory ensheathing cells, olfactory bulb-derived ensheathing cells,\(^ {67}\) and mesenchymal stem cells (MSCs)\(^ {68}\) increase angiogenesis when applied after SCI by expressing a wide range of growth factors and modulating the microenvironment. The effect of these cell types is shown in Table 2.

As not all implanted cells survive the hypoxic environment at and around the injury site, cell-based therapies to date can only unfold a fraction of their potential.\(^ {69}\) To overcome this limitation, other strategies rely on indirectly utilizing the therapeutic potential of stem cells. Especially the isolation of exosomes from different stem cells and their injection after experimental SCI showed similar results in terms of angiogenesis and functional outcome.\(^ {70-72}\) Exosomes derived from many different cell types result in increased angiogenesis after injection. Amongst
these are NSC-derived exosomes,70 exosomes derived from human placenta-derived MSCs,71 and mesenchymal stromal cells-derived exosomes.72

Another promising strategy is the combinatorial release of stem cells via biomaterials to enhance cell survival at the injury site by modulating the environment and by providing guidance for the regenerating tissue.69,73

5) Biomaterials carrying various factor delivery

Biomaterials are materials engineered to interact with biological tissue and can be divided into natural materials sourced from plants or animals, synthetic materials and hybrid biomaterial combinations.10 Many different biomaterials improve angiogenesis when implanted in combination with stem cells or angiogenic factors or even without concomitant application of other therapeutics. The implantation of biomaterials alone already holds the potential to support the ingrowth of blood vessels into the lesion site. This angiogenic potential was shown using many different biomaterials, such as a reduced graphene oxide scaffold,74 an oxygen-generating hydrogel scaffold,75,76 a nanofiber-hydrogel composite,77 "NeuroGel,"78 an aligned fibrin hydrogel,79 and a collagen type I scaffold80 (Fig. 4E). Biomaterials can be combined with other therapeutics at will, such as angiogenic factors and/or stem cells to potentiate their regenerative potential.

Both natural and synthetic biomaterials were previously used successfully in animal studies to promote vascular repair after SCI with different advantages and disadvantages. Natural biomaterials are often intrinsically biodegradable and therefore

| Table 2. Study overview of experimentally transplanted cells to promote vascular repair after experimental spinal cord injury (SCI) |
|---|---|---|---|---|
| Species | SCI model | Method | Outcome | References |
| Rat | T10 Contusion | EPCs | Increased axonal and blood vessel regeneration with functional improvement. | Wang et al.57 (2018) |
| Rat | T10 Contusion | BMSCs overexpressing VEGF | Increased axonal and blood vessel regeneration with functional improvement. Increased VEGF protein expression. | Liu et al.58 (2020) |
| Rat | T8, 9 Compression | ADSCs | Increased blood vessel regeneration, vascular branching, and axonal regeneration. Increased formation of functional blood vessels, which are associated with blood vessels. Functional improvement. | Menezes et al.107 (2020) |
| Rat | T10 Contusion | HUCBCs | Increased blood vessel regeneration with functional improvement. | Ning et al.60 (2013) |
| Rat | T8 – 10 Contusion | NSCs | Increased blood vessel regeneration, VEGF protein expression, and remyelination with functional improvement. | Li et al.61 (2014) |
| Rat | T9 Contusion | AMSCs | Increased blood vessel regeneration, axonal regeneration, VEGF protein expression, and functional improvement. The BSCB – disruption was reduced at 7 days indicating the regeneration of functional vessels. | Zhou et al.62,63 (2016, 2020) |
| Rat | T10 Contusion | hiPSCs | Increased blood vessel regeneration, myelination, and axonal regeneration with functional improvement. Transplanted cells differentiated into astrocytes, oligodendrocytes, and neurons which integrated with the host neural circuitry. | Nori et al.64 (2011) |
| Mice | T9 Contusion | PBSCs | Increased blood vessel regeneration, myelination, and axonal regeneration with functional improvement. | Takahashi et al.66 (2016) |
| Rat | C3, 4 Dorsolateral crush | LP and OB OECs | Increased axonal and blood vessel regeneration. The motor function was not assessed. | Richter et al.67 (2005) |
| Rat | T8 Contusion | MSCs | Increased axonal and blood vessel regeneration with no functional improvement. | Kumagai et al.68 (2013) |

EPC, endothelial progenitor cell; BMSC, bone mesenchymal stem cell; VEGF, vascular endothelial growth factor; ADSC, adipose-derived stem cell; HUCBC, human umbilical cord blood stem cell; NSC, neural stem cell; AMSC, amniotic mesenchymal stem cell; hiPSC, human-induced pluripotent stem cell; PBSC, peripheral blood stem cell; LP OEC, lamina propria-derived olfactory ensheathing cell; OB OEC, olfactory bulb-derived ensheathing cell; MSC, mesenchymal stem cell.
useful to modify the delayed release of angiogenic factors or cells.\textsuperscript{81} Synthetic biomaterials, unless modified accordingly, are nondegradable and guarantee more structural and long-lasting stability as well as reduced batch-to-batch variance. For implantation and combination with factor delivery, they can be sterilized and chemically modified to allow for an optimal release profile\textsuperscript{10,81} (Table 3). Due to their high modifiability, both natural and synthetic biomaterials can be adapted to provide optimal release kinetics of incorporated factors at a defined location.\textsuperscript{10} Release kinetics can be modified by using the intrinsic degradation rate of the biomaterial itself\textsuperscript{82} or noncovalent interactions between the incorporated therapeutics and the biomaterial.\textsuperscript{40}

After implantation or injection, biomaterials can occupy the space of a posttraumatic cavity and provide a cell-friendly environment with reduced infiltration of inflammatory cells.\textsuperscript{77,81} Therefore, biomaterials are often used in combination with stem cells, which highly depend on such an environment.\textsuperscript{83}

Exemplary, the number and density of blood vessels could be increased after implantation of an oligopolyethylene-glycol-fumarate-hydrogel combined with Rapamycin and Schwann-cells,\textsuperscript{83} of a prevascularized poly-L-lactic acid (PLLA–polylactide-co-glycolide acid (PLGA) scaffold containing dental pulp stem cells,\textsuperscript{84} a fibrous porous silk scaffold containing human umbilical vein ECs,\textsuperscript{85} a hydrogel PLGA-scaffold containing NSCs and ECs,\textsuperscript{73} a gelatine sponge containing MSCs,\textsuperscript{86} and a PLGA-scaffold containing human MSCs.\textsuperscript{86} The implantation of a hydrogel containing NSCs and EPCs also increased the formation of blood vessels inside the scaffold.\textsuperscript{87} These findings show the great potential of combinatorial approaches using biomaterials containing angiogenic factors and/or stem cells of different types.

The application of biomaterials to promote vascular repair after SCI varies in time, location, and mode of application in the analysed studies (Table 3, Supplementary Table 1). In nearly all studies showing vascular changes, biomaterials are applied directly after induction of the injury with monitoring for up to 8 months.\textsuperscript{30,32-34,38-40,43,44,76,78,80,82-104} Only one study reports an increased blood vessel density after the implantation of a nanofiber-hydrogel composite 3 days after injury.\textsuperscript{77}

Table 3. Study overview of experimentally used biomaterials to promote vascular repair after experimental spinal cord injury (SCI)

<table>
<thead>
<tr>
<th>Species</th>
<th>SCI model</th>
<th>Method</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural biomaterials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Lateral hemisection</td>
<td>NSCs, EPCs, hydrogel</td>
<td>NSCs and blood vessels infiltrate the hydrogel functional improvement</td>
<td>Marrotte et al.\textsuperscript{87} (2021)</td>
</tr>
<tr>
<td>Rat</td>
<td>Lateral hemisection</td>
<td>AFG/isAP hydrogel</td>
<td>Increased axonal regeneration with more myelinated axons, blood vessel regeneration at the lesion site with a larger diameter, increased vessel density, blood vessels and axons colocalized, functional improvement</td>
<td>Man et al.\textsuperscript{101} (2021)</td>
</tr>
<tr>
<td>Rat</td>
<td>Compression injury</td>
<td>CORM-2-lipid nanoparticles</td>
<td>Increased formation of functional blood vessels and reduced BSCB-permeability at 1 day postinjury, functional improvement</td>
<td>Joshi et al.\textsuperscript{76} (2020)</td>
</tr>
<tr>
<td>Synthetic biomaterials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Lateral hemisection</td>
<td>rGO scaffold</td>
<td>Regeneration of functional blood vessels growing inside the scaffold, association with regenerating axons</td>
<td>López-Dolado et al.\textsuperscript{74} (2016)</td>
</tr>
<tr>
<td>Rat</td>
<td>Transection</td>
<td>DPSCs PLLA/PLGA-scaffold</td>
<td>Increase in axonal regeneration with myelin sheaths and angiogenesis at the injury site, vessel density increased in the rubrospinal tract, spinothalamic tract, dorsal column, and spinocerebellar tract, but not in corticospinal tract, functional improvement</td>
<td>Guo et al.\textsuperscript{84} (2020)</td>
</tr>
<tr>
<td>Rat</td>
<td>Contusion</td>
<td>VEGF, Ang-1, FGF2, PLGA-microspheres</td>
<td>Increased angiogenesis and neural regeneration with axons and mature oligodendrocytes mostly associated with blood vessels, functional improvement</td>
<td>Yu et al.\textsuperscript{33} (2016)</td>
</tr>
</tbody>
</table>

NSC, neural stem cell; EPC, endothelial progenitor cell; AFG, aligned fibrin hydrogel; fSAP, functionalized self-assembling peptides derived from VEGF and brain-derived neurotrophic factor; CORM-2, carbon monoxide-releasing molecule-2; BSCB, blood-spinal cord barrier; rGO, reduced graphene oxide; DPSC, dental pulp stem cell; PLLA, poly-L-lactic acid; PLGA, polylactide-co-glycolide acid; VEGF, vascular endothelial growth factor; Ang-1, angiopoietin-1; FGF2, fibroblast growth factor 2.
als are mostly applied at the injury site as scaffolds replacing the lesion after implantation or injection with only a few hydrogels being implanted on top of the injured spinal cord or injected systemically.

POTENTIAL FOR CLINICAL IMPLEMENTATION

Taken together, all 5 experimental approaches discussed in this review show the potential to improve vascular repair and angiogenesis. The application of angiogenic factors (1) is a well-studied approach. Especially growth factors like VEGF have shown a promising potential to regenerate functional blood vessels. Genetic engineering (2) allows for direct activation of the endogenous expression of VEGF and other growth factors. Even if it is not applied as frequently as other approaches after SCI, it holds the potential to regenerate functional blood vessels. As physical stimulation techniques (3) also displayed the ability to induce vascular repair, they might be a useful supplementary therapy in a clinical setting as soon as intensive rehabilitation is possible. Cell transplantation (4) is another promising strategy to regenerate functional blood vessels after traumatic SCI, especially as they can be taken from a variety of sources. Their potential is inhibited by the toxic environment, which needs to be overcome to allow the cells to integrate at the injury site. The implantation of cells still poses a promising approach when combined with the implantation of biomaterials (5). These materials can be taken from many sources and are easily modifiable. Some have an inherent angiogenic potential and are biodegradable. As they can be modified to release incorporated therapeutics in the desired time frame at defined locations and provide guidance for regenerating axons, these combinatorial approaches seem promising for future research and potential clinical implementation. But before implementing promising biomaterials into clinical trials, several questions need to be addressed. For most biomaterials, especially when integrated in a combinatorial approach, the exact degradation time in SCI is neither known for humans nor for animals. As degradation byproducts might cause immunological reactions, biomaterials need to be actively characterized in preclinical and clinical studies. Furthermore, most of the biomaterials summarized are solid materials filling a transection or hemisection injury, but contusion SCI is most common clinically. This and the overall limited comparability from controlled animal models into the individual human SCI makes it difficult to translate the results of preclinical studies into the design of clinical trials and shows the need for using clinically relevant SCI animal models with contusion or compression injuries.

Before applying these approaches in a clinical setting, future research needs to evaluate the ideal combinations to accurately address the multifaceted pathophysiology and the time course of BSCB de- and regeneration to allow for the regeneration of functional blood vessels as a basis for neural regeneration.

CONCLUSION

SCI is characterized by the injury of both neural and vascular components and results in extensive tissue loss. The disruption of the vasculature and its insufficient regeneration with a prolonged state of BSCB-permeability exacerbate the primary injury by amplification of secondary injury mechanisms. To restore a functional vasculature to prevent neural loss and to promote neural regeneration is one of the most important challenges in SCI research. Several therapeutic approaches show an improved vascularization after SCI, like the application of angiogenic factors, genetic engineering, physical stimulation, cell transplantation, and biomaterials carrying various factor delivery. Combinatorial approaches, like implanted biomaterials with the ability to release angiogenic factors or therapeutic cells in a temporally and spatially controlled manner seem most promising to restore functional vasculature and to be translatable into clinical patient care in the future.

NOTES

Supplementary Material: Supplementary Table 1 can be found via https://doi.org/10.14245/ns.2244290.145.

Supplementary Table 1. Complete list of studies using biomaterials to promote vascular repair after spinal cord injury identified by the systematic literature search.

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Targeting Vascular Repair After Spinal Cord Injury

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<table>
<thead>
<tr>
<th>Species</th>
<th>SCI model</th>
<th>Method</th>
<th>Time &amp; duration (day)</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Wistar, M</td>
<td>C6 Lateral</td>
<td>rGO scaffold</td>
<td>Acute (0)</td>
<td>Morphology: Functional blood vessels were observed in inner parts of the scaffold at 30 days; blood vessels were identified in close relation with regenerated axons inside the scaffold at 30 days; no significant alterations indicating toxicity Function: / Survival: 10, 30 days</td>
<td>López-Dolado et al. (2016)</td>
</tr>
<tr>
<td>Rat, Wistar, F</td>
<td>T8, 9 Transection</td>
<td>Polyethylene glycol (PEG 600), mechanical microconnector system (mMS)</td>
<td>Acute (0) and chronic (5)</td>
<td>Morphology: After acute implantation of mMS blood vessels in close proximity with axonal structures could be detected in the mMS lumen at 5 wk; after scar resection and PEG 600 implantation the injury site was invaded by endothelial cells Function: Significant improvement at 10 and 30 days with mMS (BBB) and with PEG (mBBB) Survival: 30 days (mMS), 39 wk (PEG)</td>
<td>Brazda et al. (2016)</td>
</tr>
<tr>
<td>Rat, Long Evans, F</td>
<td>T9, 10 Lateral</td>
<td>VEGF165, FGF2 (in microspheres) PLGA multiple channel bridge</td>
<td>Acute (0)</td>
<td>Morphology: VEGF-levels at injury site were significantly (20-fold) greater than without VEGF-treatment at 1 week; significantly more blood vessels inside bridges with 2 μg VEGF and 1 μg FGF2 at 6 wk; the number of blood vessels was significantly increased; neurite growth was 1.7-fold greater at 6 wk in bridges with VEGF and FGF2 Function: / Survival: 1, 6 wk</td>
<td>De Laporte et al. (2011)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T10 Transection</td>
<td>DPSCs PLLA/PLGA-scaffold</td>
<td>Acute (0)</td>
<td>Morphology: Angiogenesis was significantly abundant at the injury site in rats treated with prevascularized scaffolds compared to DPSC-scaffolds, empty scaffolds and untreated rats; the mean diffusivity (indicator of molecular diffusion rate and demyelination) was significantly lower in prevascularized scaffolds at 8 wk, total vessel volume and vessel density in the lesion site were significantly higher in prevascularized scaffolds (increased vessel density in the rubrospinal tract, spinobulbar tract, dorsal column and spino cerebellar tract, but not in corticospinal tract) Function: Significant improvement at 2 and 4 wk (BBB) Survival: 8 wk</td>
<td>Guo et al. (2020)</td>
</tr>
<tr>
<td>Rat, Wistar, F</td>
<td>T7 Transection, (5 mm long)</td>
<td>FGF2 Hyaluronate collagen scaffold (CRS)</td>
<td>Acute (0)</td>
<td>Morphology: The number of blood vessels was significantly increased caudal, rostral and at the injury site in the FGF2-CRS and CRS groups compared to the control group at 12 wk as well as the FGF2-CRS group compared to the CRS group Function: Significant improvement after 4 wk (BBB) Survival: 12 wk</td>
<td>Shang et al. (2019)</td>
</tr>
<tr>
<td>Mice, C57BL/6, M</td>
<td>T9 Hemisection</td>
<td>HUVECs Fibrous porous silk scaffold (FPSS)</td>
<td>Acute (0)</td>
<td>Morphology: Microvessel density and microvessel count in the FPSS-cells group were significantly higher at 28 days; significantly more regenerating axons formed along the blood vessels in the white matter at the injury site at 4 wk Function: Significant improvement after 4 wk (BBB) Survival: 4 wk</td>
<td>Zhong et al. (2020)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9, 10 Transection (4 mm long)</td>
<td>Oxygen-generating scaffold (CPO/PLGA-microspheres in hydrogel)</td>
<td>Acute (0)</td>
<td>Morphology: Oxygen-generating scaffolds had a significantly oxygen level up to 21 days than hydrogel; blood vessels were observed in the scaffold and neovascularization was significantly greater than in control groups Function: Significant improvement after 2 wk (BBB) Survival: 12 wk</td>
<td>Liu et al. (2020)</td>
</tr>
<tr>
<td>Rat, Fischer, F</td>
<td>T9 Transection, (2 mm long)</td>
<td>OPG+ hydrogel scaffold SCs, SCs + RAPA (PLGA-microspheres in hydrogel)</td>
<td>Acute (0)</td>
<td>Morphology: Mean length density (L) of blood vessels was lowest in RAPA channels; blood vessel surface area was significantly larger in SC group; significantly larger mean vessel volumes in the SC group; mean diameter of blood vessels in SC channels was significantly greater; mean cross-sectional area per blood vessel in SC channels was significantly larger; number of axons regenerating had positive correlations to the surface and volume area densities of vessels and to the diameter of blood vessels; for SC channels significant negative correlations were shown between peak axonal density of total axon amplitudes and vessel cross-sectional area for total axons → SCs in hydrogel channels supported neurovascular bundle regeneration significantly in axon and vessel density and in physiologic parameters of vessel diameter and radial diffusion distances Function: / Survival: 6 wk</td>
<td>Siddiqui et al. (2021)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T8 Transection (2 mm long)</td>
<td>Hydrogel scaffold with CBZ-SDF1α + Taxol liposomes</td>
<td>Acute (0)</td>
<td>Morphology: The number of blood vessels was significantly higher in the full treatment group at 10 days; axonal fibers with a regenerative length longer than 1 mm at the lesion site were always close to regenerated blood vessels Function: Significant improvement after 3 wk (BBB) Survival: 5, 10 days, 6 wk</td>
<td>Liu et al. (2021)</td>
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<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9</td>
<td>Contusion, (175 kDyne)</td>
<td>Nanofiber-hydrogel composite (NHC) (Injection into injury site)</td>
<td>Subacute (3)</td>
<td>Morphology: The blood vessel density increased in time in the injury with NHC or HA but decreased in the control group; the blood vessel density was significantly higher at 28 days&lt;br&gt;Function: No significant improvement (BBB)&lt;br&gt;Survival: 3, 7, 28, 56 days</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9</td>
<td>Lateral hemisection (3 mm long)</td>
<td>Microsolv electrospun oriented fiber scaffold pDNA/liposome (NGF) + IL-4</td>
<td>Acute (0)</td>
<td>Morphology: The number of blood vessels was significantly higher; neovascularization was significantly higher at 4 and 8 wk&lt;br&gt;Function: No significant improvement at 3 wk (BBB) and 4 wk (Inclined Plane Test)&lt;br&gt;Survival: 4, 8 wk</td>
</tr>
<tr>
<td>Rat, Wistar, M</td>
<td>T10</td>
<td>Lateral hemisection</td>
<td>VEGF/PDGF Hydrogel patch&lt;br&gt;Mini-pump&lt;br&gt;At injury site</td>
<td>Acute (0) For 2 days (patch)/7 days (pump)</td>
<td>Morphology: The blood vessel density 200 µm from the lesion cavity was not significantly affected by VEGF/PDGF treatment&lt;br&gt;Function: No significant improvement (BBB)&lt;br&gt;Survival: 3, 3 mo</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9–11</td>
<td>Lateral hemisection</td>
<td>VEGF, NT-3, BMSCs PLGA-microspheres with acellular spinal cord scaffold (ASCS)</td>
<td>Acute (0)</td>
<td>Morphology: The levels of VEGF and NT-3 were significantly increased at the injury site 1 and 4 wk, in the VEGF/NT-3-ASCS- and BMSC-treatment groups; the blood vessel density was significantly higher; more intensive blood vessels were ordinarily accompanied with lower infiltration of macrophages and vice versa at the lesion site&lt;br&gt;Function: Significant improvement at all timepoints (BBB)&lt;br&gt;Survival: 1, 4, 8 wk</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9</td>
<td>Contusion injury</td>
<td>VEGF, Ang-1, FGF2 PLGA-microspheres Injection into injury site</td>
<td>Acute (0)</td>
<td>Morphology: The levels of VEGF, Ang-1 and FGF2 were significantly higher at the injury site at 2, 4, and 8 wk in animals treated with angiogenic microspheres; the numbers of blood vessels at the injury site at 4 and 8 wk were significantly higher; the numbers of cells positive for nestin or βIII-tubulin (marker of neural precursor recruitment) at the injury site were significantly higher and mostly associated with blood vessels; the density of neurofilament (NF)-positive fibers was significantly greater at the injury site at 8 wk in treated animals often aligned with blood vessels; serotonergic (5-HT) fibers were associated with blood vessels and significantly longer in treated rats; the numbers of MBP-positive mature oligodendrocytes were significantly higher in treated rats and aggregated around blood vessels in the white matter region; most axons in treated animals were myelinated and followed blood vessels at 12 wk&lt;br&gt;Function: Significant improvement after 14d (BBB)&lt;br&gt;Survival: 2, 4, 8, 12 wk</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9, 10</td>
<td>Lateral hemisection (4 mm long)</td>
<td>NPCs, ECs Hydrogel + PLGA-scaffold</td>
<td>Acute (0)</td>
<td>Morphology: Significantly more vessels in the implant + NPCs/ECs treated rats in the lesion epicenter at 8 wk; only implant + NPCs/ECs treated rats had EBA-positive vessels (marker of functional BSCB) at the injury epicenter; the vessel density was significantly increased at the injury epicenter&lt;br&gt;Function: /&lt;br&gt;Survival: 3, 8 wk</td>
</tr>
<tr>
<td>Rat, Fischer F344, F</td>
<td>T9, 10</td>
<td>Lateral hemisection</td>
<td>NSCs, EPCs Hydrogel</td>
<td>Acute (0)</td>
<td>Morphology: Infiltration of native NSCs into lesion area and formation of blood vessels appeared in NSC/EPC hydrogel group, the acellular hydrogel group and in the control group with connective tissue formation&lt;br&gt;Function: significant improvement after 2 wk (BBB)&lt;br&gt;Survival: 4 wk</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T2</td>
<td>Clip compression (26 g for 60 s)</td>
<td>FGF2&lt;br&gt;HAMC, PLGA-nanoparticles, (Intrathecal injection)</td>
<td>Acute (0)</td>
<td>Morphology: The number of blood vessels was significantly higher 500 µm rostral and caudal to the lesion site at 4 wk in HAMC/PLGA/FGF2-treated rats in the dorsal horn&lt;br&gt;Function: No significant improvement (BBB)&lt;br&gt;Survival: 4 wk</td>
</tr>
<tr>
<td>Rat</td>
<td>Cervical hemisection</td>
<td>BDNF&lt;br&gt;PHEMA-scaffold</td>
<td>Acute (0)</td>
<td>Morphology: Blood vessels grew into the entire PHEMA-scaffold within 2 wk and persisted until 4 wk&lt;br&gt;Function: /&lt;br&gt;Survival: 1, 2, 4 wk</td>
<td>Bakshi et al.85 (2004)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9, 10</td>
<td>Dorsal hemisection, (3 mm × 1.5 mm)</td>
<td>VEGF, BDNF PLGA-microspheres, HA-antiNgr -scaffold</td>
<td>Acute (0)</td>
<td>Morphology: The number of blood vessels and axonal fibers were significantly higher in HA + PLGA scaffolds treated rats at 8 wk; more myelinated axons were found in HA + PLGA scaffolds at 14 wk compared to HA scaffolds and they often had contact with blood vessels&lt;br&gt;Function: Significant improvement after 2 wk (BBB, CatWalk)&lt;br&gt;Survival: 4, 8, 14 wk</td>
</tr>
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(Continued)
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</table>
| Rat, Sprague-Dawley, F | T9, 10 Transection, (4 mm long) | NGF, ChABC Allogeneic beads; electrospun PDS scaffold | Acute (0) | Morphology: Many parallel aligned blood vessels in contact with regenerating axons were present in the implant; some endothelial cells were in close association with electrospun monofilaments at 7 days, after 2–3 wk blood cells were observed in this lumen  
Function: Significant improvement at 21 days (BBB)  
Survival: 7, 21 days | Colelló et al. (2016) |
| Rat, Sprague-Dawley, F | T10 Transection, (1.5 mm long) | MSCs PLGA, GS-scaffold | Acute (0) | Morphology: The number of blood vessels was significantly increased in GS+MSCs treated rats at the injury site at 1 wk; only MSCs surrounding blood vessels expressed VEGF  
Function: /  
Survival: 1, 8 wk | Zeng et al. (2011) |
| Rat, Sprague-Dawley, M | T9 Clip compression (4 mm long) | pSV-VEGF PLGA/DC-Chol-nanospheres Injection into injury site | Acute (0) | Morphology: Arteriole density was significantly higher in VEGF-loaded PLGA/DC-Chol nanosphere treated rats at 4 wk  
Function: Significant improvement after 2 wk (BBB)  
Survival: 2, 4, 6 wk | Gwak et al. (2016) |
| Rat, Sprague-Dawley, F | T8, 9 Lateral hemisection, (3 mm long) antiNgR HA-PLL-hydrogel | Acute (0) | Acute (0) | Morphology: antiNgR was detectable for 8 wk; some blood vessels and axons were seen in the edge and epicenter of HA-PLL/antiNgR and HA-PLL treated rats at 8 wk  
Function: /  
Survival: 2, 4, 8, 12 wk | Wei et al. (2010) |
| Rat, Wistar, F | T12 Transection, (3 mm long) | PDWHF, NGF Collagen-I | Acute (0) | Morphology: Axonal regrowth and number of blood vessels were significantly greater in PDWHF and NGF groups; the number of vessels was significantly greater in PDWHF group compared to NGF group  
Function: No significant improvement observed  
Survival: 4, 8, 12 wk | Hiraizumi et al. (1996) |
| Rat, Sprague-Dawley, M | T9–11 Lateral hemisection, (3 mm long) | VEGF165 PLGA-nanospheres, ASCS | Acute (0) | Morphology: Vessel branches increased significantly at 1 wk in V-ASCS group compared with control and B-ASCS groups but in the following weeks the density of vessel branches decreased in B-and V-ASCS groups, vessel volume/tissue volume (VV)/TV were significantly increased in B-and V-ASCS groups at 1 wk and VV/TV were significantly greater in V-ASCS compared with B-ASCS; VV/TV was not significantly different between V-ASCS and B-ASCS groups at 8 wk and data in V-ASCS group was significantly lower than in Sham group; vessel density (VDm) was significantly highest in V-ASCS group, higher in B-ASCS group and the lowest in control group at 1 wk; VDm was significantly higher in V-ASCS group compared with B-ASCS at 8 wk; average vessel diameter was significantly greater in V-ASCS and B-ASCS groups compared with control group at 1 wk but there was no significant difference at 4 and 8 wk, density of vessel branches (VBRm) was significantly higher in V-ASCS group compared with control and B-ASCS groups at 1, 4 and 8 wk  
Function: Significant improvement after 3d (BBB)  
Survival: 4, 8, 8 wk | Xu et al. (2017) |
| Cat | L2 Incomplete cord injury (5 mm longitudinal insertion of Teflon catheter sheaths) | PDWHF Hydron (coated on Teflon catheter sheaths) | Acute (0) | Morphology: The number of vessels was significantly greater in PDWHF-treated animals and the number of vessels appeared significantly more 1 mm from the lesion site  
Function: No significant improvement observed  
Survival: 3 wk | Hiraizumi et al. (1993) |
| Rat, Sprague-Dawley, M | T9 Transection, (3 mm long) | VEGF Collagen scaffold (CS) | Acute (0) | Morphology: The microvessel density and microvessel count in the CS/VEGF group were significantly higher at 12 wk  
Function: Significant improvement after 7 wk  
Survival: 4, 10, 12 wk | Wang et al. (2018) |
| Rat, Long Evans, F | T9, 10 Lateral hemisection, (4 mm long) | VEGF164 Alginite/fibrinogen-hydrogel, chitosan-nanoparticles | Acute (0) | Morphology: Endothelial, β-III tubulin and growing neurites staining intensity were significantly greater in rats treated with VEGF-loaded hydrogels at 4 wk  
Function: No significant improvement (CatWalk)  
Survival: 4 wk | des Rieux et al. (2014) |
| Rat, Sprague-Dawley, F | T5, 3 Transection, (3 mm long) | NeuroGel (PHPMA)-hydrogel | Acute (0) | Morphology: Vascular response with proliferating capillary sprouts into the hydrogel at 7 days as well as gial cells; extensive ingrowth of sinusoidal capillaries  
Function: Significant improvement observed after 2 wk  
Survival: 2, 4 mo | Woerly et al. (2001) |
| Rat, Fischer, F | T9, 10 Transection, (4 mm long) | BDNE EGF1 PLA-foam scaffold, fibrin glue | Acute (0) | Morphology: The number of blood vessels was significantly higher in fibrin only group at 2, 4, and 8 wk and in BDNF + foam group at 8 wk  
Function: No significant improvement (BBB)  
Survival: 2, 4, 8 wk | Patist et al. (2004) |

(Continued)
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<tr>
<td>Cat</td>
<td>T6, 7</td>
<td>NeuroGel</td>
<td>Acute (0)</td>
<td>Morphology: At 17 months large capillaries crossed the injury site and a profuse network of blood vessels in proximity of the spinal stumps were seen&lt;br&gt;Note: Improvement observed (treadmill test&lt;br&gt;Survival: 6, 9, 17 mo</td>
<td>Woerly et al.³⁹ (2004)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9, 10</td>
<td>NeuroGel (PHPMA hydrogel)</td>
<td>Acute (0)</td>
<td>Morphology: Blood vessels were found in the lesion site in AFG/ISAP-treated rats with a larger diameter compared with AFG-treated rats at 12 wk; the microvesSEL density was significantly greater in AFG/ISAP-treated rats at the lesion site compared with AFG-treated rats and control group at 12 wk; regenerating blood vessels and axons showed colocalization&lt;br&gt;Note: Significant improvement after 3 wk (BBB) and at 12 wk (Catwalk, MEP&lt;br&gt;Survival: 1, 8, 12 wk</td>
<td>Man et al.³⁰ (2021)</td>
</tr>
<tr>
<td>Rat, Fischer, F</td>
<td>T9, 10</td>
<td>AFG/ISAP hydrogel (aligned fibrin hydrogel/functionized self-assembling peptide nanofiber hydrogel)</td>
<td>Acute (0)</td>
<td>Morphology: Vessel length and vessel surface area were significantly greater in SC + Empty-MS treated rats compared with MG + Empty-MS at 6 wk but not different to SC + Low or medium RAPA-MS; vessel length and surface area in SC-loaded scaffolds with high doses RAPA was not different from MG-only scaffolds without RAPA; the mean blood vessel diameter in SC + Empty-MS was greater than in MG-only scaffolds; the number of vessels with Pericytes (PC)/Endothelial cells (EC) was greater in SC + Empty-MS treated rats; PC/EC ratio was highest in SC + Low RAPA-treated rats; surface area of functional vessels was significantly higher in RAPA treated rats compared to MG + Empty-MS group indicating an improved vascular connectivity to the systemic circulation&lt;br&gt;Note: Significant improvement after 4 wk (BBB)</td>
<td>Hakim et al.³¹ (2019)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>C3, 4</td>
<td>Collagen-1 scaffold</td>
<td>Acute (0)</td>
<td>Morphology: At 10 wk blood vessels were seen inside the scaffold but most of them were not associated with ZO-1-immunoreactive tight junctions, ZO-1-immunoreactivity was intensive at the transition zones, density of blood vessels was significantly greater at the transition zone of the scaffold compared to the contralateral non-lesioned white matter but staining within the scaffold was not significantly greater than that of the contralateral white matter; the number of functional vessels was significantly lower within the scaffold at 10 wk than the total number of vessels and most functional vessels within the scaffold were not positive for ZO-1 tight junction&lt;br&gt;Note: Improvement observed (treadmill test)&lt;br&gt;Survival: 10 wk</td>
<td>Altimova et al.³² (2020)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9, 10</td>
<td>Aligned fibrin hydrogel (AFG)</td>
<td>Acute (0)</td>
<td>Morphology: The number of blood vessels was significantly greater in AFG-treated rats at 2 and 4 wk&lt;br&gt;Note: Improvement observed (treadmill test)&lt;br&gt;Survival: 1, 2, 4, 8 wk</td>
<td>Yao et al.³³ (2018)</td>
</tr>
<tr>
<td>Canine, Beagle, F</td>
<td>T9, 10</td>
<td>Gelatin sponge (GS), NT-3/fibronectin particles (NF)</td>
<td>Acute (0)</td>
<td>Morphology: Blood vessels or capillaries were identified only in the NF-GS group at 4 wk&lt;br&gt;Note: Improvement observed (treadmill test)&lt;br&gt;Survival: 4 wk</td>
<td>Li et al.³⁴ (2018)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T9, 10</td>
<td>MSCs, PLGA-scaffold</td>
<td>Acute (0)</td>
<td>Morphology: The number of blood vessels was significantly increased around the lesion site at 6 wk in the transplant group&lt;br&gt;Note: Improvement observed (treadmill test)&lt;br&gt;Survival: 6 wk</td>
<td>Ropper et al.³⁵ (2017)</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, F</td>
<td>T10</td>
<td>CORM-2-SLNs (Carbon monoxide-releasing molecule-2 solid lipid nanoparticle) (i.p. injection)</td>
<td>Acute (0)</td>
<td>Morphology: The fluorescence intensity of Eivan’s Blue dye was significantly lower in the treatment group at the injury site at 1d indicating reduced RSCB permeability; the number of blood vessels was significantly greater in the treatment group at 21 days&lt;br&gt;Note: Improvement observed (treadmill test)&lt;br&gt;Survival: 1, 3, 14, 21 days</td>
<td>Joshi et al.³⁶ (2020)</td>
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Targeting Vascular Repair After Spinal Cord Injury

Roolfs L, et al.  

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| Rat, Wistar, F | T8 | Complete transection of CST | VEGF165, Ad.CMV. VEGF165 (Injection in lesion site, controlled release via Matrigel) | Acute (0) For 30 days | Morphology: The number of vessels in VEGF-treated rats was significantly higher (ca. 300%), retrograde axonal degeneration was significantly reduced in VEGF-treated rats, regenerating CST axons (HRP-labeled) where located mostly in the ventral gray matter  
Function: /  
Survival: 0, 3, 7, 10, 16, 18, 30 days | Facchiano et al.\(^{104}\) (2002) |
| Rat, Sprague-Dawley, M | T7 | Contusion injury | VEGF165 Gelfoam placed on injury site | Acute (0) | Morphology: Significant increase in BSCB permeability after VEGF-treatment in non-enhancing-areas (magnetic resonance imaging) in the epicenter in the subacute (7–14 days) and chronic (28–56 days) periods  
Function: Significant improvement at 28 days, but not at 56 days (BBB)  
Survival: 56 days | Patel et al.\(^{30}\) (2009) |

/ , not assessed; AFG, aligned fibrin hydrogel; fSAP, functionalized self-assembling peptides; CORM-2, carbon monoxide-releasing molecule-2; rGO, reduced graphene oxide; DPSCs, dental pulp stem cells; PLGA, polylactide-co-glycolide acid; PLLA, poly-L-lactic acid; PEG 600, polyethylene glycol, PLG(A) - polylactide-co-glycolide (acid), PLLA - poly-l-lactic acid; mMS, mechanical microconnector system; BBB, Basso, Beattie and Bresnahan score; VEGF, vascular endothelial growth factor; FGF2, fibroblast growth factor 2; DPSCs, dental pulp stem cells; CRS, hyaluronate collagen scaffold; HA, hyaluronic acid; AntiNgR, anti-Nogo receptor antibody; ChABC, chondroitinase ABC; PHEMA, poly-2-hydroxyethylmethacrylate hydrogel; PDWHF, platelet-derived wound healing formula; BSCB, blood-spinal cord barrier; CST, corticospinal tract; Ad.CMV/VEGF, replication-defective adenovirus coding for VEGF.
The Importance of Vascular Repair as the First Step in Spinal Cord Injury Treatment: Commentary on “Therapeutic Approaches Targeting Vascular Repair After Experimental Spinal Cord Injury: A Systematic Review of the Literature”

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The first goal of treatment after spinal cord injury (SCI) is to minimize secondary injury and promote neuronal regeneration, which has been the topic of many studies. In secondary injuries, hemodynamic management is clinically known as a significant treatment. The American Association of Neurological Surgeons/Congress of Neurological Surgeons 2013 SCI guideline recommends maintaining the mean arterial pressure at least between 85 and 90 mmHg for the first 7 days following an acute SCI. In addition, many studies have actively investigated various neuroprotective substances and stem cell treatments after the acute phase. However, there is an overlooked aspect of these treatments—namely, the importance of vascular repair, which could enable proper perfusion pressure, flow, and drug/cell delivery. In order to maintain proper perfusion pressure in the injured spinal cord tissue, the blood vessels must be distributed appropriately. Furthermore, in order for a substance (e.g., an administered drug or cells) to reach the damaged area, it must be distributed through a blood vessel. In particular, the relationship between vascular repair after SCI and axonal regeneration underscores the importance of vascular repair. Therefore, vascular repair is one of the most important issues in the treatment of SCI, and this review paper is very important in this regard.

This review paper is broadly divided into a section on the pathophysiology that occurs within spinal cord tissue after damage and a section discussing studies on treatments for vascular regeneration in the spinal cord. In particular, 5 categories of treatments are described: (1) delivery of organic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) the delivery of biomaterials carrying various factors. Each category is well represented with appropriate pictures and tables that present the material in an easy-to-understand manner. Angiogenic factors have shown clinically significant results, focusing on substances validated in other tissues, such as vascular endothelial growth factor.
Importance of Vascular Repair as the First Step in SCI Treatment

Kim KT

and fibroblast growth factor-2. Genetic engineering is relatively understudied compared to other treatments, but has high potential in terms of vascular regeneration. Physical stimulation techniques can be a good treatment alternative for acute treatment, and there have also been many recent clinical attempts to treat chronic SCI using electric stimulation. Cell transplantation and the delivery of biomaterials carrying various factors are the most popular approaches in recent research on regenerative medicine. In particular, the development of drug/cell delivery systems provides an environment where we can deliver certain cells in a precise and safe manner. In particular, several cell therapy techniques that can help regenerate nerves and surrounding cells are leading SCI treatment in a different direction than previous treatment methods. Proper biomaterials and cell combinations are likely to exert very high synergy. In particular, advances in biomaterials that can deliver and maintain various cell treatments, thereby creating a favorable environment for spinal cord regeneration, constitute a new paradigm for SCI treatment.

The treatment of SCI can never be fully addressed by a single therapeutic approach. This is because recovery after SCI is not just a matter of neuronal regeneration; instead, recovery is only possible when the organic network of spinal cord tissues that surround and support neurons is regenerated and restored. In the future, combined approaches (such as implanted biomaterials with the ability to release angiogenic factors or therapeutic cells) will be the most powerful treatments for SCI.

Conflict of Interest: The author has nothing to disclose.

REFERENCES

Spinal Metastases and the Evolving Role of Molecular Targeted Therapy, Chemotherapy, and Immunotherapy

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Metastatic involvement of the spine is a common complication of systemic cancer progression. Surgery and external beam radiotherapy are palliative treatment modalities aiming to preserve neurological function, control pain and maintain functional status. More recently, with development of image guidance and stereotactic delivery of high doses of conformal radiation, local tumor control has improved; however recurrent or radiation refractory disease remains a significant clinical problem with limited treatment options. This manuscript represents a narrative overview of novel targeted molecular therapies, chemotherapies, and immunotherapy treatments for patients with breast, lung, melanoma, renal cell, prostate, and thyroid cancers, which resulted in improved responses compared to standard chemotherapy. We present clinical examples of excellent responses in spinal metastatic disease which have not been specifically documented in the literature, as most clinical trials evaluate treatment response based on visceral disease. This review is useful for the spine surgeons treating patients with metastatic disease as knowledge of these responses could help with timing and planning of surgical interventions, as well as promote multidisciplinary discussions, allowing development of an individualized treatment strategy to patients presenting with widespread multifocal progressive disease, where surgery could lead to suboptimal results.

Keywords: Spine metastases, Metastatic cancer, Targeted therapy, Mutation, Chemotherapy, Immunotherapy

INTRODUCTION

Metastatic cancer to spine remains a debilitating consequence of uncontrolled cancer progression with a poor prognosis, that historically portended an overall survival (OS) of less than 6 months from the time of diagnosis.¹ The incidence of spinal metastases is increasing due to a variety of factors including early detection due to improvements in imaging modalities, enhanced response to first-line cancer therapies allowing longer survival and development of distant metastases as a late-stage manifestation of the disease progression, and the inherent poor response of spinal metastases to existing therapies as compared to visceral disease. The incidence of spinal metastases averages approximately 40% depending on the primary cancer and is estimated to exceed 100,000 new patients annually.²⁻⁴ Left unchecked, continued metastatic tumor growth within the spinal column ultimately leads to neurologic compromise, intractable pain, spinal deformity, instability, and significant limitation in the quality of life. The incidence of spine metastatic disease has been estimated to be 16%–74% in patients with lung cancer, 65%–75% in patients with breast cancer, and 65%–90% in prostate cancer patients.⁵ Conversely while looking at all spine metastases diagnosed in the United States yearly, 14% are derived from breast, 16.3% from lung, 4.1% from melanoma, 13.1% from renal cell, 6.8% from prostate, and 2.3% from thyroid primary cancer.⁶ Mechanistically, metastatic spread to the spine...
may occur via direct local invasion from neighboring tissues, migration along neural structures, or hematogenous spread of cancer cells from the site of origin into the bone of the spinal column.7,8

Several frameworks and scoring systems are available to aid with decision making while treating patients with spinal metastatic disease, including the NOMS (neurologic, oncologic, mechanical stability and systemic disease) framework, Tomita score, SINS (spinal instability neoplastic score) score, and Tokuhashi score.9-13 These various algorithms were created to integrate multidisciplinary assessment, evidence-based medicine, and new technology to optimize patient care. At our institution, the overall philosophy for treating patients with metastatic spine disease includes in depth evaluation of their functional status, systemic disease burden and failure of prior treatments. Surgical interventions are performed to decompress the spinal cord in cases of neurological compromise, to allow clearance for spinal stereotactic radiosurgery and to perform stabilization of symptomatic spinal fractures; however, the magnitude of surgery needs to be adjusted on a case-by-case basis to be minimally disruptive to oncological management as prolonged postsurgical recovery can negatively impact performance status and survival. With the advent of genomic analysis, the identification of targetable mutations in an increasing percentage of patients across various tumor types has changed their oncologic management and outcomes. Examples include non-small cell lung cancer (NSCLC) with ALK rearrangements identified in 4%-5% of patients and epidermal growth factor receptor (EGFR) mutations present in 10%-15% of lung cancer patients; ERBB2, CD340, and human epidermal growth factor receptor 2 (HER2)/Neu alterations in breast cancer samples, with HER2 overexpression detected in 18%-25% patients; and BRAF V600E mutation detectable in 33%-55% melanoma patients. Systemic cancer therapy is rapidly changing with the introduction of antiangiogenic agents, immunotherapy, targeted therapy, and cell cycle inhibitors, although this may not be directly translatable to patients with spine metastases. This manuscript represents a narrative overview of the results of clinical trials. Our intention is to raise awareness of the effectiveness of modern chemotherapy, targeted therapy, and immunotherapy for the treatment of patients with bulky spinal metastases derived from primary lung, breast, melanoma, renal cell, prostate, and thyroid cancers, where systemic treatment can be extremely effective in achieving local control within the spine in combination with surgery and/or radiation therapy.

**BREAST CANCER**

Patients with breast cancer are typically treated with an alkylating agent (cyclophosphamide) and antimetabolites (methotrexate, 5-fluorouracil), doxorubicin containing combination of agents, or combinatorial regimens including platinum-based compounds (cisplatin) or taxanes (paclitaxel, docetaxel) as first-line therapies (Table 1). According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, patients with breast cancer have 6% distant metastases at the time of diagnosis, with 29% 5-year relative survival (SEER; Table 1).14 Up to 5% of patients with breast cancer have identifiable bone metastases at the time of diagnosis, with a median survival of less than 2 years.15 Amongst these patients, over 20,000 patients annually present with epidural compression.16 Patients with hormone receptor (HR)-positive breast cancer are treated with endocrine therapies including estrogen receptor antagonist tamoxifen irrespective of their HER2 status, which has led to improved disease-free survival with minimal toxicity as shown in several clinical trials HERA (78.6% 4-year disease-free survival vs. 72.2% in the control group), NSABP trial BP-31 (12% improvement in disease-free survival at 3 years with 33% reduction in risk of death) and NCCTG N9831 (37% improvement in OS, with 10 year survival increase from 75.2% to 84%) (Table 1).17 Aromatase inhibitors, luteinizing hormone releasing hormone analogs and selective estrogen degraders are other classes of endocrine therapies used in HR+ breast cancer patients with improved progression free survival (PFS) (Table 1).17,18,19 In patients with HER2 amplification, use of humanized monoclonal antibodies including trastuzumab and pertuzumab or lapatinib improves patient outcomes; phase III randomized double blind CLEOPATRA trial initially evaluated a combination of these as first-line therapy with improvement in the median OS of 57.1 months (vs. 40.8 months) and 37% patients alive at 8 years (vs. 23%), with somewhat positive results reported in APHINITY trial, with 7.1% disease recurrence in the trial group (vs. 8.7%) and 94.1% patients invasive disease free at 3 years (vs. 93.2%) (Table 1).17,18,19 Anti-vascular endothelial growth factor receptor (VEGFR) inhibitor bevacizumab has been trialed for treatment of patients with breast cancer with improvements in PFS but not OS: E2100 trial reported 11.8 month PFS (vs. 5.9) with median OS of 26.7 months (vs. 25.2), while AVADO trial reported 10.1 month PFS (vs. 8.2) with median OS of 30.2 months (vs. 31.9), and RIBBON2 reported 7.2 month PFS (vs. 5.1) with median OS of 18 months (vs. 16.4).21 Heat shock protein 90 inhibitors (including 17-allylamino
Table 1. Systemic, targeted and immunotherapy treatments used to treat patients with breast, melanoma, non-small cell lung, renal cell, prostate, and thyroid cancers

<table>
<thead>
<tr>
<th>Histology</th>
<th>Subtype</th>
<th>Incidence of distant metastases at presentation</th>
<th>Early vs. late manifestation</th>
<th>Radio-sensitivity</th>
<th>Systemic treatment options</th>
<th>Investigational treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>HR+ HER2+ 10% cases</td>
<td>37.9%</td>
<td>3 Months</td>
<td>RS</td>
<td>Endocrine therapy&lt;br&gt;ER antagonist tamoxifen&lt;br&gt;Aromatase inhibitors&lt;br&gt;LHRH analogs&lt;br&gt;Estrogen degraders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR- HER2+ 4% cases</td>
<td>44.7%</td>
<td>2 Months</td>
<td>-</td>
<td>Taxanes with&lt;br&gt;Humanized MAB: trastuzumab, pertuzumab, lapatinib, tucatinib, neratinib +/- capecitabine&lt;br&gt;Anti-VEGFR bevacizumab&lt;br&gt;HSP90 inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR+ HER2- 68% cases</td>
<td>30.6%</td>
<td>28 Months</td>
<td>-</td>
<td>Endocrine sensitive:&lt;br&gt;Endocrine therapy selective estrogen receptor modulators or downregulators, aromatase inhibitors&lt;br&gt;CDK4/6 inhibitors: Palbociclib, ribociclib, abemaciclib&lt;br&gt;PI3KCA mutant: alpelisib + fulvestrant&lt;br&gt;Endocrine resistant:&lt;br&gt;Capecitabine&lt;br&gt;Platinum&lt;br&gt;Doxorubicin&lt;br&gt;PARP1 talazoparib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR- HER2- 10% cases</td>
<td>12.2%</td>
<td>45.5 Months</td>
<td>-</td>
<td>Capecitabine&lt;br&gt;Platinum +/- etoposide&lt;br&gt;Doxorubicin&lt;br&gt;Methotrexate, high dose</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAFV600E</td>
<td>-</td>
<td>-</td>
<td>RR</td>
<td>Dacarbazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BRAFV600E negative</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>EGFRmut</td>
<td>-</td>
<td>-</td>
<td>RR</td>
<td>Paclitaxel kanglaite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EML4-ALK</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Fluavastatin&lt;br&gt;RANKL MAB denosumab bisphosphonates i.e. Zoledronic acid&lt;br&gt;Platinum based</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>EML4-ALK</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Fluavastatin&lt;br&gt;RANKL MAB denosumab bisphosphonates i.e. Zoledronic acid&lt;br&gt;Platinum based</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Histology</th>
<th>Subtype</th>
<th>Incidence of distant metastases at presentation</th>
<th>Early vs. late manifestation</th>
<th>Radiosensitivity</th>
<th>Systemic treatment options</th>
<th>Investigational treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell</td>
<td>Clear cell VHL/VEGFR, PBRM1, SETD2, BAP1, mTOR</td>
<td>-</td>
<td>-</td>
<td>RR</td>
<td>Bevacizumab/IFN alpha IL2</td>
<td>VEGFR/PDGFRi Axitinib, pazopanib, sorafenib, sunitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pazopanib, sunitinib or temsirolimus</td>
<td>Cabozantinib VEGFR/AXL/cMet</td>
</tr>
<tr>
<td></td>
<td>Papillary MET NFR2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Lenvatinib FGFR/VEGFRi/everolimus</td>
</tr>
<tr>
<td></td>
<td>TP53, PTEN, CDKN2A loss, SMARKB1 loss, TFE3-TFEB fusion</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Everolimus/sorafenib</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>mTORi everolimus, temsirolimus</td>
<td>-</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>RS</td>
<td>Androgen receptor antagonist flutamide, bicalutamide, abiraterone, ketoconazole LHRH agonist/antagonist leuprolone, goserelin, degarelix</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Androgen resistant</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Doxorubicin Docetaxel Cabazitaxel mitoxantrone</td>
<td>EGFRi gefitinib, erlotinib</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>EGF/HER2i lapatinib</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>EGFR MAB cetuximab</td>
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<td></td>
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<td></td>
<td>MET/VEGFR2 cabozinib</td>
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<td></td>
<td>PARPi Olaparib</td>
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<td></td>
<td></td>
<td></td>
<td>RANKL denosumab</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>antiCTLA4 ipilimumab</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>antiPD1/PD-L1 nivolumab, pembrolizumab, atezolizumab</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sipuleucel-T vaccine</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Differentiated thyroid carcinoma</td>
<td>-</td>
<td>-</td>
<td>RR</td>
<td>-</td>
<td>VEGFR/Flt3/RET/cKIT/BRAFi Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Anaplastic carcinoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>VEGFR/FGFR/PDGFR/KIT/RETi Lenvatinib</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid carcinoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

HR, hormone receptor; HER2, human epidermal growth factor receptor 2; RR, radiation resistant; RS, radiation sensitive; ER, estrogen receptor; LHRH, luteinizing hormone releasing hormone; MAB, monoclonal antibody; HDAC, histone deacetylase inhibitor; PI3Ki, phosphatidylinositol-3-kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor; CDK4/6, cyclin dependent kinases 4/6; PARPi, poly-ADP-ribose polymerase inhibitor; PDL1, programmed death ligand 1; EGFRi, epidermal growth factor receptor inhibitor; BRAFi, v-Raf murine sarcoma viral oncogene homolog B1 inhibitor; MEKi, mitogen activated protein kinase kinase inhibitor; MEK162, mitogen activated protein kinase kinase 162; CTLA4i, cytotoxic T lymphocyte associated protein 4 inhibitor; PD-1, programmed cell death protein 1; T-VEC, talimogene; GMCSF, granulocyte macrophage colony stimulating factor; RANKL, receptor activator of nuclear factor kappa-B ligand; VHL, von Hippel Lindau; VEGFR, vascular endothelial growth factor receptor; PBRM1, polybromo 1; SETD2, su(var), enhancer of zeste, trithorax - domain containing 2; BAP1, ubiquitin carboxyl-terminal hydrolase 1; FGFR, fibroblast growth factor receptor; VEGFRi, vascular endothelial growth factor inhibitor; TP53, tumor protein p53; PTEN, phosphatase and TEnAin homolog deleted on chromosome 10; CDKN2A, cyclin dependent kinase inhibitor 2A; SMARC1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin; TFE3, transcription factor enhancer 3; TFE2, transcription factor EB; RET, rearranged during transfection; PDGFR, platelet derived growth factor receptor; RETi, rearranged during transfection inhibitor; ALK, anaplastic lymphoma kinase.
17-demethoxygel danamycin) have been trialed in breast carcinoma spine metastases with some success in phase I trials.22

Several CDK4/6 inhibitors, including palbociclib, ribociclib and abemaciclib, have been used for treatment of metastatic HR+ HER2- breast cancer patients that develop hormone resistant disease; PALOMA3 trial reported median PFS of 9.5 months (vs. 4.6) with palbociclib use, while MONARCH2 trial reported 16.4 month PFS (vs. 9.3) with abemaciclib.17,23 Palbociclib has been FDA approved in 2015.17,23 Histone deacetylase inhibitors (entinostat, vorinostat), phosphatidylinositol 3 kinase (PI3K) inhibitors (buparlisib, pilaralisib) and mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus) have also shown promising results in patients with hormone resistant and HER2+ metastatic breast as a part of combination therapy (Table 1).23,24 NCT00676663 reported 4.3 month PFS (vs. 2.3) with median OS of 28.1 months (vs. 19.8) with entinostat use.23

Systematic categorization in The Cancer Genome Atlas (TCGA) helped identify other mutations that could be targeted in the future, including fibroblast growth factor receptor (FGFR), PTEN, TP53, AKT1/2, KRAS, and SRC (TCGA). Although breast cancer had historically been considered less immunogenic, several clinical trials of anti-PD1 and anti-PDL1 in patients have been conducted with some success, including vaccinating patient with HER2-derived peptide; phase I/II trial reported 89.7% 5 year PFS (vs 80.2%), with PFS as high as 94.6% 5 year PFS in optimally boosted patients (Tables 2, 3, Supplementary Table 1).17,25 Poly-ADP-ribose polymerase (PARP) inhibitors (olaparib, veliparib) with or without immunotherapy, EGFR inhibitors and monoclonal antibodies are being trialed in patients with most difficult to treat triple negative breast cancer; phase II trial reported median PFS of 3.7 months (vs. 1.5 months) and median OS of 12.9 months (vs. 9.4 months) with

Table 2. U.S. Food and Drug Administration approved immunotherapy treatments based on primary cancer

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>ImmunoTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Triple negative breast cancer:</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab+paclitaxel protein-bound PD-L1 &gt; 1% as first line</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab, neoadjuvant and adjuvant, in combination with chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Sacituzumab</td>
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<tr>
<td></td>
<td>HER2+ metastatic breast cancer:</td>
</tr>
<tr>
<td></td>
<td>Margetuximab</td>
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<tr>
<td></td>
<td>Pertuzumab + trastuzumab</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Adjuvant ipilimumab, nivolumab, or pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>First-line therapy</td>
</tr>
<tr>
<td></td>
<td>- Ipilimumab, nivolumab or pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>- Combination nivolumab+ipilimumab</td>
</tr>
<tr>
<td></td>
<td>Tebentafusp</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Unresectable stage III: chemoRT, then durvalumab</td>
</tr>
<tr>
<td></td>
<td>First-line therapies</td>
</tr>
<tr>
<td></td>
<td>- Pembrolizumab TPS &gt; 50%</td>
</tr>
<tr>
<td></td>
<td>- Squamous NSCLC: pembrolizumab + carboplatin and nab- paclitaxel</td>
</tr>
<tr>
<td></td>
<td>- Nonsquamous NSCLC: pembrolizumab + pemetrexed/platinum vs atezolizumab</td>
</tr>
<tr>
<td></td>
<td>- paclitaxel and carboplatin</td>
</tr>
<tr>
<td></td>
<td>Second line therapies</td>
</tr>
<tr>
<td></td>
<td>- Pembrolizumab TPS &gt; 1%</td>
</tr>
<tr>
<td></td>
<td>- Atezolizumab or nivolumab</td>
</tr>
<tr>
<td></td>
<td>Amivantamab</td>
</tr>
<tr>
<td></td>
<td>Cemiplimab</td>
</tr>
<tr>
<td></td>
<td>Ramucirumab + erlotinib</td>
</tr>
<tr>
<td></td>
<td>Nivolumab + ipilimumab, combined with platinum doublet</td>
</tr>
<tr>
<td>RCC</td>
<td>Advanced RCC:</td>
</tr>
<tr>
<td></td>
<td>First-line therapy nivolumab + ipilimumab</td>
</tr>
<tr>
<td></td>
<td>Second line therapy anti-angiogenic therapy followed by nivolumab</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>Nivolumab + cabozaotinib</td>
</tr>
</tbody>
</table>

PD-L1, programmed death-ligand 1; HER2, human epidermal growth factor receptor 2; TPS, tumor proportion score; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.
### Table 3. Indications for most common immunotherapy agents

<table>
<thead>
<tr>
<th>Immunotherapy agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTLA4 inhibitor, ipilimumab, YERVOY</strong></td>
<td>Unresectable or metastatic malignant melanoma, BRAF V600wt unresectable or metastatic</td>
</tr>
<tr>
<td></td>
<td>Cutaneous melanoma, stage IIIB/IV post resection including LN, adjuvant</td>
</tr>
<tr>
<td></td>
<td>First line, metastatic or recurrent NSCLC, no EGFR/ALK aberrations, with nivolumab and 2 cycles of platinum doublet chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Relapsed and stage IV RCC failing TKI, VEGF or mTOR inhibitor use, with nivolumab</td>
</tr>
<tr>
<td><strong>PD-1 inhibitor, nivolumab, OPDIVO</strong></td>
<td>First-line failing systemic Tx or metastatic melanoma regardless of BRAF status</td>
</tr>
<tr>
<td></td>
<td>Unresectable or metastatic BRAF V600Emut melanoma progressive on BRAF inhibitor</td>
</tr>
<tr>
<td></td>
<td>Unresectable or metastatic melanoma, BRAF V600Ewt or BRAF V600Dwt</td>
</tr>
<tr>
<td></td>
<td>Unresectable or metastatic melanoma post complete resection, adjuvant</td>
</tr>
<tr>
<td></td>
<td>Metastatic NSCLC, progressing on platinum chemotherapy, failed targeted inhibitors for EGFR/ALK aberrations</td>
</tr>
<tr>
<td></td>
<td>First line, advanced RCC, combined with cabozantinib</td>
</tr>
<tr>
<td><strong>PD-1 inhibitor, Pembrolizumab, KEYTRU-DA</strong></td>
<td>Triple negative breast cancer, early stage, high risk, combined with chemotherapy as neoadjuvant, then single agent adjuvant post resection</td>
</tr>
<tr>
<td></td>
<td>Triple negative breast cancer, locally recurrent unresectable or metastatic, PD-L1+, in combination with chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Previously untreated melanoma regardless of BRAF status</td>
</tr>
<tr>
<td></td>
<td>Metastatic melanoma, limited resectability, no residual, adjuvant</td>
</tr>
<tr>
<td></td>
<td>Unresectable or metastatic melanoma</td>
</tr>
<tr>
<td></td>
<td>First line in metastatic NSCLC with high PD-L1 &gt; 50%, no EGFR/ALK mutation</td>
</tr>
<tr>
<td></td>
<td>First line w/pemetrexed and carboplatin for metastatic nonsquamous NSCLC, no EGFR/ALK mutation, any PD-L1 status</td>
</tr>
<tr>
<td></td>
<td>First line in metastatic nonsquamous NSCLC with high PD-L1 &gt; 1%, no EGFR/ALK aberrations</td>
</tr>
<tr>
<td><strong>PD-L1 inhibitor, avelumab, BAVENCIO</strong></td>
<td>First-line advanced RCC, together with Axitinib</td>
</tr>
<tr>
<td><strong>PD-L1 inhibitor, durvalumab, IMFINZI</strong></td>
<td>Stage III unresectable NSCLC, not progressing on concurrent platinum-based chemotherapy and radiation therapy</td>
</tr>
<tr>
<td><strong>PD-L1 inhibitor, atezolizumab, TECENTRIQ</strong></td>
<td>Triple negative breast cancer, locally advanced or metastatic, PD-L1+ expression, combined with paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Melanoma, unresectable or metastatic, BRAF V600mut, combined with cobimetinib and vemurafenib</td>
</tr>
<tr>
<td></td>
<td>First line, metastatic nonsquamous NSCLC, no EGFR/ALK genomic aberrations, combined with calcium blockers, paclitaxel,</td>
</tr>
<tr>
<td></td>
<td>Stage II-IIIA NSCLC, PD-L1++, post resection and platinum chemotherapy, adjuvant</td>
</tr>
<tr>
<td></td>
<td>Metastatic NSCLC, EGFR/ALK genomic aberrations, progressive on targeted therapy</td>
</tr>
</tbody>
</table>

CTLA4, cytotoxic T-lymphocyte antigen 4; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin; PD-1, programmed-death 1; TX, treatment; LN, lymph node; VEGFR, vascular endothelial growth factor receptor.
Successful use of CDK4/6 inhibitor Palbociclib

In patients with BRAF V600E mutations, the use of MEK inhibitors including trametinib, selumetinib, cobimetinib, and MEK162 have similarly resulted in improved PFS and OS; COLUMBUS trial reported median PFS of 14.9 months versus 7.3 months comparing encorafenib plus binimetinib versus vemurafenib, with the corresponding median OS of 33.6 versus 16.9 months. 28

In patients with advanced metastatic disease, the use of immune checkpoint inhibitors has changed the treatment approach for these patients. These novel agents target immune regulatory molecules including ipilimumab targeting cytotoxic T-lymphocyte antigen 4 (CTLA4), nivolumab and pembrolizumab targeting PD-1 and the combined inhibition of CTLA-4 and PD-1 (Tables 2, 3). With this approach, significant clinical improvements have been achieved in patients with advanced melanoma, with 5 year OS of 18.2% (vs. 8.8%) reported by the NCT00-324155 trial. 29 Moreover, recent studies showed 82% 1-year survival and 75% 2-year survival in patients receiving a combination of nivolumab and ipilimumab; CheckMate067 reported median OS of 72.1 months versus 36.9 with nivolumab alone versus 19.9 with ipilimumab alone, with 6.5 year OS rates of 57% versus 43% versus 25% with BRAF mutant tumors, and 46% versus 42% versus 22% with BRAF wild type tumors, respectively. 30 Despite these impressive results, immune checkpoint inhibitors can be associated with a significant toxicity profile related to autoimmune manifestations and must be monitored closely. 31,32 In patients without BRAF V600E mutations, immune checkpoint inhibition is considered first-line therapy (Tables 2, 3). Amongst patients with the targetable BRAF V600E mutation, targeted inhibitors are typically given up-front, followed by immune checkpoint inhibition. 31,32

Additional focus has been directed on modulating the immune system towards an antitumor state. For example, recent studies have focused on applications of HSV-1 based oncolytic viruses (e.g., talimogene laherparepvec [T-VEC]) to induce lysis of melanoma cells in patients, with resulting antigen release
Fig. 2. Successful use of pembrolizumab in a patient with widely metastatic melanoma. Patient is 61-year-old with widely metastatic melanoma refractory to several lines of systemic treatment. Per discussion with medical oncology team, the consensus was for systemic treatment. Panel A demonstrates several sites of bulky metastatic disease (arrows) and a large spinal metastasis at T11 (circle) treated with spinal stereotactic radiosurgery 3 months prior to starting anti-programmed-death 1 therapy. Panel B demonstrates complete resolution of the bulky metastatic disease including the epidural spinal cord compression 8 months after treatment with pembrolizumab. The patient currently remains disease free with a follow-up of 90 months.

and immune response when combined with granulocyte-monocyte colony-stimulating factor (GM-CSF) and immunotherapy and median OS of 23.3 months with T-VEC and 18.9 months with GM-CSF, with the corresponding durable response rates of 16.3% versus 2.1%. T-VEC is the first FDA approved oncolytic virus and is additionally being studied in combination with immune checkpoint inhibitors. Other oncolytic viruses and dendritic cell vaccines are being investigated for treating melanoma patients. Several studies are focused on understanding the mechanisms of immune resistance in melanoma patients, exploring prognostic features of response to immunotherapy, and explore ways to reverse immune evasion. Fig. 2 demonstrate an example of successful use of immunotherapy in a 61-year-old patient with widely metastatic melanoma refractory to several lines of treatment, who presented complete resolution of bulky metastatic disease and remains disease free for more than 90 months after starting treatment anti-PD-1 inhibitor pembrolizumab.

NON-SMALL CELL LUNG CANCER

NSCLC is likewise associated with poor prognosis with an OS of 8 to 11 months due to rapid lung progression and distant metastatic progression. Skeletal metastasis is common in NSCLC, occurring in 30% of patients and roughly half of skeletal metastases are in the spinal column. According to SEER, 56% patients with lung cancer have distant metastases at the time of diagnosis, with 6.3% 5-year relative survival (Table 1). Paclitaxel and kangelait are commonly used chemotherapeutic agents in patients with lung cancer that has metastasized to bone. Additionally, up to 80% of patients with squamous cell lung adenocarcinomas and nearly 60% of patients with lung adenocarcinomas contain targetable mutations in membrane growth factor receptors (EGFR, VEGFR) or protein kinases (RAS, RAF, MEK).

Immune checkpoint inhibitor use has been trialed in patients with NSCLC as well (Tables 2, 3; Supplementary Table 1). The CTLA4 inhibitor ipilimumab resulted in marginal improvement in patients with advanced NSCLC in a phase II clinical trial, with
no benefit shown in phase III trial, with median OS of 13.4 months (vs. 12.4 months) and median PFS of 5.6 months (vs. 5.6 months) with combined use of chemotherapy with immunotherapy. Another CTLA4 inhibitor tremelimumab has been studied in phase II trial as a maintenance therapy; CCTG BR34 trial reported median OS of 16.6 months (vs. 14.1 months) and median PFS of 7.7 months (vs. 3.2 months) in patients with metastatic NSCLC when combined with durvalumab and platinum-based chemotherapy versus immunotherapy, with no significant improvement. In contrast, anti-PD1 inhibitors nivolumab and pembrolizumab as well as PD1 inhibitors MEDI4736, MPDL3280A and BMS-936559 show much more promising results; Checkmate017 and Checkmate057 phase III trials show improved survival in NSCLC patients who failed platinum-based chemotherapy of 23% (vs. 8%) 2-year OS in squamous and 29% (vs. 16%) in nonsquamous NSCLC patients when treated with nivolumab vs docetaxel, with pembrolizumab currently approved as first-line treatment in patients with PD-L1 overexpression (Table 3). EGFR mutations are most common in Asian patients, females and patients with NSCLC. EGFR inhibitors including erlotinib and gefitinib have been shown to improve the OS in NSCLC patients with metastatic spine disease for up to 36 months (Table 1). Afatinib is another EGFR inhibitor targeting EGFR/HER2/HER4 and has been trialed in lung cancer patients; phase III trial reported with median PFS of 11.1 months (vs. 6.9 months) with afatinib use, with 13.6 month median PFS in patients with exon 19 deletions and L858R EGFR mutations. Significant improvement in OS and PFS has been noted in patients with NSCLC treated with bevacizumab; phase III BEYOND trial reported median PFS of 12.4 months (vs. 7.9 months) in patients with EGFR mutant tumors, median PFS of 8.3 months (vs. 5.6 months) in wild type tumors and OS of 24.3 months (vs. 17.7 months) when treated with bevacizumab in addition to carboplatin and paclitaxel. In patients with targetable EGFR mutations including T790M, osimertinib has been shown to prolong survival and is first-line therapy, with median PFS of 10.1 months (vs. 4.4 months) as compared to platinum and pemetrexed. In patients with EML4-ALK fusion commonly present in younger patients and never smokers, a phase II trial with crizotinib has shown promising results; studies report 24.1 month PFS. Buparlisib, which is a PI3K inhibitor, is a potential therapy which may result in antitumor activity by inhibiting osteoclast formation. Other targeted inhibitors including BRAF, MAP2K and HER2 inhibitors are being studied. As an example of effectiveness of targeted therapies, Fig. 3 describes the successful use of erlotinib in a 60-year-old patient with advanced EGFR mutant NSCLC, she had complete response of all her epidural disease without adjuvant radiotherapy for 16 months. Unfortunately, she progressed with brain, lung and spinal metastasis before could be switched to second generation EGFR inhibitors.

**RENAI CELL CARCINOMA**

Renal cell carcinoma (RCC) is diagnosed in approximately 75,000 people yearly, with approximately 30% of patients developing bone metastases. According to SEER, 16% patients with RCC present with distant metastatic disease, with 5-year rela-
in a patient with advanced clear cell RCC is poorly responsive to hormonal and cytotoxic chemotherapies, with anti-VEGFR tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors, and other TKIs being the mainstay of treatment (Table 1, Supplementary Table 1). Multiple histologic and molecular RCC subtypes have been described with the most frequent subtype being clear cell, a subtype seen in approximately 70% of patients that is associated with VHL mutation and resulting downstream activation of angiogenesis via VEGFR, with additional mutations in PBRM1, SETD2, and BAP1 described by TCGA, as well as alterations of the mTOR pathway components. In contrast, papillary RCC has been associated with alterations in Met and NART2. Other RCC subtypes harbor mutations in TP53 and PTEN, showing alterations of the mTOR pathway components. In contrast, papillary RCC has been associated with alterations in Met and NART2. Other RCC subtypes harbor mutations in TP53 and PTEN, showing alterations of the mTOR pathway components.

Miller et al. studied 100 advanced RCC patients and reported improved OS with combined stereotactic radiosurgery (SRS)/TKI as compared to SRS alone, reporting lower levels of local failure; at 12 months, local failure occurred in 4% patients treated with first-line TKI, as compared to 19%–27% in therapy naïve patients or patients undergoing SRS w/wo TKI post failing first-line therapy. After nephrectomy with or without resection of metastatic disease, RCC patients usually undergo treatment with first-line systemic therapy including bevacizumab/IFN alpha, high dose IL2, pazopanib, sunitinib or temsirolimus. Second line therapies include axitinib, cabozantinib, lenvatinib/everolimus and nivolumab; other options include everolimus and sorafenib (Tables 1-3).

Some of the commonly used targeted inhibitors include VEGFR inhibitors and TKI, including bevacizumab targeting VEGFR, lenvatinib targeting FGFR/VEGFR and Cabozantinib targeting VEGFR/AXL/cMet, with their benefits documented in several phase III clinical trials including CABOSUN, which reported improved PFS of 8.2 months (vs. 5.6 months) as compared to sunitinib with 34% reduction in rate of progression or death. In our hands, cabozantinib has resulted in robust response in bulky spinal involvement as illustrated in Fig. 4 where complete resolution of severe spinal cord compression is demonstrated.

Axitinib, pazopanib, sorafenib, sunitinib targeting VEGFR/PDGFR had likewise shown promising results in patients with metastatic RCC; median PFS was reported as high as 15.7 months with median OS of 29.9 months, with median PFS of 7.4 months and median OS of 13.6 months in sorafenib refractory patients.

Multiple phase 3 clinical trials are ongoing including CLEAR ( pembrolizumab- lenvatinib vs. everolimus-lenvatinib vs. sunitinib with PFS of 23.9 months vs. 9.2 months), CheckMate214 (nivolumab-ipilimumab vs. sunitinib with median OS not reached vs. 38.4 months), IMmotion151 (atezolizumab-bevacizumab vs. sunitinib with final OS 36.1 months vs. 38.7 months), JAVE...
LIN Renal 101 (avelumab-axitinib vs. sunitinib with median PFS of 13.3 months and 5.6 months), KEYNOTE-426 (pembrolizumab-axitinib vs. sunitinib with median PFS of 20.6 months vs. 11.3 months), and ADAPT (DC immunotherapy/sunitinib vs. sunitinib with median OS of 27.7 months vs. 32.4 months, and PFS of 6 months vs. 7.83 months) (clinicaltrials.org) for patients with metastatic RCC (Supplementary Table 1).

**PROSTATE CANCER**

Prostate cancer will commonly metastasize to bone and OS in patients with spine metastases is roughly 2.5 years. According to SEER, 7% patients diagnosed with prostate cancer have distant metastases at presentation, with 30.6% 5-year relative survival. Androgen receptor antagonists including flutamide, bicalutamide and abiraterone are commonly used as first-line androgen deprivation agents resulting in improvement in patient outcomes; as reported by STAMPEDE trial median OS was not reached with addition of zoledronic acid, 81 months with addition of docetaxel, 76 months with addition of both, and 71 months with standard of care (Table 1). Other androgen deprivation therapies include ketoconazole or abiraterone that inhibit CYP17 with resulting androgen synthesis blockade, and use of LHRH agonists/antagonists including leuprolone, goserelin, degarelix with resulting downregulation in LHRH receptor signaling, with degarelix inducing and maintaining androgen deprivation for up to 1 year (Table 1).

In patients with androgen resistant prostate cancer, a variety of other therapies have been utilized (Table 1). Small TKIs gefitinib, erlotinib targeting EGFR and lapatinib targeting EGFR/HER2 had shown some success with improvement in prostate-specific antigen (PSA) levels; phase II trial of lapatinib resulted in no radiologic evidence of metastatic disease in 7 of twenty nine patients. Monoclonal EGFR antibody cetuximab has been used alone and in combination with various chemotherapy agents including doxorubicin, docetaxel, and mitoxantrone with some improvement in PSA levels and/or median survival; combination of cetuximab with doxorubicin resulted in stable disease in 65% patients with castration resistant prostate cancer with bone disease (Table 1). MET/VEGFR2 inhibitor cabozantinib has likewise been trialed in patients with metastatic prostate cancer in several phase III trials including COMET-1/2, with no significant improvement in OS, with 15% (vs. 17%) responders and median OS of 11 months (vs. 9.8 months). PARP inhibitors including olaparib have been used in patients with androgen resistant prostate cancer, where phase II TOPARP-A trial showed an overall 33% response rate, especially in patients with underlying mutations in DNA damage repair pathways or BRCA1/2, while TOPARP-B trial reported 54.3% composite response, with radiographic response in 24.2% and PSA response in 37%.

In addition, anti-CTLA4 immunotherapy including ipilimumab has been trialed in patients with prostate cancer in phase III trials with improvement in PFS of 5.6 months (vs. 3.8 months) and measured PSA levels (Tables 2, 3). Some success was noted with use of PD1/PD-L1 inhibitors, including nivolumab, pembrolizumab, and atezolizumab, especially in patients with mismatch repair impairment, hypermutated prostate cancer lesions and those with microsatellite instability; in CheckMate 9KD trial, combination of nivolumab with docetaxel resulted in 9-month radiographic PFS and OS of 18.2 months (Tables 2, 3). Several tumor vaccines including an autologous Sipuleucel-T vaccine comprised of antigen presenting cells co-cultured with PA2024 prostatic acid phosphatase linked to GM-CSF have been successfully used to treat prostate cancer, with significant improvement in the reported OS in patients of up to 13 months in several phase III trials including IMPACT trial. Another area of investigation focuses on the development of chimeric antigen receptor T cells (CAR-T cells) for treating patients with metastatic prostate cancer, which had been previously tested and successfully applied for treatment of patients with hematologic malignancies.

**THYROID CANCER**

Although the percentage of patients with spine metastases arising from primary thyroid cancer, including differentiated thyroid carcinoma, anaplastic carcinoma and medullary thyroid carcinoma is not high, it is a common endocrine malignancy, and up to 30% patients will develop resistance to standard therapy and progress to metastatic disease (Table 1). According to SEER, 3% patients with thyroid cancer have distant metastases at the time of diagnosis, with 53.3% 5-year relative survival. Targeted inhibitors for the mitogen-activated protein kinase pathway have been trialed in patients with metastatic thyroid cancer. Sorafenib targeting VEGFR/Fit3/RET/cKIT/BRAF and lenvatinib targeting VEGFR/FGFR/PDGFR/KIT/RET have been trialed in patients with differentiated thyroid carcinoma with improvement in PFS and OS, respectively, by several phase II trials, as well as DECISION and SELECT phase III trials, the former of which reported median PFS of 10.8 months (vs. 5.8 months) with sorafenib use in radioactive iodine-refractory lo-
OS with vandetanib use, with 26.6 (vs. 21.1) median OS with cabozantinib use, including 44.3 months (vs. 18.9 months) median OS in patients with RET M918T positive disease.\(^{67,70}\) More recent studies focus on targeting PI3K pathway, ALK translocations, as well as HER2/3 receptors (Supplementary Table 1).\(^{71}\) Pannier et al reported ELM4-ALK and STRN-ALK fusions in patients with papillary and poorly differentiated thyroid carcinomas.\(^{72}\) Other studies are investigating the effects of immunotherapy including anti-CTLA4 and anti-PD1, and vaccine use (Table 3; Supplementary Table 1).\(^{74,75}\)

**CONCLUSION**

The number of patients with metastatic spine disease continues to rise. Moreover, even the most extensive surgical resection and aggressive radiation therapies are frequently insufficient to control the disease without adjunct medical therapy, which can successfully address residual microscopic disease and prevent recurrence, specifically within the bone environment. Historically, the ultimate demise in patients with metastatic spine disease is due to a combination of their extensive systemic disease burden and aggressive spine disease resulting in neurologic compromise. In the recent years, development of individualized, targeted therapies and novel treatment protocols had heavily depended on the identification of novel mutations and improved understanding of the biology of many cancers, giving hope to patients with spinal metastases to prevent disease progression, avert neurologic deficit and improve their quality of life. However, there remains a large void with developing therapeutic agents that can specifically target cancer within the unique bone milieu. Current literature is lacking in safety, efficacy, and estimates of overall response rates from the use of many of the new treatment agents when administered to patients with spine metastatic disease, however robust response can be achieved in select cases as described in this manuscript. Identification of predictors of favorable response to targeted inhibition, chemotherapy or immunotherapy of spine metastases derived from various primary cancers is a necessary next step.

**NOTES**

**Supplementary Materials:** Supplementary Table 1 can be found via https://doi.org/10.14245/ns.2244290.145.

**Supplementary Table 1.** Targeted therapies and immunotherapies approved by the U.S. Food and Drug Administration in the last 2 years.

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**Fig. 5.** Successful use of multitargeted tyrosine kinase inhibitor Lenvatinib in a patient with recurrent follicular thyroid carcinoma. Patient is a 70-year-old female who had undergone prior corpectomy with cage placement and posterior spinal fusion, followed by treatment with iodine, external beam radiation therapy and spine stereotactic radiosurgery, with significant progression of her disease shortly thereafter. Sagittal and axial magnetic resonance imaging of cervical and thoracic spine prior to initiation of treatment showing significant anterior cord compression C4–7 (A, B) and 3 months after treatment with Lenvatinib (C, D), showing resolution of the lesion and significant improvement in cord compression.
Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: EF, CT; Data curation: EF, CT; Formal analysis: EF; Funding acquisition: CT; Methodology: EF, CT; Project administration: CT; Visualization: EF; Writing - original draft: EF; Writing - review & editing: EF, JB, CAB, LR, CT.

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REFERENCES


**Supplementary Table 1.** Targeted therapies and immunotherapies approved by the U.S. Food and Drug Administration in the last 2 years

<table>
<thead>
<tr>
<th>Date approved</th>
<th>Name/trial/mechanism</th>
<th>Cancer type</th>
<th>Eligibility</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/25/22</td>
<td>Tebentafusp-tebn, NCT03070392, bispecific GP100 peptide-HLA-directed CD3 T cell engager</td>
<td>Unresectable or metastatic uveal melanoma</td>
<td>HLA-A*02:01 positive adult patients, no prior systemic or liver-directed therapy, no symptomatic untreated brain metastases, no cardiac disease, ok post resection</td>
<td>OS 21.7 months with trial vs. 16 months, PFS 3.3 months with trial vs. 2.9 months</td>
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<tr>
<td>12/3/21</td>
<td>Pembrolizumab</td>
<td>Stage IIIB of IHC melanoma post complete resection</td>
<td>Adjuvant Tx, adult and pediatric &gt; 12 years</td>
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<tr>
<td>11/17/21</td>
<td>Pembrolizumab, KEYNOTE-564</td>
<td>RCC, intermediate high or high risk of recurrence</td>
<td>Adjuvant Tx, post nephrectomy, with resection of metastatic lesions</td>
<td>Statistically significant improvement in DFS with trial Tx, 109 (22%) in Pembro arm and 151 (30%) in placebo</td>
</tr>
<tr>
<td>10/15/21</td>
<td>Atezolizumab</td>
<td>Stage II-IIIA NSCLC</td>
<td>Adjuvant Tx, post resection and platinum based chemoTx, &gt;1% PD-L1 expression in tumor cells</td>
<td>Median DFS not reached in trial Tx, 35.3 months in BSC arm</td>
</tr>
<tr>
<td>10/12/21</td>
<td>Abemaciclib+, first CDK4/6 inhibitor approved for adjuvant Tx, monarchE NCT03155997</td>
<td>HR+ HER2- LN+ early breast ca with high-risk recurrence, Ki67 &gt; 20%</td>
<td>Adjuvant Tx, combined with endocrine Tx (tamoxifen or aromatase inhibitor)</td>
<td>Statistically significant difference in IDFS with trial Tx 86.1% at 36 months vs. 79% with only tamoxifen or aromatase inhibitor</td>
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<tr>
<td>9/17/21</td>
<td>Cabozantinib, COSMIC-311 NCT03690388</td>
<td>Differentiated thyroid cancer, locally advanced or metastatic</td>
<td>Adult or pediatric &gt; 12 yo, progressive post VEGFR targeted Tx, ineligible of refractory to radioactive iodine</td>
<td>PFS 11 months with trial Tx vs. 1.9 months with placebo</td>
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<td>9/15/21</td>
<td>Mobocertinib</td>
<td>Locally advanced or metastatic NSCLC, Study 101 NCT02716116</td>
<td>Adult patients, EGFR exon 20 insertion mutations, progressive on platinum-based chemoTx</td>
<td>ORR 28% with median response duration of 17.5 months</td>
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<td>8/17/21</td>
<td>Dostarlimab-gxly, GARNET NCT02715284</td>
<td>Recurrent or advanced solid tumors, dMMR</td>
<td>Adult patients, mismatch repair deficient dMMR</td>
<td>ORR 41.6%, 9.1% complete, 32.5% partial response; DOR 34.7 months, with 95.4% patients with duration of &gt; 6 months</td>
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<td>8/13/21</td>
<td>Belzutifan, HIF1alpha inhibitor, study 004 NCT03401788</td>
<td>RCC, VHL associated</td>
<td>Adult patients, ok for associated CNS hemangioblastoma or pNET not requiring urgent surgery</td>
<td>ORR 49%, median DOR not reached, 56% of responders DOR &gt;12 months, median TTR of 8 months</td>
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<td>8/10/21</td>
<td>Lenvantinib +, CLEAR Study 307 KEYNOTE-581 NCT02811861</td>
<td>Advanced RCC</td>
<td>First line, in combination with pembrolizumab, regardless of PD-L1 status</td>
<td>PFS 23.9 months with trial Tx vs. 9.2 months with sunitinib, ORR 71% vs. 36%, complete response 16% vs 4% respectively</td>
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<td>7/26/21</td>
<td>Pembrolizumab +, KEYNOTE-522 (NCT03034888)</td>
<td>High risk, early-stage triple negative breast cancer TNBC</td>
<td>Neoadjuvant Tx combined with chemoTx, followed by adjuvant single agent post resection, 1-2 cm lesions LN+ or all lesions &gt; 2 cm regardless of PD-L1</td>
<td>CR was 63% with trial Tx vs. 56% with chemoTx only, event-free survival 123 (16%) in trial Tx vs. 93 (24%) in chemoTx alone</td>
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<tr>
<td>11/13/20</td>
<td>Pembrolizumab +, KEYNOTE-355 NCT02819518</td>
<td>Locally recurrent unresectable or metastatic TNBC</td>
<td>Combined with chemoTx, expressing PD-L1 CPS &gt;10</td>
<td>Median PFS 9.7 months pembrolizumab + chemoTx vs. 5.6 months placebo</td>
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<tr>
<td>5/28/21</td>
<td>Sotorasib, RAS GTPase family inhibitor, CodeBreaK100 NCT03600883</td>
<td>Locally advanced or metastatic NSCLC</td>
<td>Adult patients, KRAS G12C mutation, at least one prior systemic Tx</td>
<td>ORR 36% with median response duration 10 months</td>
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<tr>
<th>Date approved</th>
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<tr>
<td>5/21/21</td>
<td>Amivantamab-vmjw, bispecific Ab EGFR/MET, CHRYSALIS NCT02609776</td>
<td>Locally advanced or metastatic NSCLC</td>
<td>Adult patients, EGFR exon 20 insertion mutations, progressive on platinum-based chemoTx</td>
<td>ORR 40% with median response duration 11.1 months</td>
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<td>4/7/21</td>
<td>Sacituzumab goveitan, ASCENT NCT02574455</td>
<td>Unresectable locally advanced or metastatic TNBC</td>
<td>Adult patients, at least 2 systemic therapies, adjuvant or neoadjuvant, at least one systemic therapy for metastatic disease</td>
<td>Median PFS 4.8 months with trial Tx vs. 1.7 months with chemoTx; median OS 11.8 months with trial Tx vs. 6.9 months with chemoTx</td>
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<td>3/10/21</td>
<td>Tivozanib, kinase inhibitor, TIVO-3 NCT02627963</td>
<td>Relapsed or refractory advanced RCC</td>
<td>Adult patients, following 2 or more systemic Tx, at least one VEGFR kinase inhibitor other than sorafenib or tivozanib</td>
<td>PFS 5.6 months with trial Tx vs. 3.9 months with sorafenib; median OS 16.4 months with trial Tx vs. 19.2 months with sorafenib ORR 18% trial Tx vs. 8% sorafenib arm</td>
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<tr>
<td>3/3/21</td>
<td>Lorlatinib, Study B7461006 NCT03052608</td>
<td>Metastatic NSCLC</td>
<td>ALK-positive patients as first line, second or third line; no prior systemic Tx for metastatic disease</td>
<td>Improved PFS with trial Tx vs. crizotinib, HR 0.28; median PFS cannot estimate with trial Tx, 9.3 months with crizotinib; in patients with intracranial lesions ORR 82% lorlatinib vs. 23% ORR crizotinib arm</td>
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<td>2/22/21</td>
<td>Cemiplimab-rwlc, Study 1624 NCT03088540</td>
<td>Locally advanced (not candidate for surgery/chemo), or metastatic NSCLC</td>
<td>High PD-L1 expression TPS &gt; 50%, first line; no EGFR, ALK or ROS1 aberrations</td>
<td>Median OS 22.1 months with trial Tx vs. 14.3 months with platinum chemoTx; median PFS 6.2 months with trial Tx vs. 5.6 months platinum chemoTx; ORR 37% trial Tx vs. 21% platinum chemoTx</td>
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<td>2/3/21</td>
<td>Tepotinib, VISION NCT02864992</td>
<td>Metastatic NSCLC</td>
<td>Adult patients, MET exon 14 skipping alterations</td>
<td>ORR 43%; median response duration of 10.8 months</td>
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<tr>
<td>1/22/21</td>
<td>Nivolumab +, CHECKMATE-9ER NCT03141177</td>
<td>Advanced RCC</td>
<td>Combination with cabozantinib vs sunitinib, first line; previously untreated</td>
<td>Median PFS 16.6 months with trial Tx vs. 8.3 months with nivolumab + sunitinib; HR 0.6; median OS not reached; ORR 55.7% trial Tx vs. 27.1% nivolumab + sunitinib</td>
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<td>12/18/20</td>
<td>Osimertinib, ADAURA NCT02511106</td>
<td>Stage IB-IIIA NSCLC, non-squamous histology</td>
<td>Adjuvant Tx, EGFR exon 19 deletions or exon 21 L858R mutations, post resection, with or without prior chemoTx</td>
<td>Median DFS not reached trial arm, 19.6 months in placebo arm</td>
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<td>12/18/20</td>
<td>Relugolix, first oral GnRH receptor antagonist, HERO NCT03085095</td>
<td>Advanced prostate cancer</td>
<td>Adult patients, at least 1 year androgen deprivation Tx with recurrence post-surgery and RL or newly diagnosed castration sensitive</td>
<td>Medical castration rate 96.7% trial Tx by day 29 of 48-week treatment</td>
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<td>12/16/20</td>
<td>Margetuximab-cmkb, SOPHIA NCT02492711</td>
<td>Metastatic HER2+ breast cancer</td>
<td>Combined with chemoTx, had 2 or more anti-HER2 regimens, at least one for metastatic disease</td>
<td>PFS 5.8 months trial Tx vs. 4.9 months in trastuzumab plus chemoTx; ORR 22% vs. 16%; median DOR 6.1 months vs. 6.0 months</td>
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<td>12/1/20</td>
<td>Pralsetinib, ARROW NCT03037385</td>
<td>Medullary thyroid cancer, advanced or metastatic</td>
<td>Adult and pediatric &gt; 12 yo, RET mutated requiring systemic Tx, or RET fusion + requiring systemic Tx and radioactive iodine refractory</td>
<td>ORR 60% in patients w/prior cabozantinib or vandetanib, with 79% responses lasting over 6 months; ORR 66% with no prior cabozantinib or vandetanib, 84% patients with responses over 6 months</td>
</tr>
</tbody>
</table>
### Supplementary Table 1. Targeted therapies and immunotherapies approved by the U.S. Food and Drug Administration in the last 2 years (Continued)

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<td>9/4/20</td>
<td>Pralsetinib, ARROW NCT03037385</td>
<td>Metastatic NSCLC</td>
<td>Adult patients, RET fusion +</td>
<td>ORR 57%, 80% responders with prior platinum Tx with response over 6 months; ORR 70%, 58% responders with responses over 6 months no prior systemic Tx</td>
</tr>
<tr>
<td>7/30/20</td>
<td>Atezolizumab, IMspire150, NCT02908672</td>
<td>Unresectable or metastatic melanoma</td>
<td>BRAF V600E mutated, combination with cobimetinib and vemurafenib</td>
<td>Median PFS 15.1 months trial Tx vs 10.6 months in the placebo arm</td>
</tr>
<tr>
<td>6/29/20</td>
<td>Pertuzumab with trastuzumab, vs. hyaluronidase-xxzf FeDeriCa NCT03493854</td>
<td>HER2+ breast cancer, locally advanced, inflammatory or early stage</td>
<td>Combined with chemoTx as neoadjuvant Tx, &gt;2 cm or LN+, part of complete Tx for early breast cancer; or Adjuvant Tx for early breast ca with high risk of recurrence</td>
<td>Combined trial Tx showed noninferior pertuzumab and trastuzumab serum trough concentrations; pCR was 59.7% trial Tx vs. 59.5% pertuzumab/trastuzumab</td>
</tr>
<tr>
<td>6/16/20</td>
<td>Pembrolizumab, KEY-NOTE-158 NCT02628067</td>
<td>Unresectable or metastatic tumors mutation burden high TMB H &gt; 10 mut/MB</td>
<td>Adult and pediatric &gt;12 years, progressive through prior Tx and no other Tx options, max 10 target lesions, max 5 target lesions per organ</td>
<td>ORR 29%, 4% complete and 25% partial response rate; median DOR not reached, 57% with responses over 12 months, 50% patients with responses over 24 months</td>
</tr>
<tr>
<td>5/29/20</td>
<td>Ramucirumab, RELAY NCT02411448</td>
<td>Metastatic NSCLC</td>
<td>Combined with erlotinib, first line, EGFR exon 19 deletions or exon 21 L858R mutations</td>
<td>Median PFS 19.4 months trial Tx vs. 12.4-month placebo plus erlotinib; ORR 76% trial Tx vs. 75%, median DOR 18.0 months vs. 11.1 months</td>
</tr>
<tr>
<td>5/26/20</td>
<td>Nivolumab plus ipilimumab +, CHECKMATE-9LA NCT03215706</td>
<td>Metastatic or recurrent NSCLC</td>
<td>Combined with 2 cycles, platinum doublet chemoTx, first line, no EGFR or ALK genomic aberrations</td>
<td>Median OS 14.1 months trial Tx vs. 10.7 months platinum doublet Tx; PFS 6.8 months trial Tx vs. 5 months platinum doublet Tx; ORR 38% vs. 25%; median response duration 10 months trial Tx vs. 5.1 months chemoTx</td>
</tr>
<tr>
<td>5/22/20</td>
<td>Brigatinib, ALTA1L NCT02737501</td>
<td>Metastatic NSCLC</td>
<td>Adult patients, ALK mutation +</td>
<td>PFS 24 months trial Tx vs 11 months crizotinib; ORR 74% trial Tx vs 62% crizotinib</td>
</tr>
<tr>
<td>5/19/20</td>
<td>Olaparib, PROfound NCT02987543</td>
<td>Metastatic castration resistant prostate cancer</td>
<td>Adult patient, HRR pathway gene mutations (including BRCA1/2 or ATM), progressive on enzalutamide or abiraterone, all had bilateral orchietomy</td>
<td>rPFS 7.4 months trial Tx vs. 3.6 months with enzalutamide or abiraterone; median OS 19.1 months vs. 14.7 months; ORR 33% trial Tx vs. 2%</td>
</tr>
<tr>
<td>5/18/20</td>
<td>Atezolizumab, IMpower110 NCT02409342</td>
<td>Metastatic stage IV NSCLC</td>
<td>High PD-L1 expression &gt;50% tumor cells, first line, no EGFR or ALK genomic aberrations, no prior chemoTx for metastatic disease</td>
<td>Median OS 20.2 months trial Tx vs. 13.1 months chemoTx platinum; median PFS 8.1 months trial Tx and 5.0 months platinum chemoTx; ORR 38% vs. 29%</td>
</tr>
<tr>
<td>5/15/20</td>
<td>Rucaparib, TRITON2 NCT02952534</td>
<td>Metastatic castration resistant prostate cancer</td>
<td>BRCA mutated, prior Tx androgen receptor therapy or taxanes, prior bilateral orchietomy vs. GhRH analog</td>
<td>ORR 44%, median DOR cannot evaluate, range 1.7-24 months; 56% responders with DOR over 6 months</td>
</tr>
</tbody>
</table>

(Continued)
### Supplementary Table 1. Targeted therapies and immunotherapies approved by the U.S. Food and Drug Administration in the last 2 years (Continued)

<table>
<thead>
<tr>
<th>Date approved</th>
<th>Name/trial/mechanism</th>
<th>Cancer type</th>
<th>Eligibility</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/15/20</td>
<td>Nivolumab plus ipilimumab, CHECKMATE-227 NCT02477826</td>
<td>Metastatic or recurrent NSCLC</td>
<td>PD-L1 expression &gt; 1%, no EGFR or ALK aberrations, no prior systemic Tx</td>
<td>Statistically significant OS 17.1 months trial Tx vs 14.9 months platinum doublet chemoTx; median PFS 5.1 months vs 5.6; ORR 36% vs 30%; median duration 23.2 months vs 6.2 months</td>
</tr>
<tr>
<td>5/8/2020</td>
<td>Selpercatinib, LIBRET-TO-001</td>
<td>Metastatic RET fusion + NSCLC; advanced or metastatic RET mutant medullary thyroid cancer requiring systemic Tx; advanced or metastatic RET fusion positive thyroid ca requiring systemic Tx or radioactive iodine refractory</td>
<td>Adult and pediatric &gt; 12yo; RET fusion +, RET mutation +; NSCLC prior platinum Tx</td>
<td>NSCLC RET fusion+, prior platinum chemo: ORR 64%, 81% responders had responses &gt; 6 months; no systemic Tx ORR 85%, 58% responses &gt; 6 months</td>
</tr>
<tr>
<td>5/6/2020</td>
<td>Capmatinib, GEOMETRY mono1, NCT02414139</td>
<td>Metastatic NSCLC, confirmed MET exon 14 skipping</td>
<td>Treatment naïve or previously treated patients</td>
<td>ORR 68%, response duration of 12.6 months in naïve, ORR 41%, response duration 9.7 months in previously treated</td>
</tr>
<tr>
<td>4/22/20</td>
<td>Govitecan-hziy, IMMU-132-01, NCT01631552</td>
<td>Triple negative breast cancer</td>
<td>Adult, at least 2 prior Tx for metastatic disease</td>
<td>ORR 33.3%, median response duration of 7.7 months</td>
</tr>
<tr>
<td>4/17/20</td>
<td>Tucatinib+, HER2CLIMB NCT02614794</td>
<td>HER2+ metastatic breast cancer</td>
<td>Adult, advanced unresectable or metastatic including brain, prior Tx trastuzumab, pertuzumab and ado-trastuzumab emtansine</td>
<td>Treatment arm PFS 7.8 months and OS 21.9 months with trastuzumab, capecitabine and tucatinib; control arm PFS 5.6 months, OS 17.4 months; with brain metastases patients PFS 7.6 vs. 5.4 months; ORR 40.6% vs. 22.8%</td>
</tr>
<tr>
<td>2/25/20</td>
<td>Neratinib+, NALA NCT01808573</td>
<td>HER2+ breast cancer</td>
<td>Adult, advanced or metastatic cancer, 2 or more prior anti-HER2 based regimens post metastatic diagnoses</td>
<td>Neratinib with capcitabine PFS 5.6 months, PFS at 12 months 29%, OS 21 months, ORR 32.8%, response duration 12 months 8.5 months; lapatinib with capcitabine PFS 5.5 months, PFS at 12 months 15%, OS 18.7 months, ORR 26.7%, median response duration 5.6 months</td>
</tr>
</tbody>
</table>

HLA, human leukocyte antigen; OS, overall survival; PFS, progression free survival; DFS, disease free survival; TX, treatment; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; PD-L1, programmed cell death ligand 1; IDFS, invasive disease free survival; VEGFR, vascular endothelial growth factor receptor; ORR, overall response rate; dMMR, mismatch repair deficient; DOR, duration of response; RCC, renal cell carcinoma; VHL, von Hippel Lindau; CNS, central nervous system; PNET, primitive neuro ectodermal tumor; TTR, time in therapeutic range; TNBC, triple negative breast cancer; LN, lymph node; CR, complete response; CPS, combined positive score; NSCLC, non-small cell lung cancer; KRAS, Kirsten rat sarcoma virus; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; HR, hormone receptor; RT, radiation therapy; RET, rearranged during transfection; pCR, pathological complete response; rPFS, radiographic progression free survival; GhRH, growth hormone releasing hormone; MTC, medullary thyro.
Advances in the Treatment of Spinal Metastasis: Commentary on “Spinal Metastases and the Evolving Role of Molecular Targeted Therapy, Chemotherapy, and Immunotherapy”

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Spinal metastasis is a common complication of systemic cancer progression, and recurrent or radiation-refractory disease remains a significant clinical challenge. Over the past two decades, an increased understanding of the biology of cancer has led to the development of new therapies. Spine surgeons should be knowledgeable about systemic cancer therapies, as it informs the planning of surgical interventions. While the impact of these therapies on the systemic and visceral response of cancer is well-documented, most clinical trials do not specifically record the response of spinal metastatic disease. Thus, more information on the response of spinal metastasis to new treatments is needed to inform surgical decision-making.

In their review, Fomchenko et al. summarize the incidence and treatment options for spinal metastasis from primary non-small cell lung cancer, breast cancer, melanoma, renal cell carcinoma, prostate cancer, and thyroid cancers. Collectively, these primary cancers account for over 55% of all spine metastases diagnosed in the United States. The authors are to be commended for their comprehensive review of the targeted molecular therapies, chemotherapies, and immunotherapies for these cancers. The review also provides the authors' own examples of patients with spinal metastatic disease who significantly responded to newer therapies, which resulted in avoidance of spinal surgery. These clinical cases demonstrate effective local control within the spine following treatment with chemotherapy, targeted therapy, immunotherapy, and radiotherapy. Awareness of these responses can help with timing and planning of surgical interventions, as well as allow development of an individualized treatment strategy for patients with spinal metastasis.

Long-term survival data show that patients with spinal metastases are living longer. These survival gains reflect a combination of earlier detection and more efficacious medical therapy and radiation techniques. Surgery for spinal metastases can improve pain, deformity, and neurologic function, and an improved understanding of spinal metastatic disease leads to better surgical selection of patients with potential for long-term survival. Several algorithms exist to guide surgical decision-making including the NOMS (neurologic, oncologic, mechanical stability and systemic disease) framework, SINS (spinal instability neoplastic score) score and Tokuhashi score. However, these algorithms were constructed on
data gathered more than a decade ago and do not account for newer genomic data. With the advent of genomic analysis, an increasing percentage of patients can be identified with a targetable mutation. The review by Fomchenko et al. provides a comprehensive collation of targetable mutations including therapies for BRAF V600E mutations in melanoma (MEK inhibitors); T790M EGFR mutations in non-small cell lung cancer (crizotinib), VEGFR/AXL/cMet mutations in renal cell carcinoma (cabozantinib), and mutations in damage repair pathways in prostate cancer (PARP inhibitors). Surgeons should be aware of the molecular subtype of their patient's primary cancer and be cautious of using these older prognostic scoring systems, which might exclude patients from surgery based on predictions calculated using old data.

Overall, the management of spinal metastasis is complex and will continue to require a comprehensive multidisciplinary team to formulate an optimal treatment strategy. Although a robust response to the new targeted therapies has been observed in patients with spinal metastasis, the current literature is lacking on reporting of the safety, efficacy, and overall response rates. Future work is also needed to identify optimal surveillance strategies for repeat spinal imaging and appropriate follow-up by the spine surgeon. Further recognition of predictors of which patients will respond to treatment will continue to evolve as new molecular targets are identified and therapies are approved, and it is important for the spine surgeon to be aware of this prognostic data when counseling patients. The review by Fomchenko et al. provides a comprehensive summary of current treatment options available for patients with spinal metastasis that will serve as a useful reference for spinal surgeons.

Conflict of Interest: The authors have nothing to disclose.

REFERENCES

Comparative Effects and Safety of Full-Endoscopic Versus Microscopic Spinal Decompression for Lumbar Spinal Stenosis: A Meta-Analysis and Statistical Power Analysis of 6 Randomized Controlled Trials

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Objective: This meta-analysis with statistical power analysis aimed to evaluate the difference between full-endoscopic and microscopic spinal decompression in treating spinal stenosis.

Methods: We searched PubMed, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CNKI (China National Knowledge Infrastructure) for relevant randomized controlled trials (RCTs) regarding the comparison of full-endoscopic versus microscopic spinal decompression in treating lumbar spinal stenosis through February 28, 2022. Two independent investigators selected studies, extracted information, and appraised methodological quality. Meta-analysis was conducted using RevMan 5.4 and STATA 14.0, and statistical power analysis was performed using G*Power 3.1.

Results: Six RCTs involving 646 patients met selection criteria. Meta-analysis suggested that, compared with microscopic decompression, full-endoscopic spinal decompression achieved more leg pain improvement (mean difference [MD], -0.20; 95% confidence interval [CI], -0.30 to -0.10; p = 0.001), shortened operative time (MD, -12.71; 95% CI, -18.27 to -7.15; p < 0.001), and decreased the incidence of complications (risk ratio, 0.43; 95% CI, 0.22–0.82; p = 0.01), which was supported by a statistical power of 98.57%, 99.97%, and 81.88%, respectively.

Conclusion: Full-endoscopic spinal decompression is a better treatment for lumbar spinal stenosis, showing more effective leg pain improvement, shorter operative time, and fewer complications than microscopic decompression.

Keywords: Full-endoscopic spinal decompression, Microscopic spinal decompression, Lumbar stenosis, Meta-analysis

INTRODUCTION

Lumbar spinal stenosis is described as pathological spinal canal narrowing,¹ which will result in a series of neurological symptoms due to subsequent compression of nerve roots, including back and leg pain, claudication, and walking difficulty.²,³ As one of the most prevalent degenerative conditions,⁴⁻⁶ lumbar spinal stenosis was associated with an increased social and economic burden because it leads to pain and disability and reduces patients’ quality of life.⁷

For patients diagnosed with lumbar spinal stenosis at the initial phase, conservative treatments are always recommended,⁴ including physical therapy, anti-inflammatory agents, and drugs for relieving pain.⁸⁻¹¹ However, patients will be advised to receive
surgical intervention if it was more appropriate according to clinical symptoms, physical disability, and magnetic resonance imaging findings. Previous studies have demonstrated that surgical intervention was involved in better clinical outcomes in patients with lumbar spinal stenosis. Unfortunately, traditional open spinal decompression will result in significant trauma, a longer length of hospitalization, and an increased risk of postoperative complications because this surgery requires extensive dissection and stretching of the fatty muscles of the spine. Subsequently, various minimally invasive methods have emerged as an alternative to traditional open spinal decompression preserving the normal vertebral structures, preventing segmental instability, and reducing soft tissue damage.

Among available minimally invasive methods, microscopic spinal decompression has become one of the most common procedures related to less blood loss, lower risk of postoperative pain, and shorter hospital stays. It’s pointed out that microscopic spinal decompression also faced some disadvantages, such as bleeding in the field of view and postoperative adhesions in the spinal canal. However, with advancements in endoscopic spinal surgery, a full-endoscopic spinal system such as uniportal endoscopic system and biportal endoscopic spinal system has been developed and used for the treatment of lumbar spinal stenosis. Several meta-analyses have investigated the therapeutic values of the full-endoscopic spinal system in the treatment of lumbar spinal stenosis compared with microscopic spinal decompression. However, the credibility of results from the published meta-analyses was greatly impaired by some limitations, such as incorrect inclusion of studies with overlapping samples and inappropriate combination of data from randomized controlled trials (RCTs) and retrospective studies. Moreover, as one of full-endoscopic surgery, transforaminal endoscopic spine system (TESSYS) was not considered in previous meta-analyses. Therefore, we performed the present meta-analysis to further evaluate the comparative effects and safety of full-endoscopic decompression versus microscopic decompression by only including RCTs.

MATERIALS AND METHODS

1. Study Design

This meta-analysis was designed according to recommendations made by the Cochrane Handbook. Meanwhile, pooled results were reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement. We did not apply for Institutional Review Board's approval because the data analysis in this meta-analysis was performed based on published studies.

2. Literature Search

Two independent investigators searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and China National Knowledge Infrastructure (CNKI) for retrieving relevant RCTs from the establishment date of each database through February 28, 2022. The search strategy was developed using the combination of medical subject heading with the free word with the following terms: “spinal stenosis,” “full endoscopic,” “biportal endoscopic spinal surgery,” “unilateral biportal endoscopic technique,” “two portal endoscopic spinal surgery,” “microscopic decompression surgery,” “micro endoscopic spine surgery,” and “random.” The sensitivity of the search strategy was modified according to the requirements of databases. No language and publication status were restricted in the literature search. We summarized detailed search strategies of target databases in Supplementary Table 1. Moreover, we screened reference lists of eligible studies and previous meta-analyses to find additional studies. A third experienced investigator was invited to solve disagreements between 2 investigators about literature retrieval.

3. Selection Criteria

Studies were eligible for our meta-analysis if (1) they enrolled eligible adult patients with diagnosed lumbar spinal stenosis, (2) they are RCTs with full texts, (3) they compared full-endoscopic spinal decompression with microscopic spinal decompression for treating lumbar spinal stenosis, and (4) they reported at least one outcome from visual analogue scale (VAS) score for leg and back pain, operative time, estimated blood loss, the length of hospital stays, and the overall incidence of complications. Certainly, studies were excluded from our meta-analysis if (1) patients suffering from spinal stenosis resulting from a herniated intervertebral disc, (2) studies were designed as ineligible design, such as literature reviews, case reports, experimental studies, (3) repeated studies with relatively poor methodological quality and insufficient information, and (4) essential data for statistical analysis were not available after contacting the leading authors.

4. Data Extraction

Two independent investigators performed the study selection process according to selection criteria from 3 steps: (1) removal...
of duplicates, (2) initial eligibility evaluation based on the titles and abstracts, and (3) final eligibility evaluation through checking full texts. Then, essential information was independently extracted by 2 investigators using predesigned standard data extraction sheet from each eligible study: reference information (the first author's name and publication year), country, sample size randomly assigned into both groups, the proportion of male patients, mean age of patients, types of full-endoscopic spinal decompression, follow-up duration, outcomes of interest, and information for methodological quality. We contacted the leading author to obtain essential information if necessary. A third senior investigator was requested to resolve discrepancies between 2 independent investigators.

5. Outcomes of Interest
We defined the VAS score for leg and back pain at the final follow-up as the primary outcomes in this meta-analysis. Moreover, we regarded operative time, estimated blood loss, the length of hospital stays, and the overall incidence of complications as the secondary outcomes.

6. Risk of Bias Assessment
Two investigators used the Cochrane risk of bias assessment tool to independently assess the methodological quality of the included RCTs. In this assessment tool, the following 6 domains were involved: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other issues. Depending on the actual information reported in the included studies, each domain could be labeled with a "low," "unclear," or "high" risk of bias.

7. Statistical Analysis
Before performing quantitative synthesis, we used the chi-square test and I2 statistic to evaluate the statistical heterogeneity across eligible studies. A fixed-effects model was selected for data analysis if the absence of statistical heterogeneity (p > 0.1, I2 < 50%); otherwise, data analysis was carried out based on a random-effects model (p ≤ 0.1, I2 ≥ 50%). For dichotomous data, we used the risk ratio (RR) with a corresponding 95% confidence interval (CI) to express the estimates, and the mean difference (MD) with a corresponding 95% CI was used to express the estimates. We evaluated publication bias for primary outcomes by utilizing Begg rank correlation test and Egger linear regression test. Statistical analysis was carried out using Review Manager (RevMan) 5.4 (Cochrane Collaboration, Oxford, UK), and publication bias examination was performed by using Stata 14.0 (StataCorp LLC, College Station, TX, USA). Moreover, we also calculated the statistical power for each outcome using G*Power software version 3.1 to determine the confidence in drawing a definitive conclusion.

RESULTS
1. Literature Search Results
We identified a total of 29 relevant studies from 4 target electronic databases through performing search strategies, including PubMed (n = 5), Embase (n = 11), CENTRAL (n = 9), and CNKI (n = 4). After screening step by step, 4 eligible RCTs were considered to meet our selection criteria. Moreover, 2 additional RCTs were determined from previous meta-analyses. Finally, 6 RCTs were included in this meta-analysis. The process of study selection is indicated in Fig. 1.

2. The Characteristics of Included Studies
The basic information of included studies is summarized in Table 1. Among the 6 eligible RCTs, the sample size of individual study varied from 62 to 161, with 646 patients. All studies were published between 2009 and 2020. Two studies compared biportal technique with microscopic decompression, 3 studies compared uniportal technique with microscopic decompression, and one study compared the TESSYS with microscopic decompression. The follow-up duration of included studies ranged from 6 months to 24 months. Moreover, four and five studies reported VAS scores for leg and back pain, respectively. All studies reported single-level operative time, 3 studies reported estimated blood loss, 3 studies reported the length of hospital stays, and 5 studies reported the incidence of complications. The outcomes of included studies are summarized in Supplementary Table 2.

3. Quality Assessment
Among 6 included studies, the majority (83.3%) were evaluated as low risk in random sequence generation except for one study, which only stated random but did not describe the details of generating random sequence. Only 2 studies were rated as low risk in allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. All studies were labeled with unclear or low risk in attrition bias domains except for one study, which had a high risk in attri-
tion bias. All studies\textsuperscript{46-51} were regarded as low risk for reporting bias and other bias. Detailed risk of bias assessment is indicated in Supplementary Fig. 1.

4. Meta-Analysis Results

1) Leg and back pain

Four studies\textsuperscript{47-51} reported VAS scores for leg pain at the final follow-up of full-endoscopic spinal decompression in the treatment of lumbar spinal stenosis. We did not detect statistical heterogeneity across studies ($I^2 = 0\%$, $p = 0.99$). Therefore, statistical analysis was carried out based on the fixed-effect model. The pooled result indicated that full-endoscopic spinal decompression was associated with more leg pain relief than microscopic decompression (MD, $-0.20$; 95% CI, $-0.30$ to $-0.10$; $p = 0.0001$) (Fig. 2A).

Five studies\textsuperscript{47-51} reported VAS scores for back pain at the final follow-up of full-endoscopic spinal decompression in the treatment of lumbar spinal stenosis. Substantial statistical heterogeneity was determined between studies ($I^2 = 82\%$, $p < 0.1$). We, therefore, selected the random-effect model to perform statisti-
cal analysis, and the result indicated no difference between full-endoscopic and microscopic spinal decompression (MD, 0.05; 95% CI, -0.22 to 0.33; p = 0.71) (Fig. 2B).

### 2) Operative time

All studies reported single-level operative time between the 2 groups. Substantial statistical heterogeneity was detected between the articles ($I^2 = 81\%$, $p < 0.1$), and thus the random-effects model was selected for statistical analysis. Meta-analysis indicated that, compared with microscopic spinal decompression, full-endoscopic spinal decompression was associated with shorter operative time (MD, -12.71; 95% CI, -18.27 to -7.15; $p < 0.01$) (Fig. 3A).

### 3) Estimated blood loss

Among included studies, 3 studies estimated the volume of blood loss during treatment. As there was statistical heterogeneity between the studies ($I^2 = 97\%$, $p = 0.06$), we, therefore,
selected the random-effects model to perform statistical analysis. Pooled results suggested no statistical difference between full-endoscopic and microscopic spinal decompression (MD, -22.59; 95% CI, -46.45 to 1.26; p = 0.06) (Fig. 3B).

4) The length of hospital stays

Four studies reported the length of hospital stays after treatment. Substantial statistical heterogeneity was detected between studies (I² = 98%, p < 0.05). We therefore used the random-effect model to perform statistical analysis. The result indicated no statistical difference between full-endoscopic and microscopic spinal decompression in terms of this outcome (MD, -1.27; 95% CI, -2.55 to 0.02; p = 0.05) (Fig. 4A).

5) Overall incidence of complications

Five studies reported the incidence of complications between full-endoscopic spinal surgery and microscopic decompression. Statistical examination did not detect the presence of substantial statistical heterogeneity between the studies (I² = 0%, p = 0.01). We therefore selected the random-effects model for statistical analysis. Meta-analysis indicated a lower overall incidence of complications in patients receiving full-endoscopic spinal decompression than microscopic spinal decompression (RR, 0.43; 95% CI, 0.22–0.82; p = 0.01) (Fig. 4B).

5. Statistical Power

We calculated the statistical power of all outcomes at the significance level of 0.05. Finally, the statistical power of individual outcomes was 98.57% for leg pain, 10.13% for back pain, 99.97% for operative time, 58.35% for the estimated blood loss, 73.70% for the length of hospital stay, and 81.88% for an overall incidence of complications.

6. Publication Bias

Although the number of eligible studies did not meet the criteria of conducting publication bias, we still sought to evaluate publication bias by performing Egger and Begg tests. As indicated in Supplementary Fig. 2, symmetric Egger and Begg plots were created of VAS score for leg (z = 1.70, p = 0.089; t = 1.85, p = 0.206) and back (z = 0.24, p = 0.806; t = 1.44, p = 0.245) pain, indicating absence of publication bias.

DISCUSSION

Full-endoscopic spinal decompression has several advantages as an emerging minimally technique, including flexibility, a wide and clear field of view, and less soft tissue damage. However, the therapeutic effects and safety of full-endoscopic spinal decompression continue to be debatable in treating lumbar spinal stenosis in clinical practice compared with microscopic spi-
Full-Endoscopic Spinal Decompression Benefits to Spinal Stenosis

Yang Z, et al.

Several meta-analyses have investigated the comparative effects and safety of full-endoscopic spinal decompression with microscopic spinal decompression to treat lumbar spinal stenosis. Unfortunately, the findings from these meta-analyses must be considered in a cautious manner due to several limitations. For example, all meta-analyses included 2 studies from the same cohort (a prospective case-control study and a retrospective). Therefore, overlapped samples were included to falsely enhance the statistical power. It must be noted that, certainly, all meta-analyses simultaneously included RCTs and retrospective studies to estimate the comparative effects and safety between full-endoscopic spinal decompression and microscopic decompression. However, according to the methodological framework, it is inappropriate to combine results from RCTs and non-RCTs.

Compared with previous meta-analyses, the present meta-analysis generated more robust and reliable findings due to methodological advantages. First, only RCTs were included for the final analysis in this meta-analysis, which significantly enhanced the comparability between studies and the statistical power. Second, all available full-endoscopic spinal decompression systems were considered in the present meta-analysis. However, previous meta-analyses only included biportal or uniportal techniques, which limited the number of eligible studies and did not comprehensively consider the types of full-endoscopic decompression. Third, we either identified relevant studies by searching 4 electronic databases or added additional studies by checking previous meta-analyses, which greatly decreased the risk of missing potentially eligible studies. Finally, we calculated the statistical power of all outcomes to achieve a creditable conclusion, demonstrating the robustness and reliability of positive results in the present meta-analysis.

The present meta-analysis has some limitations, which could not be ignored. First, only 6 eligible RCTs with inadequate sample size were included in the final statistical analysis. Therefore, our findings may be fluctuated due to inadequate statistical power. Second, follow-up duration was different from one to another eligible study. However, we only extracted data at the final follow-up to evaluate the comparative effects and safety, which may introduce bias to impair the robustness of our findings. Third, this meta-analysis identified 3 available full-endoscopic spinal surgeries for lumbar spinal stenosis, including uniportal technique, biportal technique, and TESSYS. However, subgroup analysis was not performed according to the types of full-endoscopic spinal decompression due to inadequate number of eligible studies, which could cause heterogeneous results.

Fourth, although on restriction on language and publication status was imposed in this meta-analysis, potential risk of missing relevant studies could not be avoided because only 4 electronic databases were considered. Fifth, we developed the methodological framework for this meta-analysis in strict accordance with the recommendations made by the Cochrane handbook; however, we did not register the formal protocol in any public platform.

CONCLUSION

This meta-analysis evaluated the comparative effect and safety of full-endoscopic spinal decompression with microscopic spinal decompression in treating lumbar spinal stenosis by including 6 RCTs. Our results suggested that full-endoscopic spinal decompression is more effective than microscopic decompression, with more significant leg pain relief, shorter operative time, and lower complications. Due to the extremely insufficient statistical power of back pain, the estimated blood loss, and the length of hospital stay, future studies with a large-scale and high quality are warranted to determine the difference between full-endoscopic spinal decompression and microscopic decompression in treating lumbar spinal stenosis. Moreover, studies are also required to investigate the comparative effects and safety of different full-endoscopic spinal decompression systems.
NOTES

Supplementary Materials: Supplementary Tables 1-2 and Figs. 1-2 can be found via https://doi.org/10.14245/ns.2244600.300.

Supplementary Table 1. Search strategy of target databases

Supplementary Table 2. Outcomes of included studies (n = 6)

Supplementary Fig. 1. Risk of bias assessment.

Supplementary Fig. 2. Egger and Begg plots of visual analogue scale score for leg and back pain between full-endoscopic (a) and microscopic spinal decompression (b). SE, standard error.

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: ZY, WL, WH; Formal analysis: HW, WH; Methodology: ZY, HW, WL, WH; Writing - original draft: ZY, HW, WL; Writing - review & editing: ZY, HW, WL.

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17. Guha D, Heary RF, Shamji MF. Iatrogenic spondylolisthesis...


44. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible sta-
### Supplementary Table 1. Search strategy of target databases

#### Search strategy for PubMed

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#### Search strategy for Embase

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(Continued)
**Supplementary Table 1.** Search strategy of target databases (Continued)

Search strategy for CENTRAL (Cochrane Central Register of Controlled Trials)

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### Supplementary Table 2. Outcomes of included studies (n = 6)

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<th>Blood loss (mL)</th>
<th>Hospital stay (day)</th>
<th>Preoperative VAS score for back pain</th>
<th>Preoperative VAS score for leg pain</th>
<th>Final follow-up VAS score for back pain</th>
<th>Final follow-up VAS score for leg pain</th>
<th>Complications (n)</th>
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<td>Kang et al. 2019</td>
<td>36 ± 11 vs. 54 ± 9</td>
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<td>NR</td>
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<td>Park et al. 2020</td>
<td>67.2 ± 19.8 vs. 70.2 ± 22.8</td>
<td>NR</td>
<td>1.9 ± 0.68 vs. 2.4 ± 1.3</td>
<td>NR</td>
<td>NR</td>
<td>2.75 ± 2.70 vs. 2.22 ± 2.9</td>
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<td>Komp et al. 2015</td>
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<td>NR</td>
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<td>57.7 ± 23.8 vs. 65.3 ± 23.8</td>
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<td>Chen et al. 2018</td>
<td>75.2 ± 24.6 vs. 77.2 ± 26.3</td>
<td>48.3 ± 11.8 vs. 85.0 ± 18.6</td>
<td>2.81 ± 2.1 vs. 5.02 ± 2.2</td>
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VAS, visual analogue scale; NR, not reported.
Supplementary Fig. 1. Risk of bias assessment.
Supplementary Fig. 2. Egger and Begg plots of visual analogue scale score for leg and back pain between full-endoscopic (a) and microscopic spinal decompression (b). SE, standard error.
Reliability and Diagnostic Accuracy of Standard Dermatomes and Myotomes for Determining the Pathologic Level in Surgically Verified Patients With Cervical Radiculopathy

Chul Gie Hong, Woo Dong Nam

Department of Orthopedic Surgery, Kangwon National University Hospital, Chuncheon, Korea

Objective: This study aimed to investigate the reliability and diagnostic accuracy of typical dermatomes and myotomes for determining the pathologic level in surgically verified patients with cervical radiculopathy.

Methods: Patients who underwent single-level surgery due to cervical radiculopathy with at least a 60% reduction in preoperative symptoms or recovery of muscle power after surgery were included. The observed clinical symptoms (pain, paresthesia, motor weakness) were compared to those of typical cervical dermatomes and myotomes.

Results: Among the 227 patients reviewed, 142 (62.6%) had a standard dermatomal pattern, and 74 of 110 (67.3%) had a standard myotomal pattern. The myotome of C5/6 radiculopathy showed much more variance than those of other cervical segments. Among the patients with severe motor weakness (muscle strength ≤ grade 3 or obvious muscle atrophy), all those with involvement of root C5, C7, and C8 showed a typical pattern (C4/5: 13 of 13 patients, C6/7: 5 of 5 patients, C7/T1: 3 of 3 patients), while only 2 of the 6 patients (33.3%) with severe motor weakness caused by C5/6 radiculopathy fit the typical pattern.

Conclusion: Among various symptoms, cervical myotome is of great value in determining the pathological level. However, it should be noted that there is high variability in human dermatomes and myotomes, especially for motor weakness due to C6 root compression, which is more variable than others.

Keywords: Cervical radiculopathy, Cervical pain, Spinal disease, Nerve root compression

INTRODUCTION

Cervical radiculopathy is a common condition that usually results from compression of the cervical nerve roots, which is frequently caused by cervical disc herniation or cervical spondylosis. Neurologic signs and symptoms of cervical radiculopathy vary depending on the pathologic level of the cervical segment, but specific diagnosis might become easier if the root(s) compression lesion shown in advanced imaging, such as magnetic resonance imaging (MRI), matches the clinically expected level. Therefore, an effort has been made to evaluate the reliability of various signs and symptoms in determining the pathologic level(s). Cervical radiculopathy is generally considered to present in a reproducible pattern of dermatome and myotome attributable to the involved cervical root.

Unfortunately, most neurologic manifestations used to determine cervical pathologic level do not have high diagnostic accuracy in the real world. Additionally, in clinical practice, patients who have severe nerve root compression on cervical spine MRI frequently do not complain of any symptoms. Therefore, the imaging findings should be carefully correlated with the neurological examination. Spine surgeons are required to differen-
tiate the pathologic level of cervical radiculopathy with asymptomatic radiographic cervical nerve root compression.\textsuperscript{6}

Riew stated that only about half of cervical radiculopathy patients had a “typical” pattern of clinical symptoms.\textsuperscript{4,5} This is well known to experienced cervical spine surgeons, and similar findings have been reported in the past. However, data on the variability with which cervical radiculopathy presents in real clinical practice and how often the actual presentation might deviate from the typical human dermatomes and myotomes remains limited. Such information would be useful to surgeons making diagnoses as to the causative root level. Therefore, the aim of this study was to determine how often patients present with typical myotome and dermatome patterns in a surgically verified population undergoing single-level cervical surgery for radiculopathy.

**MATERIALS AND METHODS**

After Institutional Review Board approval of Kangwon National University Hospital (A-2019-08-002-004), a retrospective review was performed on the records of all patients with single-level cervical radiculopathy who underwent surgery. Patients with single-level radiculopathy were selected to correlate the presenting symptoms with a specific root level. Surgical treatment methods included anterior cervical discectomy and fusion (ACDF), anterior disc replacement (ADR), and posterior foraminotomy (PF); all the surgical procedures were performed by the same surgeon between March 2011 and March 2018. ACDF was the most common surgical method and ADR was performed in relatively young patients without dynamic instability (\(> 2.0 \text{ mm translation on flexion-extension lateral radiographs}\)) and without severe spondylosis. Patients with a high amount of neck pain due to facet arthropy were not indicated for ADR surgery. The electronic medical records were reviewed to obtain data consistent with the study’s inclusion criteria, which included (1) MRI imaging demonstrating evidence of single-level nerve root compression at the level thought to be causing symptoms; (2) relief of symptoms, especially radiating pain and/or motor weakness, after decompression surgery; and (3) at least a 60% reduction in preoperative symptoms or recovery of G1 or more of muscle power by the 6-month postoperative follow-up. Patients with myelopathic symptoms and identifiable cervical spinal cord compression and cord signal change in MRI imaging and those in which bilateral root compression was present were excluded. All patients included in this study underwent a nonsurgical treatment, such as physical therapy, medications, or epidural steroid injection, for at least 3 months before surgery, or were assessed to have a progressive or clinically significant motor weakness in the muscle strength test. The single nerve roots involved in this study were limited to the fifth, sixth, seventh, and eighth cervical roots.

We analyzed patient demographics, level of root lesion, clinical symptoms (pain, sensory change, and motor weakness), duration of symptoms, and the degree of pre- and postoperative pain. To evaluate pre- and postoperative pain, the Neck Disability Index (NDI) and visual analogue scale (VAS) for neck/arm pain scores were also analyzed.\textsuperscript{7}

All manual motor grade scores were evaluated by a single skilled examiner. The most commonly accepted method of assessing muscle strength is the Medical Research Council (MRC) scale.\textsuperscript{8} This method involves testing key muscles against the examiner’s resistance and grading the patient’s strength on a 0 to 5 scale. (grade 0, no muscle activation; grade 1, trace muscle activation, such as a twitch, without achieving full range of motion; grade 2, muscle activation with gravity eliminated, achieving full range of motion; grade 3, muscle activation against gravity; grade 4, muscle activation against some resistance; grade 5, muscle activation against examiner’s full resistance). Testing the strength of the elbow flexors, elbow extensors, wrist extensors, finger flexors, and hand intrinsic muscles allows for a methodical evaluation of the C5 to C8 nerve roots (Table 1). Severe motor weakness was defined by an MRC score \(\leq\) grade 3 or by the observation of distinct muscle atrophy.

The location and characteristics of clinical symptoms (pain, paresthesia, and numbness) reported by the patient were described on pictorial maps (Fig. 1). Depending on the severity of symptoms, more marking could be done. To determine the involved level through the pain pattern, the dermatomal pattern of arm pain was considered first. If it was difficult to select just one level using the pattern of arm pain, both arm and axial neck pain were considered together. When the pain pattern was broad, the level was determined as the most painful area. The pathologic disc level using clinical symptoms was assessed by 2 independent examiners (1 staff and 1 fellow). In case of a disagreement on the disc level, the conclusion was drawn through a mutual discussion.

The data were analyzed using the IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA). For surgical outcomes, the change from the baseline in each group was evaluated using paired t-tests. Differences between the 2 groups were evaluated using Student t-test for continuous variables and the chi-square test for categorical variables.
RESULTS

The medical records of 227 patients met the inclusion criteria of the study and were reviewed. Baseline patient characteristics and the surgical procedures performed are presented in Table 2. Overall, 227 cervical segments were included in this study (C4/5:30; C5/6:115; C6/7:69; C7/T1:13), and there was no significant difference in the demographics of the patients who underwent surgery on different cervical segments. The symptom onset varied between 0.5 and 100 months (mean, 8.1 months).

Among the 227 patients, 209 (92%) underwent anterior decompression surgery and 18 (8%) underwent posterior decompression surgery (PF). No differences in VAS scores for arm and neck pain or NDI scores in the pre- and postoperative period were noted between the anterior (ACDF and ADR) and posterior (PF) surgery groups (Table 2).

Arm pain was the most common presenting symptom, occurring in 213 patients (93.8%). The mean VAS score of preoperative arm pain was 7.26 ± 2.02 (range, 0–10), while that postoperatively was 1.34 ± 1.79 (range, 0–6) (p < 0.01). Pain in the axial neck (around the neck, shoulder, scapula, and interscapula) was recorded in 185 patients (81.4%). The mean preoperative axial neck pain was 6.29 ± 2.47 (range, 0–10), which decreased to 1.13 ± 1.42 (range, 0–6) postoperatively (p < 0.01) (Table 3).

Among the 30 patients with C4/5 radiculopathy, 20 (66.6%) showed a typical dermatomal pattern in which the involved root and the location of the symptom were consistent. Mean while, 7 patients (23%) at this level complained of different dermatome pain (C6: 4 patients and C7: 3 patients), and in 3 patients (10%), symptoms were too broad or poorly localized to be characterized as one specific level. In patients with C5/6 radiculopathy, 69 patients (60.0%) showed a typical dermatomal

Table 1. Compression of cervical root: summary of "typical" clinical findings

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<td>Deltoid</td>
<td>Biceps</td>
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<tr>
<td>C5/6</td>
<td>C6</td>
<td>Radial forearm to thumb and index finger</td>
<td>Biceps</td>
<td>Biceps</td>
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<tr>
<td>C6/7</td>
<td>C7</td>
<td>Midradial forearm to index and middle finger</td>
<td>Wrist extensor</td>
<td>Brachioradialis</td>
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<tr>
<td>C7/T1</td>
<td>C8</td>
<td>Ulnar forearm to ring and little finger</td>
<td>Wrist flexor</td>
<td>Triceps</td>
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Fig. 1. Dermatomes diagram demonstrates the dermatomal map of radiating arm pain (A) and axial neck pain including neck, scapular, interscapular (B). The red X marks indicate the location of the patient’s reported pain.
pattern, and 46 patients (40.0%) showed an atypical dermatomal pattern (C5:11 patients, C7:25 patients, C8:10 patients). There were 45 patients (65.2%) with a typical pattern and 23 (33.3%) with an atypical pattern (C5:4 patients, C6:12 patients, C8:7 patients) in the C6/7 radiculopathy group. There were 8 patients (61.5%) with a typical pattern, 4 (30.7%) with an atypical pattern similar to that of C7 nerve compression, and 1 patient (7.6%) with poorly described pain in the C7/T1 radiculopathy group (Fig. 2).

Objective muscle weakness was initially recorded in 110 of 227 patients (48.5%), and severe motor weakness was observed in 27 patients (11.9%). No patient experienced greater weakness after the surgical treatment. In total, 20 of 23 patients (56.9%) with C4/5 radiculopathy, 20 of 42 patients (47.6%) with C5/6 radiculopathy, 24 of 34 patients (70.5%) with C6/7 radiculopathy, and 10 of 10 patients (100%) with C7/T1 radiculopathy showed typical motor weakness (Fig. 3). All patients with involvement of root C5 (C4/5 radiculopathy) and C7 (C6/7 radiculopathy) showed typical motor weakness (C4/5: 13 of 13 patients, C6/7: 5 of 5 patients). However, among the patients

Table 2. Demographic data

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<td>6.4 ± 2.7</td>
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<td>7.2 ± 2.1</td>
<td>7.4 ± 2.0</td>
<td>7.8 ± 2.5</td>
<td>7.26 ± 2.02</td>
</tr>
<tr>
<td>Preoperative NDI</td>
<td>14.9 ± 6.6</td>
<td>18.8 ± 8.3</td>
<td>16.2 ± 9.1</td>
<td>10.9 ± 9.9</td>
<td>17.3 ± 8.44</td>
</tr>
<tr>
<td>No. of motor weaknesses</td>
<td>23 (76.7%)</td>
<td>42 (36.5%)</td>
<td>34 (49.3%)</td>
<td>10 (76.9%)</td>
<td>110 (48.5%)</td>
</tr>
<tr>
<td>No. of severe weaknesses</td>
<td>13 (43.3%)</td>
<td>6 (5.2%)</td>
<td>5 (7.2%)</td>
<td>3 (23.1%)</td>
<td>27 (11.9%)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
BMI, body mass index; VAS, visual analogue scale; NDI, Neck Disability Index; ACDF, anterior cervical discectomy and fusion; ADR, artificial disc replacement; PF, posterior foraminotomy.

Table 3. Surgical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anterior surgery (ACDF and ADR)</th>
<th>Posterior surgery (PF)</th>
<th>p-value</th>
<th>Total cases</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.28 ± 2.47</td>
<td>6.47 ± 2.56</td>
<td>0.78</td>
<td>6.29 ± 2.47</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>1.11 ± 1.41</td>
<td>1.35 ± 1.66</td>
<td>0.51</td>
<td>1.13 ± 1.42</td>
<td></td>
</tr>
<tr>
<td>VAS arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.24 ± 2.01</td>
<td>7.53 ± 2.26</td>
<td>0.59</td>
<td>7.26 ± 2.02</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>1.34 ± 1.82</td>
<td>1.35 ± 1.50</td>
<td>0.98</td>
<td>1.34 ± 1.79</td>
<td></td>
</tr>
<tr>
<td>NDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Preoperative</td>
<td>17.73 ± 8.16</td>
<td>12.42 ± 10.32</td>
<td>0.03</td>
<td>17.3 ± 8.44</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>6.16 ± 4.65</td>
<td>4.71 ± 4.97</td>
<td>0.22</td>
<td>6.04 ± 4.68</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
ACDF, anterior cervical discectomy and fusion; ADR, anterior disc replacement; PF, posterior foraminotomy; VAS, visual analogue scale; NDI, Neck Disability Index.
with severe motor weakness, only 2 of the 6 patients (33.3%) with involvement of the C6 nerve (C5/6 radiculopathy) paradoxically showed typical weakness pattern, such as elbow flexion and wrist extension (Fig. 4).

**DISCUSSION**

In our series, we included patients with single-level cervical radiculopathy who underwent surgery via different surgical methods. Although there are various options available for the operative intervention of cervical radiculopathy, anterior cervical decompression surgeries, such as ACDF and ADR have become the most common surgical methods. However, an anterior cervical exposure is more difficult at the lower level of the cervical spine such as the C7/T1 cervical segment. An alternative treatment option in this region is mini open PF alone or with concurrent discectomy.

In clinical practice, when determining the surgical level causing symptoms in patients with cervical radiculopathy, the typical dermatomal map and the function of the muscle innervated by the specific nerve are considered first. The most common symptoms associated with cervical radiculopathy are pain and/or paresthesia through the upper extremities in the dermatomal distribution of the involved nerve roots.

McAnany et al. reported that, among 239 patients with single-level cervical radiculopathy, only 129 (54%) showed radiation pain and numbness following the standard dermatomal pattern. In present study, 62.6% (142 of 227) of the patients were identified as having the standard dermatomal pattern, which was slightly higher than that in the results reported in previous studies. Presumably, the reason for the greater prevalence of patients with a standard pattern in our study is that we determined the surgical level using the pattern of pain in the axial neck (neck, shoulder, trapezius, and periscapular pains) and in the distal part of the arm and our study was performed at a single center.

Previous studies have investigated axial pain patterns provoked by cervical discography and injections into the facet joints of the cervical spine. These studies suggested that stimulation of each disc results in consistent and predictable patterns of neck pain. Although the dermatomal distribution of arm pain and sensory dysfunction is the most important clue, axial neck pain including cervicogenic headache, shoulder pain, and parascapular pain might help determine the surgical target level.

According to our result, ipsilateral axial neck pain occurred in 81.4% of patients, and some patients complained of only axial neck pain without particular arm pain or sensory dysfunction. Therefore, when determining the surgical target level, it seems advantageous to combine the 2 types of pain distribution, although the neck, shoulder, and parascapular pain distributions alone is of little value for localizing the level of cervical
Weakness of single muscles or muscle groups is of great value in the localization of a lesion to a single nerve root. However, there are many charts in the literature, which differ from one another. Thus, some authors stated that localized weakness is not of decisive value in establishing the segmental level of a radicular lesion. Weakness of the deltoid with less severe weakness of the biceps muscle has been described in lesions of root C5. Involvement of the C6 root frequently causes marked weakness in the biceps, brachioradialis, and wrist extensor muscles. Other authors have considered that weakness in the deltoid and triceps was caused by lesions of root C6. Lesions of root C7 have resulted in weakness mainly in the triceps according to some authors, but others have included weakness in the biceps and deltoid also. Most authors agree that lesions of C8 cause most marked weakness in the intrinsic muscles of the hand.

Based on our results, relative to muscle weakness, the pathologic nerve could be localized correctly in 67.3% (74 of 110). However, the motor weakness of C5/6 radiculopathy (C6 nerve lesion) showed much more variance, with typical motor weakness demonstrated in 47.6% (20 of 42) of the patients. When the patient had severe motor weakness (distinct muscle atrophy and motor power grade 3 or less), a single nerve root lesion except for the lesion of C6 root could be determined much more accurately. In all cases with severe weakness involving root C5, C7, or C8, the pathologic nerve root could be correctly localized. However, in C6 radiculopathy patients with severe motor weakness, 4 of 6 patients (66.7%) had weakness that did not conform to the standard pattern.

This result in our study was similar to that of a study that identified electrodiagnostic patterns for each level of cervical radiculopathy. Levin et al. compared 50 cases of surgically proven solitary-root lesions with their preoperative electrodiagnostic patterns. With C5, C7, and C8 radiculopathies, changes were relatively stereotypical, with involvement of the supra- and infraspinatus, deltoid, biceps, and brachioradialis with C5; the pronator teres, flexor carpi radialis, triceps, and anconeus with C7; and the first dorsal interosseous, abductor digiti minimi, abductor pollicis brevis, flexor pollicis longus, and extensor indicis proprius with C8. The root lesion with the most variable presentation was C6. In half the patients with C6 radiculopathy, the findings were similar to C5 radiculopathies, whereas in the other half, the findings were identical to those of patients with C7 radiculopathies.

Discrepancies from the usual clinical findings in single cervical root compression might be the result of variations in the brachial plexus and the intradural connection of rootlets. In cadaveric studies of the human nervous system, more than 50% of the anatomical variations occurred in the brachial plexus. Standard textbooks describe the roots of the brachial plexus as arising from the last 4 cervical nerves and the first thoracic nerve with an occasional contribution from the fourth cervical (pre-fixed) and second thoracic (post-fixed) nerves. These variations may lead to deviation from the expected dermatome distribution as well as differences in the motor innervation of muscles of the upper limb. Additionally, when evaluating motor function, certain joint motions cannot separate the actions of individual muscles. Muscle function tests for the biceps and brachioradialis are such examples. It has been proposed that the biceps and brachioradialis can be separately evaluated by changing the forearm position for pronation/supination. However, we feel that it is difficult to definitely separate the actions of these 2 muscles. In this regard, normal biceps may have masked the brachioradialis dysfunction associated with the C6 lesion. Involvement of the C6 nerve root is the second most common cause of cervical radiculopathy. In patients with C6 radiculopathy, motor weakness in the wrist extensors and biceps are common but weakness of the supinator, pronator teres, and triceps muscles may also be present. The diversity of muscle units in which the C6 nerve root is involved may confuse C6 radiculopathy with C5 and C7 nerve root symptoms.

Our study has certain limitations inherent to retrospective studies. First, the examiner was not blinded to other information. The MRI findings were sometimes known prior to the examination. More importantly, if, for example, the examiner came to believe that the patient had a C6 lesion during the muscle tests and other neurological examinations, then the overall findings may have been biased. Second, we used a 60% or greater reduction in preoperative symptoms as an inclusion criterion for the study, with the 60% or greater improvement used as an indicator that the correct level of pathology had been addressed. However, it remains possible that radiculopathy at other levels could account for the remaining symptoms left unresolved in those who did not get 100% relief.

CONCLUSION

Identification of the exact root level(s) causing radiculopathy can be important in all patients and critical in those who elect to have surgical treatment. Determining the single nerve root involved in the basis of clinical signs and symptoms may be desirable and reasonably expected based on our findings. Of the
various signs and symptoms, severe motor weakness of the upper extremity is of great value in permitting specific localization to a single root. However, it should be noted that greater variation may occur when determining the pathologic disc level by evaluating the pattern of muscle weakness in patients with C6 radiculopathy. Clinicians who attempt accurate localization of cervical root lesions on a clinical basis alone must be aware of the possible variations and frequent lack of positive findings in any given patient.

NOTES

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Author Contribution: Conceptualization: WDN; Data curation: CGH; Formal analysis: CGH; Methodology: CGH, WDN; Visualization: CGH; Writing - original draft: CGH; Writing - review & editing: CGH.

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Woo Dong Nam: 0000-0001-5117-2521

REFERENCES
Surgical Versus Conservative Management for Treating Unstable Atlas Fractures: A Multicenter Study

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4Department of Neurosurgery, St. Vincent’s Hospital, The Catholic University of Korea, Suwon, Korea
5Department of Neurosurgery, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea
6Department of Neurosurgery, Eunpyeong St. Mary’s Hospital, The Catholic University of Korea, Seoul, Korea
7Department of Neurosurgery, Yeungnam University Medical Center, Daegu, Korea
8POSTECH Biotech Center, Pohang University of Science and Technology, Pohang, Korea

Objective: This multicenter study compared radiological parameters and clinical outcomes between surgical and nonsurgical management and investigated treatment characteristics associated with the successful management of unstable atlas fractures.

Methods: We retrospectively evaluated 53 consecutive patients with unstable atlas fracture who underwent halo-vest immobilization (HVI) or surgical fixation. Clinical outcomes were assessed using neck visual analogue scale and disability index. The radiological assessment included total lateral mass displacement (LMD) and the anterior atlantodental interval (AADI).

Results: Thirty-two patients underwent surgical fixation and 21 received HVI (mean follow-up, 24.9 months). In the surgical fixation, but not in the HVI, LMD and AADI showed statistically significant improvements at the last follow-up. The osseous healing rate and time-to-healing were 100% and 14.3 weeks with surgical fixation, compared with 71.43% and 20.0 weeks with HVI, respectively. Patients treated with HVI showed poorer neck pain and neck disability outcomes than those who received surgical treatment. LMD showed an association with osseous healing outcomes in nonoperative management. Clinical outcomes and osseous healing showed no significant differences according to Dickman’s classification of transverse atlantal ligament injuries.

Conclusion: Surgical internal fixation had a higher fusion rate, shorter fracture healing time, more favorable clinical outcomes, and a more significant reduction in LMD and AADI compared to nonoperative management. The pitfalls of external immobilization are inadequate maintenance and a lower probability of reducing fractured lateral masses. Stabilization by surgical reduction with interconnected fixation proved to be a more practical management strategy than nonoperative treatment for unstable atlas fractures.

Keywords: Cervical trauma, Unstable fracture, Jefferson fracture, Atlas fracture, Halo-vest, Surgery

INTRODUCTION

Atlas fracture is rare and accounts for 1.3% to 2% of all spinal injuries and 2% to 13% of all cervical spine fractures.1,2 Atlas fractures are classified as stable or unstable based on the integrity of the transverse atlantal ligament (TAL).2 The transverse ligament prevents anterior displacement of the C1 on the C2 and inhibits the translation of lateral masses of the C1 ring. Severe displace-
ment in an atlas fracture incurs potentially life-threatening neurological risk since the atlas lies at the brainstem level, and a TAL tear induces occipito-atlantoaxial instability. It is essential to restore the integrity of the TAL or replace its role with other stabilizers to treat unstable atlas fractures. The “rule of Spence,” according to which a TAL injury can be diagnosed if the total lateral mass displacement (LMD) exceeds 6.9 mm, has been widely used. However, recent studies have shown that existing concepts are inaccurate and should be discarded for predicting TAL integrity or atlantoaxial stability and treatment decision-making. Dickman classified TAL injuries using magnetic resonance imaging (MRI); a TAL type I injury, characterized by a rupture in the substance of the ligament, should be implemented with early surgery, whereas a TAL type II injury, involving an avulsion fracture at the insertion site of the ligament, has a successful healing rate when treated nonoperatively.

Various surgical options for treating unstable atlas fractures with favorable outcomes have recently been introduced, such as anterior C1 ring osteosynthesis, C1 open reduction and internal fixation (ORIF), posterior C1–2 fixation, or occipitocervical fusion. Nonoperative management with halo-vest immobilization (HVI) or cervical braces often results in nonunion of C1–2, persistent neck pain, pin site loosening, abscess formation, or late atlantoaxial instability. However, some researchers have reported that unstable atlas fractures with TAL rupture can be successfully managed by nonoperative treatment. According to Dickman’s suggestion, an atlas avulsion fracture with transverse ligament rupture could be managed by external immobilization, such as a rigid brace or a halo-vest device. Conservative treatments have been widely performed as the method of choice in most cases, while accepted surgical indications are an intraligamentous tear of the TAL, atlantooccipital instability, and an especially unstable atlas fracture. Advocates of surgery have argued that surgical techniques are preferable in fixing fractures as conservative treatments result in delayed atlantoaxial instability, craniovertebral settling, high nonunion rate, and late neurological sequelae. Whether unstable atlas fractures should be treated surgically or conservatively remains a matter of debate.

This multicenter study compared radiological parameters and clinical outcomes: patient-reported pain, neck disability, neurological impairment, and difference in the effectiveness of nonoperative management and surgical fixation in patients with unstable atlas fractures with TAL injuries.

**MATERIALS AND METHODS**

A retrospective cohort study was conducted with approval from the local ethics committee and Institutional Review Board (approval number: 2018-10-007). In total, 116 consecutive cases with isolated or associated atlas fractures treated from January 2000 to December 2019 were obtained from 4 universities (Yonsei University, Inje University, The Catholic University, and Yeungnam University) for analysis. The inclusion criteria were isolated unstable atlas fractures identified on radiographs, > 6.9-mm LMD and confirmed fractures on 3-dimensional computed tomography (3D CT) or TAL injuries on MRI, nonoperative or surgical management performed during the acute traumatic phase, patient age of over 18 years, and a minimum follow-up period of 12 months. The exclusion criteria were stable fractures, concomitant cervical fractures, and nonacute or pathological fractures. Finally, this study included 53 patients who had unstable fractures with TAL injuries (Fig. 1).

The diagnosis was made using modalities such as radiographs, CT, and MRI. According to the “rule of Spence,” a fracture was determined to be unstable if the total LMD overhang exceeded 6.9 mm on an open-mouth radiograph. The type of transverse ligament injury was assessed with CT or MRI in all patients, and 3D CT angiography was performed to assess fractures, such as the presence of an avulsion fracture at the TAL insertion site, a comminuted fracture, or a lateral mass. MRI was used to assess the TAL injuries, with relevant features including high signal intensity of the TAL on T2-weighted or gradient echo imaging, ligament discontinuity, or insertion site bleeding. The treating surgeon decided upon surgical fixation or nonoperative treat-

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**Fig. 1.** Patient flowchart. HVI, halo-vest immobilization.
ment based on the patient’s comorbidities, shared decision-making, and the surgeon’s preference and experience.

The total LMD and the anterior atlantodental interval (AADI) were calculated. Cervical lordosis was examined using the Cobb angle (Fig. 2). The range of motion (ROM) of C2–7 was determined as the difference in the Cobb angle between flexion and extension at 3, 6, and 12 months postoperatively, but not preoperatively due to the possibility of neurological deterioration. All patients underwent regular follow-up assessments on the seventh day after treatment and at scheduled follow-up appointments. After 12 weeks, dynamic cervical views were ascertained for fracture healing. Osseous healing was defined as confirmation of trabeculation across the fracture on CT scans and stability confirmed by the absence of a difference in the AADI on dynamic observations. Nonunion was defined as unsatisfactory osseous healing, pseudoarthrosis, instability on dynamic films, significant postural pain, or any combination thereof at 6 months. We repeatedly assessed the x-ray every month if osseous healing was not achieved. The halo-vest device for nonsurgical management and neck collars for the surgical operation was continued until bony fusion was confirmed. After 1 year, follow-up radiological outcomes were assessed with dynamic x-rays every 6 months.

A patient-reported visual analogue scale (VAS) for neck pain and the Neck Disability Index (NDI) were measured preoperatively and during the last follow-up visit. The American Spinal Injury Association was used to determine the grade of neurological deficits. All patients received assessments 1 week after surgical treatment, and a follow-up visit was scheduled.

Table 1. Patient demographics (n = 53)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.23 ± 14.62</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>32:21</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>37</td>
</tr>
<tr>
<td>Fall down</td>
<td>16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.53 ± 4.26</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>-1.67 ± 1.38</td>
</tr>
<tr>
<td>Smoking</td>
<td>29 (54.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (20.8)</td>
</tr>
<tr>
<td>Management starting time (day)</td>
<td>2.68 ± 1.72</td>
</tr>
<tr>
<td>Management</td>
<td></td>
</tr>
<tr>
<td>Surgical reduction with fixation</td>
<td>32 (60.4)</td>
</tr>
<tr>
<td>HVI</td>
<td>21 (39.6)</td>
</tr>
<tr>
<td>Fracture type*</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>25 (47.2)</td>
</tr>
<tr>
<td>III</td>
<td>28 (52.8)</td>
</tr>
<tr>
<td>TAL injury type†</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>29 (54.7)</td>
</tr>
<tr>
<td>II</td>
<td>24 (45.3)</td>
</tr>
<tr>
<td>ASIA grade E</td>
<td>53</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). MVA, motor vehicle accident; BMI, body mass index; BMD, bone mineral density; HVI, halo-vest immobilization; ASIA, American Spinal Injury Association Impairment Scale; fracture type. *Landels & Van Peteghem classification. †Transverse atlantal ligament injury Dickman classification.

Fig. 2. Radiological measurements. (A) In an open-mouth view, the sum of (a) and (b) is greater than 6.9 mm, and the rule of Spence suggests a transverse ligament injury. (B) The anterior atlantodental interval (AADI) and cervical lordosis (CL) are shown in the picture.

https://doi.org/10.14245/ns.2244352.176
Data were expressed as mean ± standard deviation or number (percentage). Paired t-test and the chi-square test were used to assess the difference in the intergroup comparison. Receiver operating characteristics (ROC) analysis was done to evaluate the sensitivity and specificity of LMDs as an objective measure of non-combination. The optimal cutoff value for LMD was determined using the maximum Youden index (sensitivity – [1 – specificity]). All data were analyzed by MedCalc v20.106 (MedCalc Software, Belgium). A p-value less than 0.05 was statistically significant.

RESULTS

All 53 patients had unstable atlas fractures according to the “rule of Spence” (> 6.9-mm preoperative LMD); 32 patients underwent surgical reduction with interconnected fixation and 21 patients underwent nonsurgical management (HVI) to achieve osseous healing. The mean age at the time of management was 48.23 ± 14.62 years (range, 23–69 years). Patients were followed for a mean of 24.9 months (range, 15.53–38.61 months). Among the 53 patients, 37 were injured in a vehicle accident, 7 were injured by diving into a pool, and 9 were injured by falling. The mean time from injury to management was 2.68 ± 1.72 days (Table 1).

Thirty-two patients (16 with Landells and Van Peteghem type II and 16 with type III fractures) underwent surgical fixation, and 21 patients (9 with Landells and Van Peteghem type II and 12 with type III fractures) were treated with nonoperative management. Regarding surgical methods, 27 patients received C1–2 fixation with crosslink compressors, 4 were treated with C1 ORIF, and 1 had C1-2-3 fixation.

There were 29 Dickman classification type I TAL injuries (17 in the surgical fixation and 12 in the nonsurgical management groups) and 24 type II injuries (15 in the surgical fixation and 9 in the nonsurgical management groups) (p = 0.776).

1. Comparison of Radiographic Parameters and Clinical Outcomes Between Patients Who Underwent Surgery and Patients Who Did Not

Baseline demographics according to treatment modality are presented in Table 2. There was no significant difference in mean age, sex, or mechanism of injury among the 2 treatment modality groups (Table 2). LMD showed a statistically significant improvement after surgical fixation, and this improvement was

---

Table 2. Patient demographics according to treatment modality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgical group (n = 32)</th>
<th>Nonsurgical group (n = 21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.47 ± 15.96</td>
<td>47.86 ± 12.68</td>
<td>0.964</td>
</tr>
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<td>Sex, male:female</td>
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<td>15:6</td>
<td>0.187</td>
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<td>Mechanism of injury</td>
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<td></td>
<td>0.417</td>
</tr>
<tr>
<td>MVA</td>
<td>21</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Fall down</td>
<td>11</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.81 ± 2.64</td>
<td>30.33 ± 9.24</td>
<td>0.092</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>-1.36 ± 1.41</td>
<td>-2.23 ± 1.30</td>
<td>0.340</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (46.9)</td>
<td>14 (66.7)</td>
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<tr>
<td>Diabetes</td>
<td>5 (15.6)</td>
<td>6 (28.6)</td>
<td>0.260</td>
</tr>
<tr>
<td>Management starting time (day)</td>
<td>2.64 ± 1.43</td>
<td>2.71 ± 2.00</td>
<td>0.689</td>
</tr>
<tr>
<td>Fracture type¹</td>
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<td></td>
<td>0.614</td>
</tr>
<tr>
<td>II</td>
<td>16 (50.0)</td>
<td>9 (42.9)</td>
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<tr>
<td>III</td>
<td>16 (50.0)</td>
<td>12 (37.5)</td>
<td></td>
</tr>
<tr>
<td>TAL injury type²</td>
<td></td>
<td></td>
<td>0.776</td>
</tr>
<tr>
<td>I</td>
<td>17 (53.1)</td>
<td>12 (37.5)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (46.9)</td>
<td>9 (42.9)</td>
<td></td>
</tr>
<tr>
<td>ASIA grade E</td>
<td>32</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
MVA, motor vehicle accident; BMI, body mass index; BMD, bone mineral density; TAL, transverse atlantal ligament; ASIA, American Spinal Injury Association Impairment Scale; fracture type.
¹Landells & Van Peteghem classification. ²Transverse atlantal ligament injury Dickman classification.
maintained at the last follow-up; however, significant improvement was not seen after nonsurgical management. In the surgery group, there was no evidence of a reduced fracture gap from immediately after surgery until the final follow-up, with measured values of 5.95 ± 2.54 mm at postoperative 7 days, 5.96 ± 2.55 mm at 3 months, and 6.08 ± 2.27 mm at 12 months after surgical fixation. In contrast, in the nonoperative management group, there was a loss of reduction in the fractured atlas ring over time, with values of 7.75 ± 1.54 mm at postoperative 7 days, 8.14 ± 1.95 mm at 3 months, and 8.27 ± 2.02 mm at the last follow-up after HVI (Table 3, Fig. 3). AADI decreased to a statistically significant extent after surgical fixation, but not after nonsurgical management. In the surgical fixation group, the AADI decreased from an initial mean value of 4.95 ± 0.57 mm to 3.00 ± 1.05 mm at the last follow-up. In the nonsurgical management group, the AADI decreased from an initial mean value of 4.90 ± 0.72 mm to 4.30 ± 0.87 mm at the last follow-up (Table 3). The osseous healing rate was 100% (32 of 32 patients) in the surgery group and 71.43% (15 of 21 patients) in the nonoperative management group (Table 3). In other words, the nonunion rate was higher in patients who received nonsurgical management than in those who underwent surgical fixation at 6 months postoperatively. The mean time to osseous healing was higher in the nonsurgical management group (20.02 ± 8.73 weeks) than in the surgical fixation group (14.38 ± 2.93 weeks). The cervical alignment in patients treated with HVI was straighter than in patients treated with surgical fixation at the last follow-up. The cervical dynamic x-rays of patients treated with HVI showed better maintenance of motion at the final follow-up than was observed in patients who underwent posterior cervical reduction and fixation (Table 3).

Patients who received nonsurgical management experienced more severe neck pain than those treated with surgical internal fixation. The preoperative NDI score was higher in the surgical fixation group than in the nonsurgical management group. At the last follow-up, the NDI score was 7.13 ± 2.04 in the surgical

### Table 3. Radiological parameters and clinical outcomes according to the treatment modality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgical fixation (n = 32)</th>
<th>Nonsurgical management (n = 21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>9.86 ± 1.59</td>
<td>9.35 ± 1.21</td>
<td>0.212</td>
</tr>
<tr>
<td>Postoperative 7 days</td>
<td>5.95 ± 2.54</td>
<td>7.75 ± 1.54</td>
<td>0.002*</td>
</tr>
<tr>
<td>Postoperative 3 months</td>
<td>5.96 ± 2.55</td>
<td>8.14 ± 1.95</td>
<td>0.001*</td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>6.08 ± 2.27</td>
<td>8.27 ± 2.02</td>
<td>0.001*</td>
</tr>
<tr>
<td>AADI (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>4.95 ± 0.57</td>
<td>4.90 ± 0.72</td>
<td>0.986</td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>3.00 ± 1.05</td>
<td>4.30 ± 0.87</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Osseous healing time (wk)</td>
<td>14.38 ± 2.93</td>
<td>20.02 ± 8.73</td>
<td>0.003*</td>
</tr>
<tr>
<td>Healing rate (%)</td>
<td>100</td>
<td>71.43</td>
<td>0.002*</td>
</tr>
<tr>
<td>C2–7 Cobb angle (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.53 ± 4.45</td>
<td>4.06 ± 3.86</td>
<td>0.288</td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>11.80 ± 7.38</td>
<td>6.54 ± 7.19</td>
<td>0.002*</td>
</tr>
<tr>
<td>C2–7 ROM (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>54.38 ± 14.41</td>
<td>63.82 ± 29.24</td>
<td>0.253</td>
</tr>
<tr>
<td>Neck VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.31 ± 0.78</td>
<td>7.19 ± 0.68</td>
<td>0.561</td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>1.91 ± 0.53</td>
<td>3.00 ± 1.52</td>
<td>0.003*</td>
</tr>
<tr>
<td>NDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>24.25 ± 5.49</td>
<td>21.04 ± 4.59</td>
<td>0.032*</td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>7.13 ± 2.04</td>
<td>11.29 ± 6.46</td>
<td>0.025*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation unless otherwise indicated.
LMD, total lateral mass displacement; AADI, anterior atlantodental interval; ROM, range of motion; VAS, visual analogue scale; NDI, Neck Disability Index.

*p < 0.05.
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Fig. 3. Reduction of total lateral mass displacement after surgical and nonoperative management. The surgical reduction and fixation group showed no loss of reduction in fractured lateral masses in the initial measurements (9.86 ± 1.59 mm) and those obtained 7 days (5.95 ± 2.54 mm), 3 months (5.96 ± 2.55 mm), and 12 months (6.08 ± 2.27 mm) after surgery. In the nonoperative group treated with HVI, initial (9.35 ± 1.21 mm) cervical traction followed by halo-vest immobilization (HVI) was found to lead to slight reductions in lateral dislocation at 7 days (7.75 ± 1.54 mm), 3 months (8.14 ± 1.95 mm), and 12 months (8.27 ± 2.02 mm) after HVI, but increased displacement continued to occur over time.

Fig. 4. Receiver operating characteristic (ROC) curves for the preoperative total lateral mass displacement (LMD). The best cutoff value of the preoperative LMD between osseous healing and nonunion was 8.86 mm. The area under the curve (AUC) was 0.767 (95% confidence interval, 0.533–0.921, p = 0.0342). The surgical fixation group and 11.29 ± 6.46 in the nonsurgical management group (Table 3).

2. Radiographic and Clinical Outcomes According to Dickman’s TAL Injury Classification

No significant differences in LMD or AADI were found according to Dickman's classification of TAL injuries. The osseous healing rate was not significantly different in the surgical fixation and nonsurgical management groups based on the classification of TAL injuries (Table 4). The neck VAS score and NDI were not significantly different between Dickman's TAL injury types.

3. ROC Analysis of Preoperative LMD

In the nonsurgical management group, the ROC analysis found that the optimal cutoff value of the preoperative LMD between osseous healing and nonunion was 8.86, with sensitivity and specificity values of 83.33% and 73.33%, respectively. The area under the curve was 0.767 (95% confidence interval [CI], 0.533–0.921; p = 0.034) (Fig. 4). In contrast, all patients who underwent surgical fixation showed complete osseous healing. Therefore, the ROC curve did not show an optimal cutoff value of the preoperative LMD for distinguishing between osseous healing and nonunion in the surgical fixation group.

Table 4. Radiological parameters and clinical outcomes according to the TAL injury

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dickman type I (n = 29)</th>
<th>Dickman type II (n = 24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative LMD (mm)</td>
<td>9.79 ± 1.48</td>
<td>9.51 ± 1.45</td>
<td>0.486</td>
</tr>
<tr>
<td>Preoperative AADI (mm)</td>
<td>4.93 ± 0.69</td>
<td>4.80 ± 0.57</td>
<td>0.463</td>
</tr>
<tr>
<td>Treatment modalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical fixation</td>
<td>17</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>HVI</td>
<td>12</td>
<td>9</td>
<td>0.776</td>
</tr>
<tr>
<td>Osseous healing (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical fixation</td>
<td>17/17 (100)</td>
<td>15/15 (100)</td>
<td></td>
</tr>
<tr>
<td>HVI</td>
<td>9/12 (75)</td>
<td>6/9 (66.7)</td>
<td>0.683</td>
</tr>
<tr>
<td>Neck VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.28 ± 0.75</td>
<td>7.25 ± 0.74</td>
<td>0.900</td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>2.24 ± 1.24</td>
<td>2.46 ± 1.06</td>
<td>0.264</td>
</tr>
<tr>
<td>NDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>23.24 ± 5.49</td>
<td>22.67 ± 5.26</td>
<td>0.701</td>
</tr>
<tr>
<td>Postoperative 12 months</td>
<td>8.72 ± 3.80</td>
<td>8.83 ± 5.82</td>
<td>0.335</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). TAL injury, transverse atlantal ligament injury; LMD, total lateral mass displacement; AADI, anterior atlanto-dental interval; HVI, halo-vest immobilization; VAS, visual analogue scale; NDI, Neck Disability Index.
4. Complications

One of the 32 patients treated with surgical reduction with fixation suffered cerebellar infarction. One patient underwent revision surgery due to malposition of the C1 lateral mass screw. No patients showed hardware failure, dura mater tear, or infection. Nonunion at 6 months postoperatively occurred in 28.57% of patients (6 of 21) who received nonoperative management with HVI. Six patients with pseudoarthrosis declined an additional surgical operation as their neck pain was bearable. Five of the 21 patients (23.81%) who underwent HVI had complications, including frequent pin loosening (9.52%, 2 of 21), wound site infection (4.76%, 1 of 21), and brain abscess (9.52%, 2 of 21).

DISCUSSION

Surgical internal fixation enabled a better reduction of fractured lateral slippage and widened AADI than nonsurgical management. The osseous healing was 100% with surgical internal fixation but 71.43% with nonsurgical management, indicating that external immobilization with halo-vest devices offered insufficient fixation of occipitocervical motion. Clinically, the patients who received nonsurgical management experienced poorer neck pain and more frequent disability compared to those treated with surgical internal fixation. There were no differences in clinical outcomes and osseous healing between surgical and conservative management based on Dickman’s classification of TAL injury. A preoperative LMD greater than 8.86 mm predicted poor osseous healing, defined by nonunion, in unstable atlas fractures that underwent nonsurgical management.

1. Outcomes Between Patients Who Underwent Surgical Operation and Patients Who Did Not

The goal for treatment of unstable atlas fractures is to reduce fracture displacement, maintain stabilization, and heal the bony fracture. Various surgical options for treating unstable atlas fractures with ligament tears have been recently described with advanced surgical techniques and good radiological outcomes. However, in these times of favorable results by surgery, it still remains debatable whether surgery or conservative management should be used for unstable atlas fractures. Moreover, a change of management for unstable fractures is needed to obtain better clinical outcomes and determine the treatment strategy. Surgery advocates have argued that these surgical techniques to fix fractures are preferable since conservative treatments result in delayed atlantoaxial instability, craniovertebral settling, a high nonunion rate, and late neurological sequelae. On the other hand, advocates of conservative management have reported that unstable atlas fractures can be managed by HVI or rigid collars. They argued that HVI or a rigid collar provides traction to align the fractured lateral masses by ligamentotaxis effect and reduces a stress force below C1–2, thereby preventing subluxation and promoting healing. However, it is doubtful whether the damaged TAL of an unstable atlas fracture can facilitate ligamentotaxis and maintain a lateral slippage until complete healing. In common, osseous injuries heal well with immobilization to treat fractured segments. However, ligamentous injuries are poorly cured by immobilization alone. Nonoperative treatment with a halo-vest for stable atlas fractures resulted in a 76.2%–84.2% consolidation rate, but there is a lack of research on osseous healing rates for the nonoperative management of unstable atlas fractures. The present study found that osseous healing was accomplished in 71.43% of nonoperative management patients and in all patients who underwent surgical internal fixation. The patients with HVI needed a longer osseous healing time than those undergoing surgical internal fixation. In addition, the LMD and AADI in surgical fixation improved at the last follow-up compared to the preoperative phase. However, the LMD and AADI did not show significant improvements in the nonsurgical management group. Patients treated with HVI had straighter cervical alignment and greater neck stiffness than those treated with surgical fixation, inconsistent with previous reports. The larger C2–7 Cobb angle in the surgical fixation group might have been due to the kyphotic fixation of C1–2. Clinically, patients treated with HVI had worse neck pain and neck disability than patients treated with surgical treatment. The adverse consequences of nonsurgical management are that the fracture site was not fixed firmly in patients who received external HVI due to an increase in fracture lateral slippage and micromotion while sitting and laying down. The pitfalls of nonoperative management are inadequate maintenance of unstable fractures with a ligament injury and a lower probability of reducing fractured lateral masses (Fig. 5). In contrast, surgical reduction with interconnected fixation secures the fractured site in place without increasing lateral displacement or micromotion (Fig. 6).

2. Outcomes According to Dickman’s TAL Injury Classification

Dickman’s TAL injury type has been considered a critical factor in determining the stability of atlas fractures and choosing a treatment strategy. Dickman et al. proposed that type I TAL injuries, in which a rupture occurs in the substance of the ligament,
should be implemented early with surgery.\textsuperscript{15,32} Type II TAL injuries, which involve avulsion fractures at the insertion sites of TAL, had a 74% success rate when managed nonoperatively.\textsuperscript{32} According to Dickman’s suggestions, atlas avulsion fractures with transverse ligament rupture could be treated by nonsurgical management with rigid collars or HVI. In most cases, these conservative treatments have been widely performed as the method of choice, while accepted surgical indications are an intraligamentous injury of the transverse ligament, atlantoaxial instability, and an especially unstable atlas fracture. Shatsky et al.\textsuperscript{33} reported that atlas fracture reduction and fixation could be performed irrelevant to the ligament injury type without resulting in C1–2 instability. Liu et al.\textsuperscript{5} studied 13 adult patients with atlas fractures who were treated nonoperatively at the acute posttraumatic phase and followed up for at least 2 years. They reported that C1–2 stability failed to be restored in 2 cases with Dickman’s classification type I injuries (100%), whereas stability was successfully restored in 6 of 7 type II (85.7%) cases that were treated nonoperatively. They concluded that Dickman’s classification of TAL injuries is highly accurate for evaluating TAL injuries and shows a significantly consistent association with the prognosis of atlas fractures. However, their study enrolled small number of patients and treated atlas fractures with only nonoperative management. The present study showed no differences in clinical outcomes and osseous healing between surgical and conservative management based on Dickman’s classification of TAL injury. Patients who underwent surgical fixation had complete osseous healing regardless of the TAL type, while patients with type I TAL injuries achieved osseous healing more frequently compared to those with type II TAL injuries after nonoperative treatment. However, the significance of Dickman TAL classification in this study was limited to applying to all atlas fractures and predicting outcomes, since only unstable atlas fractures were registered except for stable atlas fractures.

**Fig. 5.** Halo-vest immobilization. (A) Preoperative open-mouth view with a sum of overhangs of the C1 lateral masses on the C2 facet of 8.71 mm. (B) The sum of lateral displacements of the fractured lateral masses was 7.67 mm 7 days after halo-vest immobilization (HVI). (C) The same value was 7.39 mm 3 months after HVI. (D) The 6-month posttreatment value was 8.41 mm. There was a loss of reduction in the fractured atlas ring over time.
3. Correlation of the “Rule of Spence” and TAL Injury

Recent studies have reported that the “rule of Spence” was inaccurate for identifying TAL injuries. Using the criterion of an LMD greater than 6.9 mm, approximately 61% to 90.9% of TAL injuries were missed. Furthermore, Radcliff et al. previously reported no correlation between bony displacement and the presence of a TAL injury. Woods et al. studied the LMD required for TAL injury using modern biomechanical techniques. The average LMD upon TAL failure was found to be 3.3 ± 1.2 mm (1.7–5.6 mm), and when the LMD exceeded 3.8 mm, there was a high likelihood of TAL failure. Perez-Orribo et al. also reported the comparison study of CT versus MRI on TAL integrity and showed that 90.9% with documented TAL injury on MRI was inconsistent with the “rule of Spence” criterion. The average LMD in these 10 patients with TAL injury was 2.4 mm (range, 0.6–8.7 mm). Heller et al. proposed that the cutoff of

Fig. 6. Surgical reduction and fixation with crosslinking. (A) Preoperative open-mouth view shows that the sum of the overhang of the C1 lateral masses on the C2 facet was 8.1 mm. (B) On computed tomography (axial view), a right anterior arch fracture and right lateral mass fracture (Landells & Van Peteghem type II) are shown. (C) There was a rupture of the transverse atlantal ligament (Dickman type II). A tear of the transverse ligament (arrow). (D) Surgical reduction and fixation with crosslinking were performed. The 12-month postoperative value was 3.8 mm.
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4. Treatment Strategy

We recommend surgical treatment for unstable and displaced atlas fractures. If a transverse ligament disruption exists with an atlas fracture and the TAL injury violates the rule of Spence or shows predominant signs of TAL injuries (e.g., hypersignal intensity on gradient echo imaging, ligament discontinuity, or insertion site bleeding), surgical reduction and interconnected fixation will correct the incompetence of the transverse ligament (Fig. 6). We insist that the TAL can heal or reduce the scar when it is anatomically aligned with reduction and fixation, consistent with the previous research. Compression using crosslinking, similar to the role of the TAL, is essential to prevent pseudoarthrosis and the late sequelae of atlas fractures according to the TAL injury type. Delayed atlantoaxial instability, pseudoarthrosis, or craniocervical settling may occur if the transverse ligament fixation is not performed as the substitute for the injured TAL (Supplementary Fig. 1). We did not analyze the radiological and clinical outcomes of each surgical technique in detail due to the small number of cases (32 total; 27 C1–2 fixation with crosslink compressors, 4 ORIF, and 1 C1–2–3 posterior fixation). Osseous healing occurred within a mean of 14.4 weeks in the surgical fixation group. Surgical treatments of C1 fractures include transoral anterior C1 fixation, C1 ORIF, posterior C1–2 fusion, and occipitocervical fusion. Transoral approach C1 internal fixation can only treat anterior half atlas fractures and has a high risk of deep operative site infection. Posterior ORIF of the C1 ring can maintain C1–2 motion better than standard C1–2 or occipitocervical fusion techniques (Supplementary Fig. 2). However, C1 ORIF has limitations in the reduction and fixation of bony fractures in cases with C1–2 articular facet damage, comminuted fractures of C1, and atlantoaxial or atlantocapital joint instability. Basilar invagination from cranial settling on occipitocervical lesions may also be a risk, leading to neurological deficits. C1–2 fusion has been reported to have good outcomes as a standard method for unstable Jefferson fractures, while C1–2 fusion restricts head rotation to 35° or less on both sides.2 Recently, posterior temporary C1–2 screw fixation with removal of screws following C1–2 fixation was reported to preserve atlantoaxial ROM, especially in younger patients. Comparative studies of various surgical techniques for unstable atlas fractures are needed to evaluate radiologic, clinical, and functional outcomes.

5. Choosing the Modality for C1 Fractures

All modalities, such as radiographs, CT, and MRI, should be used to diagnose C1 fractures. Initially, radiographs should be taken, including anteroposterior, lateral, and open-mouth x-rays. The open-mouth view provides effective visualization of the C1, C2 body, atlantoaxial joints, odontoid process, and lateral spaces between the lateral border of the C2 body and lateral masses of C1 (when the patient’s shoulders are on the same horizontal plane to prevent rotation and the midsagittal plane is perpendicular to the plane of the table).

CT scan is the screening method of choice in many trauma centers. In this study, CT was performed to assess fractures, such as the presence of an avulsion fracture at the TAL insertion site, a comminuted fracture, or a lateral mass. CT offers a more precise resolution of bony fragments associated with atlas fracture and is not susceptible to magnification error.27 Even though CT can provide accurate imaging of bony fractures and displacements, the integrity of the transverse ligament cannot be assured. The transverse ligament should be directly imaged with MRI, as it is a more sensitive indicator of TAL disruption than the “rule of Spence” or CT. MRI scans, including axial and coronal thin-section T1- and T2-weighted images and gradient echo images, should be performed to identify TAL injuries based on anatomical disruption, the presence of fluid signal, ligament discontinuity, or insertion site bleeding. When making decisions regarding treatment and imaging modalities for C1 fractures, transverse ligament injuries with associated C1–2 instability
were determined based on > 6.9-mm LMD on open-mouth radiograph and confirmed fractures, such as avulsion fracture at the TAL insertion site, a comminuted fracture, or a lateral mass on CT and documented disruption of TAL on MRI.

6. Study Limitations

This study, in its nature, has several limitations. First, this was a retrospective study with relatively few patients, and inherent differences between groups were inevitable. In addition, some concerns have been raised regarding late fusion in cases of pseudoarthrosis due to the short-term follow-up. Selection bias due to the multicenter design of the study likely affected the decision to manage unstable fractures. Furthermore, management strategies were determined by the treating surgeon, and differences in regional, institutional, and surgeon preferences might have impacted nonoperative management with HVI or surgical treatment, including whether C1 ORIF, posterior C1–2 fixation, or occipitocervical fusion was performed. An optimal treatment modality for unstable atlas fractures could not be determined from this comparative study with few enrolled patients, which could lead to possible bias. In the future, additional prospective and multicenter studies should be conducted to derive radiological and clinical outcomes in patients who have executed surgical internal fixation or non-surgical external immobilization for unstable atlas fractures. Nonetheless, we hope that the present study findings will be helpful in the management of patients with unstable atlas fractures.

CONCLUSION

The radiological outcomes of surgical treatment were superior to those of nonsurgical treatment. Surgical internal fixation of unstable atlas fractures had a higher fusion rate, a shorter fracture healing time, and better reduction of fractured lateral masses than nonoperative management. The pitfalls of conservative management for unstable atlas fractures are inadequate maintenance and a lower likelihood of reducing fractured lateral masses. Clinically, patients with nonsurgical management experienced poorer neck pain and disability more frequently compared to those treated with surgical internal fixation. In this study, clinical outcomes and osseous healing were not significantly different between surgical and conservative management based on Dickman’s classification of TAL injury. An LMD greater than 8.86 mm was associated with a high probability of poor osseous healing after nonoperative treatment. Therefore, surgical reduction with interconnected fixation for cases with an LMD greater than 8.86 mm may lead to more favorable osseous healing over nonsurgical management.

NOTES

Supplementary Materials: Supplementary Figs. 1-2 can be found via https://doi.org/10.14245/ns.2244352.176.

Supplementary Fig. 1. Atlantoaxial joint fusion without cross-link fixation.

Supplementary Fig. 2. C1 open reduction and internal fixation.

Conflict of Interest: The authors have nothing to disclose.

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Supplementary Fig. 1. Atlantoaxial joint fusion without crosslink fixation. (A) A preoperative open-mouth view of a 74-year-old male patient with an atlas fracture after a traffic accident. The sum of the overhang of the C1 lateral masses on the C2 facet was 6.7 mm. (B) The computed tomography (CT) findings were classified as type II Landells and Van Peteghem. (C) There was a rupture of the transverse atlantal ligament (Dickman type I). (D) The patient underwent nonoperative management with halo-vest immobilization for 6 weeks. He complained of continuing neck pain and headache. Follow-up CT findings showed additional slippage of the fractured lateral masses compared to the initial phase. (E) Postoperative CT showed C1 lateral mass screw-2 pedicle screw fixation with atlantoaxial joint fusion, but without crosslinking. (F) Twelve-month postoperative CT showed good fusion in the left atlantoaxial joint, but nonunion in the right atlantoaxial joint. The patient’s neck pain was tolerable, but neck motion was restricted. (Courtesy of Prof. SW Kim).
Supplementary Fig. 2. C1 open reduction and internal fixation. (A) Preoperative open-mouth view. (B) C1 open reduction and internal fixation. (C) The sum of the overhang of the C1 lateral masses on the C2 facet was 7.8 mm on the preoperative computed tomography scan. (D) The 12-month postoperative value was 1.8 mm. The reduction and fusion of the fractured atlas were satisfactory.
Commentary on “Surgical Versus Conservative Management for Treating Unstable Atlas Fractures: A Multicenter Study”

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Traumatic atlantoaxial instability caused by atlas fracture has been a well-known lesion for a long time, however, surgical indication and appropriate operation based on injury type are still controversial. It must be a clue that preoperative radiological evaluation whether a tense structure of the transverse atlantal ligament (TAL), which is composed primarily of collagen fibers with very few elastic fibers, is intact or not as well as a complexity of atlas fracture. Instability related to the TAL is divided into 2 types using magnetic resonance imaging by Dickman’s classification: a TAL type I injury, characterized by a direct rupture of the ligament, whereas a TAL type II injury, involving an avulsion fracture at the attached site of the ligament. Several previous reports have described surgical indication should be differentiated considering this classification. Recently, more precise information about radiological findings can be helpful to make a decision for optimal management, and innovative development of spinal fixation has improved quality and safety of spinal fusion even in this complicated area. Therefore, ideal and comprehensive treatment should be changed according to modest concept.

Based on these perspectives, the authors have reported clinical outcomes of multicenter comparative study between conservative and surgical management for isolated atlas fracture, which have a high potential for instability. The authors have also evaluated preoperative radiological parameters associated with faster osseous fusion and better clinical outcome after treatment in both groups. All patients enrolled in the study had atlas fracture with lateral mass displacement (LMD) following “rule of Spence” and dysfunction of TAL including either type I or type II injury. Surgical treatment provided more rapid bone healing with significantly better clinical and radiological outcomes compared to those in conservative management with halo-vest immobilization (HVI). Specifically, total LMD and the anterior atlantodental interval were significantly improved in the surgical group indicating satisfactory restoration was maintained anatomically. Contrary to previous expectations, clinical outcome and bone fusion rate did not correlate with Dickman’s classification of TAL injury.

Interestingly, about 70% of patients with unstable atlas fractures achieved bone fusion and acceptable stability even though conservative treatment. However, it should be kept in our mind that there was limitation of external immobilization with HVI for good healing if patients had preoperative LMD which is wider than 8.86 mm as the authors indicated.
“Rule of Spence” can fulfill a role to find out highly probable TAL dysfunction rather than covering detection of this dysfunction in all cases. Actually, Spence et al. reported the spread of the lateral masses on open-mouth radiographic views ranged from 4.8 to 7.6 mm in case with transverse ligament rupture. Therefore, TAL failure related to atlas fracture can be underestimated only focusing on LMD. Definition and surgical indication of unstable atlas fracture should be reconsidered with precise evaluation of atlas fracture and TAL condition. Additionally, as the authors described, surgical indication and methods depended on surgeon’s preference and experience in this study. The ideal selection of surgical fixation should be investigated by determination of more cases in prospective and multicenter studies.

Conflict of Interest: The author has nothing to disclose.

REFERENCES

Full Endoscopic Ligamentum Flavum Sparing Unilateral Laminotomy for Bilateral Recess Decompression: Surgical Technique and Clinical Results

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2Department of Neurological Surgery, University of Washington, Seattle, WA, USA

Objective: Interlaminar endoscopic spine surgery has been introduced and utilized for lumbar lateral recess decompression. We modified this technique and utilized it for bilateral lateral recess stenoses without significant central stenosis. Here we present the surgical details and clinical outcome of ligamentum flavum sparing unilateral laminotomy for bilateral recess decompression (ULBRD).

Methods: Prospectively collected registry for full-endoscopic surgeries was reviewed retrospectively. One hundred eighty-two consecutive cases from a single center between September 2015 and March 2021 were reviewed and 57 of them whom underwent ULBRD were enrolled for analysis. Basic patient demographic data, perioperative details, surgery-related complications, and clinical outcome were reviewed. The detailed surgical technique is presented as well.

Results: Among the 57 patients enrolled, 37 were males while the other 20 were females. The mean age was 58.53 ± 14.51 years, and a bimodal age distribution at the age of mid-fifties and mid-sixties or older was noted. The later age-peak was related to coexistence of degenerative scoliosis. The average operative time per lamina was 70.34 ± 20.51 minutes and mean length of stay was 0.56 ± 0.85 days. Four perioperative complications were reported (7.0%) and the overall reoperation rate at the index level within 1 year was 8.8%. The preoperative back/leg visual analogue scale scores and functional outcome scales including EuroQol-5 dimension questionnaire, Oswestry Disability Index presented significant improvement immediately after surgery and were maintained until final follow-up.

Conclusion: ULBRD for bilateral lateral recess stenoses without significant central stenosis resulted in good clinical outcomes with acceptably low perioperative complications rates. Sufficient decompression was achieved with the central ligamentum flavum being preserved.

Keywords: Endoscopic spine surgery, Lateral recess stenosis, Radiculopathy, Minimally invasive spine surgery, Interlaminar endoscopic lateral recess decompression

INTRODUCTION

Radiculopathy of the lumbar spine is one of the most common pathologic conditions that spine physicians encounter in their daily practice. Lumbar spine diseases presenting with radiculopathy exert an enormous socioeconomic burden with increasing numbers of patients and costs associated with this disease.1 Radiculopathy can be a consequence of various pathologic changes of the lumbar spine such as herniated intervertebral discs, lateral recess stenoses (LRSs), spondylolisthesis, and rarely may be due to tumors or infections.

Diagnosis of symptomatic LRS is occasionally controversial,
given that radicular symptoms often correlate poorly with imaging findings on magnetic resonance imaging (MRI).\(^2\) The lateral recess is a distinct anatomic area located ventral to the superior articular process (SAP) of the lower lumbar vertebrae, and is delineated by the intervertebral disc (IVD) ventrally and the facet joint dorsally. Since it was first reported in the early 1980s,\(^4,6\) LRS defines a degenerative condition resulting in subsequent neural compression characterized by significant compression of the traversing root at the entry zone of the foramen of lumbar roots. While the majority of lumbar central canal stenoses are seen in older patients due to the degenerative nature of the disease,\(^5,6\) LRS without central canal stenosis can be seen in the early stage of degeneration. Unlike the central stenoses which clinically present with neurogenic claudication, LRS usually present clinically very similar to herniated IVDs, making LRS a distinct pathology. For LRS patients not responding to thorough conservative treatment, surgical decompression of the lateral recess is recommended,\(^7,8\) and open laminectomy is widely accepted as a safe and cost-effective surgical approach for these intractable LRSs.\(^10,11\) However there are significant drawbacks to traditional open laminectomies, including possible surgical injuries to the paraspinal structures. In addition, a certain amount of bony resection is necessary to create a path to the lateral recess and to achieve optimal bony decompression. Since the lateral recess is adjacent to the facet joint, there is a risk of iatrogenic segmental instability, which in some cases require arthrodesis surgeries.\(^12-14\) Thus, various minimally invasive spine surgery techniques, including tubular retractor surgeries and endoscopic surgeries, which minimize approach-related injuries to the adjacent structure have been introduced.\(^15-19\) Among these, full-endoscopic decompression for various lumbar degenerative lesions has gained popularity because of several advantages over open surgery, including lesser paraspinal injury, lesser blood loss, and rapid return to work and daily activities.\(^7,17,19-21\) The use of full-endoscopic technique in the field of spine surgery has undergone considerable evolution,\(^22\) and scientific evidence is mounting regarding favorable clinical and radiologic outcomes, specifically for lateral recess decompressions.\(^7,17,18,23-26\) However, previous research has focused primarily on unilateral decompressions, or lateral recess decompressions accompanied by central stenosis decompression for cases of bilateral decompression. These reports do not address the subset of LRS cases, often associated with a younger population, which require bilateral decompression of the lateral recess, but do not require decompression of the central canal. The objective of our research was to use our prospectively collected endoscopic spine surgery database to determine complication and clinical outcomes for patients at our institution who underwent unilateral laminotomy for bilateral recess decompression (ULBRD).

MATERIALS AND METHODS

1. Patient Cohort and Clinical Data Measures

A prospectively collected database of consecutive endoscopic interlaminar lumbar surgeries by a single surgeon was retrospectively screened and queried for ULBRD between September 2015 and March 2021. The University of Washington Human Subjects Division reviewed and approved this study and all patients provided informed consent for participation. Patients enrolled included those with history of more than 6 weeks of conservative nonsurgical treatment including systemic medication (analgesics, nonsteroidal anti-inflammatory drugs). Patients with significant instability, grade C and D central stenosis,\(^27\) or significant disc herniation at the index level were excluded from analysis. Demographic information and clinical variables were obtained from the medical record, including preoperative imaging study results, clinical outcomes, intraoperative estimated blood loss (EBL), length of stay (LOS), underlying comorbidities, American Society of Anesthesiologists (ASA) physical status (PS) classification grade, perioperative complications, preoperative preparation time for anesthesia, positioning and drape, and incision to closure operative time. Clinical outcomes were measured by visual analogue scale (VAS) for both back and leg pains, Oswestry Disability Index (ODI) scores, and EuroQol-5 dimension (EQ-5D) self-reported questionnaires at preoperative, 2-week postoperative, 3-month postoperative, chronic (6-month to 1-year postoperative) and final postoperative follow-up. Follow-up clinical data was available for 52 of 57 patients (91.2%); 5 patients were lost to follow-up immediately after surgery and an additional 4 patients were lost to follow-up after the 2-week follow-up. Mean follow-up duration for the remaining 48 patients (84.2%) was 26.5 ± 18.7 months (range, 3–54 months).

2. Preoperative Image Data Collection

All patients underwent routine imaging evaluation including radiographs and MRI. Preoperative radiographs consisted of plane anteroposterior and lateral and flexion/extension images. Instability at the index level was defined as excessive motion more than 3 mm on flexion/extension images.\(^28\) MRI included multiple sequences of T1 and T2 weighted images. The presence of central canal stenosis and LRS was graded as previously described.\(^17,27\)
3. Surgical Technique–ULBRD

1) Preparation for surgery

Under monitored general endotracheal anesthesia, the patient is positioned on surgical table with a Wilson frame. Similar to most endoscopic spine surgery techniques, ULBRD is facilitated with maximum flexion of the lumbar spine, resulting in maximized size of the interlaminar window for approach. Once the patient is positioned, an intraoperative C-arm fluoroscopic image is taken to check the level for surgery and to determine an optimal entry point for the endoscopic procedure. The endplate view of the lower vertebral body is found, and then by tilting the C-arm caudally, the maximized view of the interlaminar window can be achieved. At this fluoroscopic view, the point for skin incision is marked at the point where the caudal margin of the target lamina meets the upper endplate line of the caudal vertebral body. This point is the exact point of the lateral recess which is the target for decompression. This step can be done either before or after the patient is prepped and draped.

2) Approach

A vertical 0.7-cm-sized incision is made at the marked point, penetrating the skin, subcutaneous layer, and the lumbar fascia simultaneously. Step-by-step serial dilators are advanced through the incision and the inferomedial margin of the rostral index level lamina is palpated. Intraoperative fluoroscopy is taken to confirm the level and to assure that the dilators are located on the target area. Then a tubular retractor is placed with the bevel initially facing medially to avoid creep of the paraspinal muscles. Radiofrequency cautery and endoscopic surgical equipment are utilized to control any bleeding and remove any remnant soft tissue or debris, optimizing the endoscopic surgical view at the caudal margin of the index lamina and the medial aspect of the facet joint.

Fig. 1. (A) For unilateral laminotomy for bilateral recess decompression, bony decompression is carried out along the bony insertion of the ligamentum flavum (LF) (principal anatomical landmark) from ipsilateral to contralateral superior articular process (SAP) (blue arrow). (B) Upon minimal resection of inferomedial aspect of the ipsilateral inferior articular process the SAP is seen. The green dotted line shows the border of the LF and SAP. (C) The medial aspect of the SAP is resected and the traversing nerve root is decompressed and mobilized. Using the diamond burr the LF attachment on the rostral edge of the caudal index level lamina is followed to the contralateral side. (D) The asterisks show bilateral opening of the LF for lateral recess decompression. (E) The contralateral recess is decompressed using the burr and Kerrison rongeur. (F) The contralateral traversing nerve root (white arrow) is decompressed and mobilized. SP, spinous process.
3) **Decompression**

Surgical decompression is performed following the yellow ligament attachment along the rostral edge of the caudal index level lamina (Fig. 1A). First, minimal the resection or the inferomedial inferior articular process is carried out with the high-speed burr until the SAP is exposed (Fig. 1B). The medial aspect of the SAP is resected to achieve decompression of the lateral recess. After adequate bone work, the traversing nerve root is decompressed spanning from the tip of the SAP to the midpoint of the caudal index level pedicle (Fig. 1C). The lateral aspect of the yellow ligament overlying the nerve root can be removed as necessary. The nerve root is then mobilized, any adhesions are resected with microscissors and decompression of the nerve root beyond the rostral and caudal aspect of the lateral recess is confirmed. After the ipsilateral decompression is completed, the working channel and endoscope is gradually tilted towards the contralateral side. Using the diamond burr the yellow ligament attachment on the rostral edge of the caudal index level lamina is followed to the contralateral side (Fig. 1D). Once the contralateral facet joint and lateral recess are visualized, the medial and ventral part of the SAP are undercut using a combination of high-speed drill and Kerrison rongeurs (Fig. 1E). The amount of ligamentum flavum removal at the bilateral lateral recesses depend on the severity of traversing root compression, but generally only the ligament overlying and compressing the nerve roots are removed and the central ligamentum flavum overlying central thecal sac is preserved. Finally, the contralateral traversing nerve root is mobilized with the blunt dissector and any adhesions are lysed (Fig. 1F). Typically, unless there is an accompanied significant disc herniation, there is no need for disc removal. The overall surgical procedure is also presented as a Supplementary videoclip 1.

4) **Wound closure and discharge**

Meticulous hemostasis should be performed prior to withdrawal of the endoscopic system and closure. Hemostasis can be assisted by radiofrequency cauterity and/or use of hemostatic agents. Wound closure proceeds in layer-by-layer sutures. Steri-strips can be applied or skin sealing bonds may be used. Wound drains are not routinely placed unless required due to intraoperative issues. Patients are encouraged to ambulate immediately after surgery and discharged the same day if their medical status permits.

4. **Statistics**

Demographic information, radiologic information, and clinical outcome measures were analyzed using descriptive statistics. Continuous variables are presented as mean ± standard deviation, while categorical variables are shown by frequency and percentage equivalence. Statistical analyses comparing clinical results pre- and postoperatively were carried out by independent Student t-test; p < 0.05 was defined as statistical significance.

<table>
<thead>
<tr>
<th>Table 1. Patient demographic and clinical characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td><strong>Value</strong></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (64.9)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (35.1)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.53 ± 14.51</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.85 ± 6.18</td>
</tr>
<tr>
<td>Scoliosis</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Age &lt; 65 yr</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age ≥ 65 yr</td>
<td>5 (20.9)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (45.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (10.5)</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30 kg/m²)</td>
<td>23 (40.3)</td>
</tr>
<tr>
<td>Prior surgery</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (33.3)</td>
</tr>
<tr>
<td>No</td>
<td>38 (66.7)</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>26.5 ± 18.7</td>
</tr>
<tr>
<td>Range</td>
<td>3–54</td>
</tr>
<tr>
<td>Level of surgery</td>
<td></td>
</tr>
<tr>
<td>1 Level</td>
<td>46 (80.7)</td>
</tr>
<tr>
<td>2 Levels</td>
<td>11 (19.3)</td>
</tr>
<tr>
<td>Index levels (n = 68)</td>
<td></td>
</tr>
<tr>
<td>L1/2</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>L2/3</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>L3/4</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>L4/5</td>
<td>40 (58.8)</td>
</tr>
<tr>
<td>L5/S1</td>
<td>12 (17.6)</td>
</tr>
<tr>
<td>ASA PS classification</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>II</td>
<td>29 (50.9)</td>
</tr>
<tr>
<td>III</td>
<td>23 (40.4)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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

BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status.
IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA) was used for analysis.

RESULTS

1. Patient Enrollment and Characteristics

A total of 57 of the 182 patients in our database had ULBD for bilateral LRS and met the inclusion criteria (Table 1). All patients had clinical and radiologic evidence of radiculopathy associated with bilateral LRS. The average age at time of surgery was 58.53 ± 14.51 years; 37 were male (64.9%) and 20 were female (35.1%). The age of patients who underwent surgery appear to cluster in a bimodal distribution, at the age of 40-mid 50 years and at > mid-60 years (Fig. 2). There were 5 patients with accompanying degenerative scoliosis of the lumbar spine (8.8%), and all were ≥ 65 years (20.9%, red circles in Fig. 2). A total of 26 patients had underlying hypertension (45.6%), 6 had diabetes mellitus (10.5%), and 23 had obesity with body mass index (BMI) higher than 30 (40.4%). The overall mean BMI was 29.85 ± 6.18 kg/m². Preoperative back VAS was 7.04 ± 2.36, leg VAS was 6.31 ± 2.78, EQ-5D was 0.574 ± 0.182, and the ODI was 50.12 ± 15.01.

Fig. 2. Graph depicting the age distribution of our patient cohort. A bimodal age distribution was observed with one patient cluster at the age of 40-mid 50 years and the other one at > mid-60 years. Red circles demarcate patients with accompanied degenerative lumbar scoliosis.

Table 2. Perioperative surgical details

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation time (min)</td>
<td>68.02 ± 15.88</td>
<td>Anesthesia, positioning, level confirmation, draping, OR setting up</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>70.34 ± 20.51</td>
<td>Per operated lamina</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>8.34 ± 15.11</td>
<td>Per operated level</td>
</tr>
<tr>
<td>Length of stay (day)</td>
<td>0.56 ± 0.85</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>2 (3.5)</td>
<td>2 Iatrogenic dural tear and subsequent CSF leaks</td>
</tr>
<tr>
<td>Perioperative</td>
<td>4 (7.0)</td>
<td>Transient urinary retention, short-term recurrence (&lt;1 mo), DVT of leg, EDH</td>
</tr>
<tr>
<td>Index level reoperations</td>
<td>5 (8.8)</td>
<td>2 Disc herniations occurred at index level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Synovial cyst recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 MISS TLIFs for instability at index level</td>
</tr>
</tbody>
</table>

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

OR, operating room; CSF, cerebrospinal fluid; DVT, deep vein thrombosis; EDH, epidural hemorrhage, MISS, minimally invasive spine surgery, TLIF, transforaminal lumbar interbody fusion.

Fig. 2. Graph depicting the age distribution of our patient cohort. A bimodal age distribution was observed with one patient cluster at the age of 40-mid 50 years and the other one at > mid-60 years. Red circles demarcate patients with accompanied degenerative lumbar scoliosis.
There were 4 perioperative complications during the immediate postoperative period (7.0%) which included transient urinary retention, recurrence within a month, deep vein thrombosis of the leg and a case of postoperative epidural hematoma which required hematoma removal. Representative pre- and postoperative T2-weighted MRI axial images are shown in Fig. 3.

### 3. Clinical Outcomes

The back VAS, leg VAS, EQ-5D, and ODI scores at final follow-up were 4.28 ± 2.87, 2.31 ± 2.89, 0.724 ± 0.170, and 32.44 ± 22.81 respectively. The detailed clinical pain outcome and functional outcome scores by different follow-up time points after surgery (2 weeks, 3 months, chronic 6–12 months, >1-year, and most recent follow-up) are presented in Table 3 and Fig. 4. The postoperative VAS, EQ-5D, and ODI scores at each time point were all statistically significantly improved compared to the preoperative data (p < 0.05). These clinical outcome measures demonstrated an overall trend toward improvement until the chronic follow-up time point. The final follow-up VAS, EQ-5D and ODI scores presented a slight worsening, however this was not statistically significant. The overall rate for reoperation at the index level within 1-year was 8.8%, and the detailed information of the causes for reoperation are presented in Table 2.

---

**Table 3. Preoperative and postoperative functional evaluation**

<table>
<thead>
<tr>
<th>Time period</th>
<th>Functional outcome</th>
<th>VAS score</th>
<th>EuroQol-5D</th>
<th>ODI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Back</td>
<td>Leg</td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td></td>
<td>7.04 ± 2.36</td>
<td>6.31 ± 2.78</td>
<td>0.574 ± 0.182</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td>4.48 ± 2.89</td>
<td>2.68 ± 3.08</td>
<td>0.682 ± 0.194</td>
</tr>
<tr>
<td>2 Weeks</td>
<td></td>
<td>4.12 ± 2.79</td>
<td>2.46 ± 2.80</td>
<td>0.738 ± 0.184</td>
</tr>
<tr>
<td>3 Months</td>
<td></td>
<td>3.84 ± 3.07</td>
<td>2.05 ± 2.68</td>
<td>0.737 ± 0.167</td>
</tr>
<tr>
<td>Chronic (6 to 12 months)</td>
<td></td>
<td>4.28 ± 2.87</td>
<td>2.31 ± 2.69</td>
<td>0.724 ± 0.170</td>
</tr>
<tr>
<td>Last follow-up</td>
<td></td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

VAS, visual analogue scale; EuroQol-5D, Euro-Quality of Life-5 Dimension; ODI, Oswestry Disability Index.

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Fig. 3. Pre- and postoperative magnetic resonance imaging (MRI) following unilateral laminotomy for bilateral recess decompression. (A) Preoperative T2-weighted MRI depicts bilateral lateral recess stenosis. (B) Postoperative imaging confirms bilateral recess decompression while midline structures including paraspinal muscles, lamina, and yellow ligament are spared.
DISCUSSION

Increased utilization of endoscopy in spine surgery is evidenced by a recent global survey by Lewandrowski et al.\textsuperscript{29} Despite a steep learning curve for the acquisition of endoscopic spine surgery skills,\textsuperscript{30} the endoscope is emerging as an essential component of the armamentarium of the modern spine surgeon. Full-endoscopic spine surgery allows favorable functional outcomes, faster recovery, earlier rehabilitation, less utilization of opioid medication while minimizing approach-related morbidity compared with open and conventional minimally invasive techniques.\textsuperscript{7,30-32}

Favorable clinical outcomes of unilateral lateral recess decompression using full-endoscopic technique have been described by several groups.\textsuperscript{7,17,18,23-26} For our study, we were interested in better understanding the demographics, and clinical outcomes for our patients who require bilateral recess decompression, in the absence of central stenosis.

About 3 quarters of the spinal levels treated in our cohort were located at the 2 most caudal lumbar levels, reflecting the anatomic nature of the lateral recess. The lateral recess becomes narrower at the caudal lumbar segments compared with rostral levels. A previous anatomic study revealed that nonpathologic anterior-posterior measurements for the lateral recess decrease in a caudal-direction from 9.1 mm at L1 to 6.0 mm at L4, and the height of the anterior-posterior lateral recess at L5 is approximately 6.1 mm.\textsuperscript{33} While the physical space of the lateral recess becomes smaller in caudal levels, the nerve roots traverse more horizontally rather than vertically compared with rostral levels, rendering the lateral recess even more vulnerable to possible compressions by adjacent structures.

Traditionally, decompression of the lateral recess for patients suffering from LRS utilized an open microsurgical approach. However, more recently, a broad range of surgical approaches for this type of decompression have been used, ranging from standard open laminectomies to endoscopic approaches using minimally invasive techniques.\textsuperscript{34-36} Our group described a series of patients with symptomatic unilateral LRS who were treated successfully using interlaminar endoscopic decompression techniques.\textsuperscript{17} Additional studies have demonstrated favorable clinical results comparing full-endoscopic with microsurgical techniques and highlighted the reduced approach-related morbidity afforded by a full-endoscopic approach.\textsuperscript{7,21,37} Aforementioned studies and the current cohort underwent interlaminar full-endoscopic approach for decompression of the lateral recess. Another endoscopic approach, the trans-SAP approach for lateral recess decompression, provides an alternative option for exposing the exiting nerve root while avoiding inadvertent injury, particularly in cases where degenerative changes have distorted a patient’s anatomy.\textsuperscript{38} While transforaminal or trans-SAP approaches cannot decompress the bilateral LRSs, our technique of ULBRD provides bilateral decompression via single approach, also providing a safe surgical corridor to access both lateral recesses in endoscopic decompression surgery. Considering the novelty of these techniques, additional research is warranted to further analyze the advantages provided by each approach for various patient populations.

The surgical approach for patients requiring bilateral recess decompression but lacking central stenosis, consists of a single
approach for bilateral decompression preserving the central ligamentum flavum. In traditional open surgery or classical minimally invasive techniques, 2 different surgical approaches from each side are needed. Alternatively, with a unilateral approach, the midline structures, including the ligamentum flavum, must be sacrificed. There are consequences for this injury to the central structures, including the possibility of iatrogenic instability or post-laminectomy spondylolisthesis, particularly in cases with no central stenosis, such as the cohort described here. The importance of preserving midline structures has led to development of less invasive normal structure preserving techniques. Minimizing medial facetectomies and preserving the midline ligamentous structures can cause a significant difference in lumbar stability compared to traditional decompressive laminectomies. These results support leaving the medial border of the facet and preserving normal ligamentum flavum when a less destructive bilateral decompression is sufficient. Driven by this impetus, various minimally invasive techniques (open, tubular, and endoscopic) have been developed and evolved with the goal of maximally preserving midline structures from unnecessary removal and have shown promising results. Our technique can provide another alternative by fully preserving the supraspinous and interspinous ligaments, and the ligamentum flavum, with minimal risks and excellent clinical outcomes.

Another potential advantage to preserving the ligamentum flavum during laminectomy is that epidural scarring can be minimized. Epidural scarring after a laminectomy surgery is known to serve as a possible factor inducing postoperative pain. Excessive production of fibrosis at the postoperative epidural bed can cause neural irritation or stretching, and sometimes even mass effects, resulting in radicular symptoms. Therefore, avoiding or at least minimizing epidural scarring can improve postoperative clinical outcomes. Although it is impossible to completely prevent epidural scarring, efforts made to minimize this phenomenon in laminectomies have demonstrated the clinical significance of ligamentum flavum preservation and support the use of endoscopic spine surgeries to minimize epidural scarring through minimizing the extent of laminectomies and ligamentum flavum resection. Further research is necessary to determine if surgical approaches preserving the ligamentum flavum benefit patients, including those in our cohort, by minimizing postoperative epidural fibrosis.

In our cohort of patients with bilateral LRS without central stenosis, age exhibited a bimodal distribution. The majority of patients were 40 to mid-50 years, with a second cluster at ≥ mid-60-years. Central lumbar stenosis is a very common condition; it is the most common indication for surgical decompression with or without fusion in the elderly. The occurrence of central spinal stenosis is associated with advanced age, typically occurring in those > 65-years, consistent with our observation that the majority of our cohort was in the age range of 40’s–50’s. While patients in our cohort had not developed central stenoses, they may be experiencing the beginning stages of spine aging, resulting in their symptomatic LRSs. In our cohort, there were no cases of scoliosis in the younger subgroup, while > 20% of the older subgroup had accompanying scoliosis by diagnostic criteria, and additional patients exhibited subclinical (not meeting the diagnostic criteria) indications of scoliosis. Coronal imbalance of the lumbar spine can result in possible LRSs. It is possible that accompanying degenerative scoliosis-related coronal deformities are an explanation for the bimodal age distribution in this cohort; further research should aim at understanding asymptomatic LRS in older patients without central stenosis.

The current study has several limitations. It is a single-center series and describes a small patient’s cohort. Moreover, given that this is the first description and analysis following ULBRD, we are planning to further study patient selection criteria in order to identify patients who require additional foraminal decompression or stabilization and might be better suited for alternative procedures. Further studies are needed to provide the scientific/clinical evidence of beneficial effect of ligamentum flavum sparing to counteract epidural fibrosis.

CONCLUSION

In this study cohort, patients receiving ULBRD for bilateral LRSs without significant central stenosis obtained good clinical outcomes with acceptable perioperative complications rates. ULBRD enabled sufficient decompression of bilateral lateral recesses via a single endoscopic incision without sacrificing central structures such as the midline ligamentum flavum. Further research is needed to understand long-term outcomes in large, diverse patient populations, with the ultimate goal of providing recommendations for the use of ULBRD under various clinical scenarios.

NOTES

**Supplementary Materials:** Supplementary videoclip 1 can be found via https://doi.org/ns.2244344.172.

**Conflict of Interest:** Dr. Hofstetter is a consultant for Johnson & Johnson, Globus, Innovasis, and Joimax. Other authors

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**REFERENCES**


**Supplementary Videoclip 1.** The overall step-by-step video for unilateral laminotomy for bilateral recess decompression is presented.
Risk Analysis Index and Its Recalibrated Version Predict Postoperative Outcomes Better Than 5-Factor Modified Frailty Index in Traumatic Spinal Injury

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Objective: To assess the discriminative ability of the Risk Analysis Index-administrative (RAI-A) and its recalibrated version (RAI-Rev), compared to the 5-factor modified frailty index (mFI-5), in predicting postoperative outcomes in patients undergoing surgical intervention for traumatic spine injuries (TSIs).

Methods: The Current Procedural Terminology (CPT) and International Classification of Disease-9 (ICD-9) and ICD-10 codes were used to identify patients ≥ 18 years who underwent surgical intervention for TSI from National Surgical Quality Improvement Program (ACS-NSQIP) database 2015–2019 (n = 6,571). Multivariate analysis and receiver operating characteristic (ROC) curve analysis were conducted to evaluate the comparative discriminative ability of RAI-Rev, RAI-A, and mFI-5 for 30-day postoperative outcomes.

Results: Multivariate regression analysis showed that with all 3 frailty scores, increasing frailty tiers resulted in worse postoperative outcomes, and patients identified as frail and severely frail using RAI-Rev and RAI-A had the highest odds of poor outcomes. In the ROC curve/C-statistics analysis for prediction of 30-day mortality and morbidity, both RAI-Rev and RAI-A outperformed mFI-5, and for many outcomes, RAI-Rev showed better discriminative performance compared to RAI-A, including mortality (p = 0.0043, DeLong test), extended length of stay (p = 0.0042), readmission (p < 0.0001), reoperation (p = 0.0175), and nonhome discharge (p < 0.0001).

Conclusion: Both RAI-Rev and RAI-A performed better than mFI-5, and RAI-Rev was superior to RAI-A in predicting postoperative mortality and morbidity in TSI patients. RAI-based frailty indices can be used in preoperative risk assessment of spinal trauma patients.

Keywords: Risk Analysis Index-administrative, Risk Analysis Index-revised, Modified frailty index, Spinal trauma, Frailty

INTRODUCTION

Traumatic spinal injury (TSI) includes injuries to the spinal cord, nerve roots, osseous structures, and discoligamentous components of the spinal column.1-3 The main cause for spinal injury is blunt trauma, most commonly caused by motor vehicle accidents, followed by falls and sport injuries.1-3 Spinal column injury can cause mechanical instability, impaired movements, and damage to neural structures can lead to partial or complete paralysis.1-3 Among TSI, traumatic spinal cord injury (tSCI) is a
subset, which leads to neurologic deficits secondary to traumatic injury. The yearly incidence of TSI has been estimated to be 54 cases per 1 million people in the United States or about 17,810 new TSI cases each year. Irrespective of TSI type, these injuries are a major cause of disability, with significant socioeconomic consequences.

While historically, TSI has been associated with average age in 40s and predominantly males, there has been a change in the epidemiological trends in recent years with an aging population, and the average of TSI continues to increase. It has been predicted that major proportion of new TSI will occur in patients above 70 years of age, with similar projections for overall TSI. It is imperative to perform risk stratification and to identify prognostic factors for TSI patients.

Frailty, a measure of physiological reserve, broadly defined as the cumulative burden of baseline comorbid conditions and functional status impairment, has been associated with worse postoperative outcomes across surgical subspecialties. In recent years, several studies have assessed the impact of baseline frailty status on postoperative outcomes in patients undergoing spine surgery, though its application to spine trauma and TSI has been limited to 2 studies. The lack of large scale, high quality, clinical studies on frailty and spine trauma has been emphasized before. Furthermore, majority of previous studies on frailty and spine surgery outcomes have employed the modified frailty index-11 (mFI-11), or its abridged version, modified frailty index-5 (mFI-5) for preoperative frailty status assessment. While the mFI indices have been classically used for frailty assessment, however mFI are more a measure of comorbidity rather than frailty. Though functional status has been commonly associated with the definition of frailty, the variables of diabetes, chronic obstructive pulmonary disease (COPD), hypertension, and congestive heart failure (CHF) are more commonly defined as comorbidities.

To more precisely incorporate the multifactorial nature of frailty, Hall et al. developed the Risk Analysis Index (RAI) in 2017 in an effort to provide an effective screening tool to assess the frailty of surgical patients. This frailty index including both the prospective clinical RAI and the retrospective administrative RAI (RAI-A) could be easily calculated from variables captured by the Veterans Affairs Surgical Quality Improvement Program and the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) databases includes both comorbidities and functional status variables that robustly measures baseline frailty status, and has recently been validated in a prospective, single-center spine surgery study, and also by us in brain tumor resection patients. Since its development the RAI has demonstrated significant utility in predicting 30-, 180-, and 365-day postoperative outcomes across multiple surgical subspecialties. Recently, Arya et al. have recalibrated and improved the original RAI (RAI-Rev) in order to better discriminate 30-day mortality and morbidity. Presently, there is a gap within the literature demonstrating the predictive utility of RAI-A and RAI-Rev within spine surgery, and, more specifically, in patients undergoing surgery for spinal trauma. The present study was performed to assess the predictive capability of RAI-A and RAI-Rev on 30-day postoperative outcomes in traumatic spine surgery patients utilizing large scale data from NSQIP. Based on the reported robustness of RAI-A and RAI-Rev in predicting postoperative outcomes in other surgical specialties, we hypothesized that RAI-A and RAI-Rev would be superior to the mFI-5 in predicting postoperative 30-day mortality and morbidity in patients undergoing surgery for spinal trauma.

**MATERIALS AND METHODS**

1. **Data Source**

The NSQIP is a nationally validated, multi-institutional database of over 700 participating hospitals with > 200 variables collected for pre-, intra-, and postoperative outcomes. Data are entered from each institution by ACS-trained surgical clinical reviewers to ensure consistency and reliability. Our data were extracted from the NSQIP database for the years 2015 to 2019. The present study was performed under the data user agreement of the ACS with the University of New Mexico (UNM) and was approved by the Institutional Review Board of UNM School of Medicine (Study ID 21-315).

2. **Patient Population and Baseline Characteristics**

Current Procedural Terminology codes (Supplementary Table 1) were used to identify all patients over 18 years old that had undergone spine surgery in the NSQIP dataset. International Classification of Diseases (ICD)-9 and ICD-10 diagnostic codes were then used to identify spinal trauma patients (Supplementary Table 2). Forty-six patients were removed due to primary diagnosis codes unrelated to spinal trauma, and another 77 were excluded due to missing length of stay (LOS) duration. The final sample size of patients who underwent surgery for spinal trauma was 6,571. The baseline study variables included age, sex, body mass index (BMI), elective versus nonelective surgery type, LOS, transfer status, and operative time. The ana-
lyzed medical comorbidities included diabetes mellitus, COPD, CHF, dyspnea, hypertension, disseminated cancer (defined as multiple metastases by NSQIP), open wound, steroid use, weight loss (substantial unintentional weight loss > 10%), bleeding disorders, preoperative transfusion, transfer status, and preoperative sepsis/septic shock/systemic inflammatory response (SIRS). Preoperative SIRS criteria are defined by NSQIP as the presence of at least 2 of the following criteria: temperature > 38°C or < 36°C, heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute or PaCO₂ < 32 mmHg, leukocytosis or leukopenia (white blood cell count > 12,000/mm³ and < 4,000/mm³, respectively) or > 10% immature (band) forms, or anion gap acidosis.23,29 Additional preoperative comorbidities extracted included functional dependence (both complete and partial dependence) and smoking status.

3. Retrospective Risk Analysis Index Scoring (RAI-A and RAI-Rev)

Retrospective RAI-A and the recalibrated RAI-Rev scoring, adapted from Hall et al. and Arya et al. are shown in Supplementary Table 3. RAI scoring system is based on 11 variables: sex, age, cancer diagnosis (excluding melanoma), weight loss defined as unintentional weight loss of 4.5 kg over 3 months, renal failure, CHF, poor appetite, shortness of breath at rest, residence defined as not independent living, cognitive deterioration, and activities of daily living (ADL) defined as functional status. Age scoring is related to having a cancer diagnosis, which can be seen in Supplementary Tables 4 and 5 for RAI-A and RAI-Rev, respectively. Cognitive deterioration over the past 3 months was originally included in Hall’s scoring method for RAI-A to be included with ADL scoring, however preoperative cognitive decline is not recorded in NSQIP and therefore was excluded from this study’s adaptation of Hall’s RAI-A scoring. Score stratification of RAI-A and RAI-Rev as they relate to frailty tiers is demonstrated in Supplementary Table 6 (nonfrail ≤ 10, prefrail 11–20, frail 21–30, and severely frail ≥ 31 RAI-A and RAI-Rev scores).

4. Modified Frailty Index-5 (mFI-5)

Although the modified frailty index was initially developed with 11 variables (mFI-11), in 2014, the NSQIP stopped mandating the reporting of some of the mFI-11 preoperative variables and as such the mFI-5 was adapted based on these 5 remaining variables: diabetes mellitus, hypertension, dependent functional status, COPD, and CHF (Supplementary Table 7). The presence of each mFI-5 variable receives one point. Thus, the mFI-5 scores range from 0 to 5, where a score of 0 is “nonfrail,” 1 is defined as “prefrail,” 2 as “frail,” and a score of 3 or more as “severely frail.”

5. Outcome Measures

The outcome measures included 30-day mortality, major complications, Clavien-Dindo physical status (PS) classification grade IV complications, 30-day unplanned readmission, 30-day unplanned reoperation, extended LOS (ELOS), and discharge destination. Major complications consisted of presence of one of the following: prolonged intubation exceeding 48 hours, unplanned reintubation, sepsis, septic shock, pneumonia, deep vein thrombosis/thrombophlebitis, pulmonary embolism (PE), acute cerebrovascular accident or stroke with neurological deficit, acute renal failure, myocardial infarction (MI), cardiac arrest requiring cardiopulmonary resuscitation, superficial surgical site infection (SSI), deep incisional SSI, organ space SSI, or wound disruption. Minor complication was defined as intra-/postoperative blood transfusion, renal insufficiency, or urinary tract infection. Clavien-Dindo PS classification grade IV complications were designated by the presence of life-threatening complications defined by single or multiple organ dysfunction requiring intensive care unit management. Clavien-Dindo PS classification grade IV complications included: sepsis or septic shock, acute renal failure, PE, MI, cardiac arrest requiring cardiopulmonary resuscitation, superficial surgical site infection (SSI), deep incisional SSI, organ space SSI, or wound disruption. ELOS was defined as > 75th percentile LOS of study population. The “nonhome discharge” location encompassed all patients discharged to any rehabilitation facility, skilled nursing facility, hospice care, and patients leaving against medical advice. Home or facility that is home are included in the “home destination.” Patients that expired were not included in either of these groups and only in mortality rate for the study.

6. Statistical Analysis

We conducted statistical analyses using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA), GraphPad Prism v 9.0 (GraphPad Software Inc., La Jolla, CA, USA), MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium), and R statistical software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables with skewed distribution are reported as median with interquartile range (IQR). The normality of the data was determined by employing the D’Agostino-Pearson, Shapiro-Wilk, and Kolmogorov-Smirnov tests. We performed univariate and multivariate analyses (employing logistic regression) for mFI-5, RAI-A, and RAI-Rev for
the following outcomes: 30-day mortality, major complications, Clavien-Dindo PS classification IV complications, 30-day unplanned reoperation, 30-day unplanned readmission, ELOS, and discharge to a nonhome destination. The effect sizes for dichotomous outcomes were summarized by odds ratio (OR) and associated 95% confidence intervals (CIs). We performed the receiver operating characteristic (ROC) curve analysis including the area under the curve (AUC)/C-statistics calculations to discern the predictive ability of mFI-5, RAI-A, and RAI-Rev for outcomes after spine surgery. We used the DeLong test to compute the significance of C-statistic comparison between mFI-5, RAI-A, and RAI-Rev. For all purposes, p < 0.05 was considered statistically significant.

RESULTS

1. Study Population Characteristics

We identified 6,571 patients that underwent surgery for TSI and met our inclusion criteria. The median age of our cohort was 64 years (IQR, 52–75 years), 57.3% patients were male, and the median BMI was 27.7 kg/m² (IQR, 24.2–32.2 kg/m²). Majority of the cases were nonelective (54.1%). Within the cohort the median LOS was 6 days (IQR, 3–10 days), and the median operation time was 160 minutes (IQR, 110–230 minutes). One point seven percent of the patient cohort expired, 5.5% were returned to the operating room, and 8% were readmitted to the hospital, all within 30 days from their respective TSI surgery. The distribution for frailty tiers based on mFI-5 was as follows: not frail 40.7%, prefrail 36.3%, frail 19.3%, and severely frail 4.2%. The distribution for frailty tiers based on RAI-A was as follows: not frail 69.6%, prefrail 25.1%, frail 4.5%, and severely frail 0.9%. The most common comorbidities within our cohort were hypertension (52.4%), current smoking status (21.7%), and diabetes mellitus (20.2%). Thirteen point four percent of the patient cohort experienced at least one or more major postoperative complications and the most common were postoperative pneumonia (4.8%), prolonged intubation (3.7%), unplanned reintubation (2.4%), and sepsis (1.8%). Clavien-Dindo PS classification grade IV complications occurred in 8.1% of the patient cohort and 44.2% of the cohort was transferred to a nonhome destination following surgery. All patient demographics and clinical characteristics are summarized in Table 1.

### Table 1. Baseline demographic and clinical characteristics, 30-day mortality, readmission, reoperation, major and minor complications, and discharge disposition of patients with spine trauma from NSQIP database 2015–2019 (n = 6,571)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64 (52–75)</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>3,766 (57.3):2,805 (42.7)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7 (24.2–32.2)</td>
</tr>
<tr>
<td>Surgery type</td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>3,006 (45.7)</td>
</tr>
<tr>
<td>Nonelective</td>
<td>3,556 (54.1)</td>
</tr>
<tr>
<td>Length of stay (day)</td>
<td>6 (3–10)</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>160 (110–230)</td>
</tr>
<tr>
<td>Mortality</td>
<td>113 (1.7)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>364 (5.5)</td>
</tr>
<tr>
<td>Readmission</td>
<td>527 (8)</td>
</tr>
<tr>
<td>mFI-5 frailty tiers</td>
<td></td>
</tr>
<tr>
<td>Not frail (mFI-5 = 0)</td>
<td>2,637 (40.1)</td>
</tr>
<tr>
<td>Prefrail (mFI-5 = 1)</td>
<td>2,387 (36.3)</td>
</tr>
<tr>
<td>Frail (mFI-5 = 2)</td>
<td>1,270 (19.3)</td>
</tr>
<tr>
<td>Severely frail (mFI-5 ≥ 3)</td>
<td>277 (4.2)</td>
</tr>
<tr>
<td>RAI-A frailty tiers</td>
<td></td>
</tr>
<tr>
<td>Not frail (RAI-A ≤ 10)</td>
<td>4,573 (69.6)</td>
</tr>
<tr>
<td>Prefrail (RAI-A = 11–20)</td>
<td>1,647 (25.1)</td>
</tr>
<tr>
<td>Frail (RAI-A = 21–30)</td>
<td>293 (4.5)</td>
</tr>
<tr>
<td>Severely frail (RAI-A ≥ 31)</td>
<td>58 (0.9)</td>
</tr>
<tr>
<td>RAI-Rev frailty tiers</td>
<td></td>
</tr>
<tr>
<td>Not frail (RAI-Rev ≤ 10)</td>
<td>692 (10.5)</td>
</tr>
<tr>
<td>Prefrail (RAI-Rev = 11–20)</td>
<td>2,131 (32.4)</td>
</tr>
<tr>
<td>Frail (RAI-Rev = 21–30)</td>
<td>2,889 (44)</td>
</tr>
<tr>
<td>Severely Frail (RAI-Rev ≥ 31)</td>
<td>859 (13.1)</td>
</tr>
<tr>
<td>Preop clinical status/comorbidities</td>
<td></td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
</tr>
<tr>
<td>Partially dependent</td>
<td>463 (7)</td>
</tr>
<tr>
<td>Totally dependent</td>
<td>75 (1.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,328 (20.2)</td>
</tr>
<tr>
<td>COPD</td>
<td>395 (6)</td>
</tr>
<tr>
<td>CHF</td>
<td>97 (1.5)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1424 (21.7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>345 (5.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3,444 (52.4)</td>
</tr>
<tr>
<td>Disseminated cancer</td>
<td>271 (4.1)</td>
</tr>
<tr>
<td>Open wound</td>
<td>222 (3.4)</td>
</tr>
<tr>
<td>Steroid use</td>
<td>317 (4.8)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>92 (1.4)</td>
</tr>
<tr>
<td>Bleeding disorders</td>
<td>353 (5.4)</td>
</tr>
<tr>
<td>Preop transfusion</td>
<td>85 (1.3)</td>
</tr>
<tr>
<td>Transfer status</td>
<td>1,626 (24.7)</td>
</tr>
</tbody>
</table>

(Continued)
2. Univariate Analysis of mFI-5, RAI-A, and RAI-Rev on Surgical Outcomes

While univariate analysis of frailty tiers by all 3 scoring systems showed that increasing frailty tiers were associated with poor postoperative outcomes, patients identified as frail and severely frail using RAI-A and RAI-Rev had the highest odds of worse outcomes (Table 2). In the RAI-A and RAI-Rev univariate analysis, each frailty index was the most predictive of 30-day mortality and discharge to a nonhome destination. For 30-day postoperative mortality, the severely frail group for RAI-A demonstrated OR of 20.78 (95% CI, 8.73–49.49; p < 0.001) and the severely frail group for RAI-Rev showed OR of 48.12 (95% CI, 6.64–348.52; p < 0.001). For discharge to a nonhome destination the severely frail group for RAI-A had OR of 9.27 (95% CI, 4.68–18.37; p < 0.001) and RAI-Rev had OR of 18.08 (95% CI, 13.70–23.84; p < 0.001). The mFI-5-based severely frail group demonstrated OR of 4.79 (95% CI, 2.50–9.17; p < 0.001) for 30-day mortality and 6.83 (95% CI, 5.18–9.02; p < 0.001) for nonhome discharge.

3. Multivariate Analysis of mFI-5, RAI-A, and RAI-Rev on Surgical Outcomes

Multivariate regression analysis of frailty scores for patients undergoing surgery for spinal trauma (adjusting for BMI, emergent surgery status, operative time, race, and ethnicity) demonstrated results similar to univariate analysis with all 3 frailty scores showing that increasing frailty tiers result in poor postoperative outcomes, and patients identified as frail and severely frail using RAI-A and RAI-Rev had the highest odds of poor outcomes (Table 3). The likelihood of an adverse event was markedly high in severely frail cohorts of both RAI-A and RAI-Rev scoring systems, however OR of mortality, major complication, Clavien-Dindo PS classification grade IV complication, readmission, ELOS, and nonroutine discharge show RAI-Rev’s superiority in its ability to predict adverse outcomes. RAI-Rev frail populations have an OR of mortality of 10.35 OR (95% CI, 1.27–78.03; p = 0.02) and severely frail had OR 28.77 (95% CI, 3.69–224.54; p = 0.001), whereas RAI-A frail had OR 2.22 (95% CI, 1.02–4.84; p = 0.04) and severely frail had OR 4.64 (95% CI, 1.59–13.59; p = 0.005) for mortality (Table 3). Surprisingly, mFI-5 frailty tiers demonstrated decreased risk of mortality across all frailty types which might indicate conservative management of comorbid individuals or the inability of mFI-5 to truly capture frailty phenotype.

Table 1. Baseline demographic and clinical characteristics, 30-day mortality, readmission, reoperation, major and minor complications, and discharge disposition of patients with spine trauma from NSQIP database 2015–2019 (n = 6,571) (Continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major postoperative complications</td>
<td>879 (13.4)</td>
</tr>
<tr>
<td>Prolonged intubation (≥ 48 hr)</td>
<td>244 (3.7)</td>
</tr>
<tr>
<td>Unplanned reintubation</td>
<td>157 (2.4)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>118 (1.8)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>49 (0.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>313 (4.8)</td>
</tr>
<tr>
<td>DVT/thrombophlebitis</td>
<td>109 (1.7)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>62 (0.9)</td>
</tr>
<tr>
<td>CVA/stroke with neurological deficit</td>
<td>36 (0.5)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>19 (0.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>53 (0.8)</td>
</tr>
<tr>
<td>Cardiac arrest requiring CPR</td>
<td>48 (0.7)</td>
</tr>
<tr>
<td>Superficial SSI</td>
<td>90 (1.4)</td>
</tr>
<tr>
<td>Deep incisional SSI</td>
<td>51 (0.8)</td>
</tr>
<tr>
<td>Organ space SSI</td>
<td>60 (0.9)</td>
</tr>
<tr>
<td>Wound disruption</td>
<td>45 (0.7)</td>
</tr>
<tr>
<td>Clavien-Dindo grade IV</td>
<td>531 (8.1)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%). NSQIP, National Surgical Quality Improvement Program; mFI-5, 5-factor modified frailty index; RAI-A, Risk Analysis Index-administrative; RAI-Rev, Risk Analysis Index recalibrated version; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; DVT, deep vein thrombosis; CVA, cerebrovascular accident; CPR, cardiopulmonary resuscitation; SSI, surgical site infection; SIRS, systemic inflammatory response syndrome; SNF, skilled nursing facility; AMA, against medical advice.

Patients considered to have major complications experienced one or more of the following postoperative adverse events: prolonged intubation of 48 hours or more, unplanned reintubation, sepsis/septic shock, DVT/thrombophlebitis, pulmonary embolism (PE), coma, CVA/stroke with neurological deficit(s), myocardial infarction (MI), cardiac arrest requiring CPR, SSI (superficial/deep/organ space), wound disruption/dehiscence, acute renal failure, and pneumonia. Patients considered to have Clavien-Dindo physical status classification grade IV complications by the presence of a life-threatening complication, defined by single or multiple organ system dysfunction requiring intensive care unit management. Clavien-Dindo physical status classification grade IV complications include the following: sepsis or septic shock, acute renal failure, PE, MI, cardiac arrest requiring CPR, ventilation > 48 hours, and unplanned reintubation.
### Table 3. Multivariate analysis of mFI-5, RAI-A, and RAI-Rev for 30-day postoperative outcomes: mortality, major complication, Clavien-Dindo physical status classification grade IV, reoperation, readmission, ELOS, and nonroutine discharge in TSI data from NSQIP 2015–2019

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mortality</th>
<th>Major complication</th>
<th>Clavien-Dindo grade IV</th>
<th>Unplanned readmission</th>
<th>Reoperation</th>
<th>Extended hospital LOS</th>
<th>Discharge to nonhome destination</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFI-5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrail</td>
<td>1.34 (0.82–2.20)</td>
<td>1.84 (1.53–2.21)***</td>
<td>1.71 (1.36–2.16)***</td>
<td>1.81 (1.45–2.26)***</td>
<td>1.47 (1.13–1.91)*</td>
<td>1.88 (1.65–2.15)***</td>
<td>2.68 (2.38–3.01)***</td>
</tr>
<tr>
<td>Frail</td>
<td>2.55 (1.55–4.19)***</td>
<td>2.93 (2.41–3.57)***</td>
<td>3.00 (2.35–3.82)***</td>
<td>2.39 (1.87–3.05)***</td>
<td>2.19 (1.65–2.91)***</td>
<td>2.83 (2.43–3.29)***</td>
<td>4.63 (4.02–5.34)***</td>
</tr>
<tr>
<td>Severely frail</td>
<td>4.79 (2.50–9.17)***</td>
<td>5.41 (4.05–7.23)***</td>
<td>4.39 (3.08–6.26)***</td>
<td>4.28 (3.03–6.07)***</td>
<td>2.57 (1.64–4.04)***</td>
<td>5.90 (4.56–7.63)***</td>
<td>6.83 (5.18–9.02)***</td>
</tr>
<tr>
<td>RAI-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrail</td>
<td>5.63 (3.61–8.76)***</td>
<td>2.32 (1.98–2.71)***</td>
<td>2.77 (2.28–3.37)***</td>
<td>1.38 (1.13–1.68)*</td>
<td>1.39 (1.09–1.76)</td>
<td>2.63 (2.33–2.97)***</td>
<td>4.13 (3.67–4.66)***</td>
</tr>
<tr>
<td>Frail</td>
<td>9.33 (5.08–17.12)***</td>
<td>4.26 (3.27–5.57)***</td>
<td>4.96 (3.64–6.75)***</td>
<td>2.42 (1.73–3.38)***</td>
<td>2.67 (1.82–3.92)***</td>
<td>4.84 (3.81–6.16)***</td>
<td>7.96 (5.92–10.70)***</td>
</tr>
<tr>
<td>Severely frail</td>
<td>20.78 (8.73–49.49)***</td>
<td>8.24 (4.88–13.94)***</td>
<td>8.99 (5.12–15.81)***</td>
<td>3.75 (2.00–7.02)***</td>
<td>4.77 (2.44–9.32)***</td>
<td>5.70 (3.37–9.66)***</td>
<td>9.27 (4.68–18.37)***</td>
</tr>
<tr>
<td>RAI-Rev</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrail</td>
<td>0.97 (0.10–9.37)</td>
<td>2.04 (1.37–3.03)***</td>
<td>2.30 (1.28–4.15)*</td>
<td>2.06 (1.29–3.29)*</td>
<td>1.53 (0.94–2.51)</td>
<td>3.33 (2.42–4.60)***</td>
<td>2.83 (2.20–3.66)***</td>
</tr>
<tr>
<td>Frail</td>
<td>12.90 (1.78–93.41)*</td>
<td>4.14 (2.83–6.04)***</td>
<td>5.45 (3.11–9.57)***</td>
<td>2.95 (1.87–4.64)***</td>
<td>2.19 (1.37–3.51)*</td>
<td>6.72 (4.92–9.18)***</td>
<td>11.64 (9.09–14.90)***</td>
</tr>
</tbody>
</table>

Values are presented as odds ratio (95% confidence interval).

mFI-5, 5-factor modified frailty index; RAI-A, Risk Analysis Index-administrative; RAI-Rev, Risk Analysis Index recalibrated version; ELOS, extended length of stay; TSI, traumatic spine injury; NSQIP, National Surgical Quality Improvement Program.

*p < 0.05. ***p < 0.001, statistically significant.
4. ROC Curve Analysis and C-Statistics

The ROC analysis was conducted to assess the comparative predictive value of the mFI-5, RAI-A, and RAI-Rev for postoperative morbidity and mortality (Fig. 1). In the analysis for prediction of 30-day mortality, C-statistics indicated significantly better performance of RAI-Rev compared to mFI-5 (C-statistic = 0.819, 95% CI, 0.810–0.829 for RAI-Rev vs. C-statistic = 0.622, 95% CI, 0.610–0.634 for mFI-5, p < 0.0001, DeLong test). Similarly, for mortality, RAI-A performed better compared to mFI-5 (C-statistic = 0.768, 95% CI, 0.758–0.779 for RAI-A vs.

Fig. 1. Receiver operating characteristic (ROC)/area under the curve (A-G) and ROC/C-statistics analysis (H) for the relative predictive abilities of the mFI-5 and RAI on mortality (A), major complication (B), Clavien-Dindo physical status classification IV complication (C), ELOS (D), nonhome discharge (E), readmission (F), and reoperation (G) in patients who underwent surgical intervention for traumatic spinal injury from NSQIP database 2015–2019. mFI-5, 5-factor modified frailty index; RAI-A, Risk Analysis Index-administrative; RAI-Rev, Risk Analysis Index recalibrated version; ELOS, extended length of stay; NSQIP, National Surgical Quality Improvement Program.
C-statistic = 0.622, 95% CI, 0.610–0.634 for mFI-5, p < 0.001, DeLong test). Interestingly, RAI-Rev performed better than RAI-A in predicting postoperative mortality (C-statistic = 0.819, 95% CI, 0.810–0.829 for RAI-Rev vs. C-statistic = 0.768, 95% CI, 0.758–0.779 for RAI-A, p = 0.0043, DeLong test). For most of other outcome variables, both RAI-Rev and RAI-A outperformed mFI-5, and for many outcomes, RAI-Rev showed better discriminative performance compared to RAI-A, including ELOS (p < 0.0001), readmission (p < 0.0001), reoperation (p = 0.0175), and nonhome discharge (p < 0.0001).

DISCUSSION

The goal of this study was to do a comparative analysis of discriminative ability of mFI-5, RAI-A, and RAI-Rev on postoperative outcomes of TSI based on large scale multicenter data from NSQIP. To the best of our knowledge, this is the first study evaluating RAI in spine trauma patients. Based on AUC/C-statistics analyses, both RAI-Rev and RAI-A outperformed mFI-5 in predicting worse postoperative outcomes, and among the 2 versions, the recalibrated RAI-Rev performed better than RAI-A for majority of outcomes. While RAI-Rev was a statistically significant predictor of worse postoperative outcomes, it performed the best for mortality, which is expected based on the fact that RAI-based frailty scales were originally developed using variables in the instrument that correlate the best with mortality.20,23 The present study data provide evidence for the usage of RAI-based frailty scales in preoperative risk stratification of this patient population.

Frailty in spine trauma outcomes is a new topic, with only 2 previously published studies on the topic, utilizing mFI scores.15,16 RAI-A, a recently developed frailty index, and its recalibrated version, RAI-Rev, have not previously been evaluated in TSI patients, however RAI has recently been reported to possess superior predictive ability in spine procedures and brain tumor resection patients.22,23 RAI-based frailty scores comprise a 14-item scoring system as compared to mFI-5 which is based on 5 items, and additionally the 14 items in RAI are more relevant to functional status of the patient as compared to mFI scores, and are thus both conceptually and mathematically superior to mFI.20,33 The present study data validates this in spine trauma patients. Previous studies have also demonstrated that how mFI-5 acts less as a metric of frailty and more as a comorbidity score.20,34,37 This is corroborated by the data from the present study where in multivariate analysis for mortality, mFI-5 yielded unexpectedly low OR with decreased risk across all frailty tiers.

As individuals age, frailty becomes more prevalent, and with an increase in frailty comes an increased risk for falls and traumatic injury to the spine and spinal cord.38,39 Not only does increased frailty predispose patients to the risk of TSI, but also individuals injured at older ages have an increased risk for mortality and morbidity.40 The management and clinical decision making involving these patients provides a significant challenge to surgeons when considering surgical intervention. Because of this, it is important to have robust frailty tools for preoperative risk stratification of these patients. Both RAI-Rev and RAI-A come out as robust predictors of postoperative outcomes of TSI, and the present study advocates for their usage in clinical practice for prognostication of these patients, and to counsel them and their families regarding the expected outcomes.

The primary limitations of this study are those inherent to performing analysis using a national multicenter large database, understanding the limits of the recorded variables and ability to interpret results of their analysis. NSQIP variable limitations required modification of the RAI-A and RAI-Rev scores to exclude preoperative cognitive status. Additionally, weight loss and poor appetite are both captured in NSQIP under the same weight loss variable, “WTLOSS,” and therefore they cannot be differentiated within our adapted scoring. Despite these limitations, the NSQIP variables-based modifications of RAI scoring were in line with previous studies which demonstrated discriminative ability of this frailty measure.20,24,25 In addition to NSQIP’s limitations impacting our RAI scoring, another limitation, particularly with reference to studying TSI, NSQIP also fails to provide an injury severity variable. Without an injury severity marker, we feel this study should be validated using a database such as the Trauma Quality Improvement Program which includes such variables. Lastly, as this study was only able to evaluate 30-day outcomes recorded in NSQIP, further analysis in long-term prospective studies is needed to further evaluate RAI’s ability to predict 90- and 180-day or further long-term outcomes.

CONCLUSION

Both RAI-A and RAI-Rev outperform mFI-5 in predicting postoperative worse outcomes following surgical intervention for TSI. Increasing RAI-Rev score was more discriminative than its former iteration, RAI-A, and mFI-5, in predicting likelihood of mortality, ELOS, readmission, reoperation, and nonhome discharge. Our analysis demonstrates that RAI-Rev may provide better preoperative risk assessment than these prior indices.
and should be included in preoperative risk stratification of TSI patients.

NOTES

Supplementary Materials: Supplementary Tables 1-7 can be found via https://doi.org/10.14245/ns.2244326.163.

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REFERENCES


https://doi.org/10.14245/ns.2244326.163
**Supplementary Table 1.** Current Procedural Terminology (CPT) codes used to identify patients undergoing spine surgery from National Surgical Quality Improvement Program database 2015–2019

<table>
<thead>
<tr>
<th>Description</th>
<th>CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal instrumentation</td>
<td>22010-22855</td>
</tr>
<tr>
<td>Spinal procedures</td>
<td>62380-63707</td>
</tr>
</tbody>
</table>
Supplementary Table 2. Most abundant International Classification of Diseases (ICD)-9 and ICD-10 codes among the spine trauma cohort, n = 6,571, from National Surgical Quality Improvement Program 2015–2019

<table>
<thead>
<tr>
<th>Description</th>
<th>ICD-9</th>
<th>N = 713/762</th>
<th>Description</th>
<th>ICD-10</th>
<th>N = 4,427/5,809</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture of vertebrae without spinal cord injury</td>
<td>805</td>
<td>387</td>
<td>Fracture of cervical vertebrae</td>
<td>S12</td>
<td>1,750</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>733</td>
<td>195</td>
<td>Injury of nerves at cervical level</td>
<td>S14</td>
<td>717</td>
</tr>
<tr>
<td>Spinal cord injury without bony injury</td>
<td>952</td>
<td>70</td>
<td>Fracture of thoracic vertebrae</td>
<td>S22</td>
<td>842</td>
</tr>
<tr>
<td>Fracture of vertebrae with spinal cord injury</td>
<td>806</td>
<td>61</td>
<td>Fracture of lumbar spine/pelvis</td>
<td>S32</td>
<td>1,118</td>
</tr>
</tbody>
</table>
**Supplementary Table 3.** RAI-A and RAI-Rev scoring adapted from Hall and colleagues, 2017 and Arya and colleagues, 2020 respectively

<table>
<thead>
<tr>
<th>RAI variable</th>
<th>NSQIP variable</th>
<th>RAI-A scoring</th>
<th>RAI-A Rev scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>SEX</td>
<td>+5 if male</td>
<td>+3 if male</td>
</tr>
<tr>
<td>Age</td>
<td>AGE</td>
<td>+ score with cancer</td>
<td>+ score with cancer</td>
</tr>
<tr>
<td>Cancer diagnosis (excluding skin cancer, except melanoma)</td>
<td>DISCANCER</td>
<td>+1</td>
<td>Variable only relevant through age</td>
</tr>
<tr>
<td>Weight loss (unintentional weight loss &gt; 4.5 kg over 3 months)</td>
<td>WTLOSS</td>
<td>+5</td>
<td>+4</td>
</tr>
<tr>
<td>Renal failure (or dialysis)</td>
<td>DIALYSIS or RENAFAIL</td>
<td>+6 if either yes</td>
<td>+8</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>HXCHF</td>
<td>+4</td>
<td>+5</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>WTLOSS</td>
<td>+4</td>
<td>+4</td>
</tr>
<tr>
<td>Shortness of breath at rest</td>
<td>DYSPNEA</td>
<td>+8</td>
<td>+3</td>
</tr>
<tr>
<td>Residence other than independent living (transferred from nonhome or intermediate care unit)</td>
<td>TRANST</td>
<td>+8</td>
<td>+1</td>
</tr>
<tr>
<td>Cognitive deterioration (over past 3 months)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>FNSTATUS2</td>
<td>Without cognitive decline</td>
<td>Without cognitive decline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+16 = totally dependent</td>
<td>+14 = totally dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+8 = partially dependent</td>
<td>+7 = partially dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+0 = independent</td>
<td>+0 = independent</td>
</tr>
</tbody>
</table>

RAI-A, Risk Analysis Index-administrative; RAI-Rev, Risk Analysis Index recalibrated version; NSQIP, National Surgical Quality Improvement Program; N/A, not applicable.
Supplementary Table 4. Age and cancer diagnosis table scoring adapted from Hall and colleagues, 2017 for RAI-A scoring

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Score with cancer</th>
<th>Score without cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 69</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>70–74</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>75–79</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>80–84</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>85–89</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>
**Supplementary Table 5.** Age and cancer diagnosis table of scoring, adapted from Arya and colleagues, 2020, for RAI-Rev

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Score with cancer</th>
<th>Score without cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 19</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>20–24</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>25–29</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>30–34</td>
<td>30</td>
<td>6</td>
</tr>
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<td>35–39</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>40–44</td>
<td>31</td>
<td>10</td>
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<td>45–49</td>
<td>31</td>
<td>12</td>
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<td>50–54</td>
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<td>14</td>
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<td>55–59</td>
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<td>60–64</td>
<td>33</td>
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<td>65–69</td>
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<td>70–74</td>
<td>34</td>
<td>22</td>
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<td>75–79</td>
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<td>24</td>
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<td>80–84</td>
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<td>26</td>
</tr>
<tr>
<td>85–89</td>
<td>36</td>
<td>28</td>
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</tbody>
</table>
**Supplementary Table 6.** RAI-A and RAI-Rev scores stratified into frailty group status

<table>
<thead>
<tr>
<th>Frailty description</th>
<th>RAI-A score range</th>
<th>RAI-Rev score range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfrail</td>
<td>≤ 10</td>
<td>≤ 10</td>
</tr>
<tr>
<td>Prefrail</td>
<td>11–20</td>
<td>11–20</td>
</tr>
<tr>
<td>Frail</td>
<td>21–30</td>
<td>21–30</td>
</tr>
<tr>
<td>Severely frail</td>
<td>≥ 31</td>
<td>≥ 31</td>
</tr>
</tbody>
</table>

RAI-A, Risk Analysis Index-administrative; RAI-Rev, Risk Analysis Index recalibrated version.
**Supplementary Table 7.** NSQIP clinical variables matched to mFI-5

<table>
<thead>
<tr>
<th>mFI-5</th>
<th>Maximum score = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonindependent functional status*</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus with oral agents or insulin</td>
<td>1</td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension requiring medication</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
</tbody>
</table>

The mFI-5 calculated using the 5 NSQIP variables resulted in an index ranging from 0 (least frail) to 5 (most frail), with a score of 1 as "prefrail", 2 as "frail", and 3 or more as "severely frail" as categorical variables.

NSQIP, National Surgical Quality Improvement Program; mFI-5, 5-factor modified frailty index; COPD, chronic obstructive pulmonary disease.

*Includes both partial and complete dependence.
Impact of Mechanism of Injury on Long-term Neurological Outcomes of Cervical Sensorimotor Complete Acute Traumatic Spinal Cord Injury

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²Krembil Research Institute, University Health Network, Toronto, ON, Canada
³Spine Program, University of Toronto Faculty of Medicine, Toronto, ON, Canada

Objective: Mechanism of injury is a largely understudied descriptor of acute traumatic spinal cord injury (tSCI). This study sought to compare the impact of high-energy and low-energy mechanisms of injury in neurological outcomes of cervical sensorimotor complete tSCI.

Methods: Patients with tSCI were identified in 4 prospective, multicenter clinical trials and registries. American Spinal Injury Association Impairment Scale (AIS) grade was assessed ≤ 72 hours postinjury and followed up between 12 to 52 weeks. Patients were included if they had a cervical and sensorimotor complete (AIS–A) injury at baseline. Study outcomes were change in AIS grade and lower extremity motor, upper extremity motor, and total motor scores. Propensity score matching between high-energy mechanisms of injury (HEMI; e.g., motor vehicle collisions) and low-energy mechanisms of injury (LEMI; e.g., falls) groups was performed. Adjusted groups were compared with paired t-tests and McNemar test.

Results: Of 667 patients eligible for inclusion, 523 experienced HEMI (78.4%). HEMI patients were younger, had lower body mass index, more associated fractures or dislocations, and lower baseline lower extremity motor scores. After propensity score matching of these baseline variables, 118 pairs were matched. HEMI patients had a significantly worse motor recovery from baseline to follow-up based on their diminished change in upper extremity motor scores and total motor scores.

Conclusion: Cervical sensorimotor complete tSCIs from HEMI were associated with significantly lower motor recovery compared to LEMI patients. Our findings suggest that mechanism of injury should be considered in modelling prognosis and in understanding the heterogeneity of outcomes after acute tSCI.

Keywords: Spinal cord injury, Injury mechanism, Cervical spinal cord injury, Neurological outcomes, Motor recovery

INTRODUCTION

Over the last few decades there seems to be a shift in the demographic composition of spinal cord injury (SCI). The prevalence of the disease, however, has remained stable imposing significant burden on health care systems across the globe. The Global Burden of Disease Study published in the Lancet provided insights into the global prevalence and incidence of SCI between 1990–2016, and overall found that the prevalence of SCI has been stable over the aforementioned 26-year period.¹,² The incidence rate was found to be 13 per 100,000 people and a prevalence of 27.04 million.² North American Data on SCI suggests 39 per million cases of traumatic SCI (tSCI), with Canadian published data reporting an incidence in 2010 of 41 per million for tSCI.³,⁶ The majority of tSCIs are in the cervical spine (60%), with over-
Mechanism of Injury in Traumatic SCI

Bak AB, et al.

all mortality largely due to cervical level injuries resulting in respiratory failure. Overtime there has been a bimodal distribution in the age of patients due to the ongoing presence of motor vehicle collisions (MVCs) in young adults, particularly males, and the aging population having superimposed falls with pre-existing degenerative pathologies, more commonly in women. This has been demonstrated in various studies showing a change in the average age of patients from the early 30s to, more recently, patients in their mid to late 40s. From the 1970s to the early 2000s those over 60 represented only 4.7% of the SCI database, while this representation rose to 10% and is continuing to rise, commensurate with the aging population. Selvarajah et al. recently reported falls to be the cause of 41.5% of tSCI with MVCs following behind at 35.5%. While demographics and etiology have been thoroughly studied, there is a paucity of literature assessing the impact of the energy of the mechanism of injury on cervical outcomes; typically with MVCs and sports injuries characterized as high-energy (high-energy mechanisms of injury, HEMI) and falls being low-energy (low-energy mechanisms of injury, LEMI).

Intuitively, one would suspect that HEMIs result in more severe injury patterns. The difference in pathology is hypothesized to be due to the extent of tissue injury and that the primary injury in HEMI results in intrinsic cord disruption while LEMI pathology is due to ongoing secondary compression. In animal models, Noyes found that peak force and displacement were predictors of injury while Dohrmann and Panjabi report on momentum and impulse determining injury – both studies allow us to extrapolate that HEMI would result in more severe injury. Animal models in ferrets by Kearney et al. explore the impact of velocity and compression on the extent of injury, wherein the increasing product of velocity and compression results in increasing injury severity at higher velocities. This similarly allows us to infer that HEMIs, which are of higher velocity and compression, will result in more severe injury. Lenehan et al. have found that incomplete injuries, less severe than complete injuries, are more common in the elderly; this could be owing to the fact that the energy of impact most commonly affecting this population is lower. The aim of our study is to explore whether the initial mechanism of energy affects patient outcomes in those with complete cervical injuries, thus identifying factors that alter outcomes which will assist with acute and long-term patient management. We isolated the complete tSCI population as there is significant uncertainty in the natural history of their disease. We postulate that the mechanism of injury plays a role in the neurological recovery of complete cervical tSCI patients.

MATERIALS AND METHODS

1. Data Sources, Participants, and Eligibility Criteria
We pooled individual patient data from 4 high-quality, prospective, multicenter acute SCI databases from December 1991 to March 2017, as previously described. This study design and data permitted a powerful quantitative analysis on highly granular patient, injury, and interventional factors for traumatic SCI outcome measures at long-term follow-up. The 4 databases that were combined included the North American Clinical Trials Network (NACTN) SCI Registry, the Sygen Trial, the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS), and the National Acute Spinal Cord Injury Study III. Patients with acute traumatic SCI were identified in the combined dataset. Patients were eligible if they had a cervical neurological level of injury that was evaluated as sensorimotor complete through the American Spinal Injury Association Impairment Scale (AIS) with a grade of A within 72 hours of initial injury. Included patients were followed up between 12 to 52 weeks after initial admission. Comparison groups were HEMI defined as injuries from motor vehicle collisions and sports injuries, and LEMI defined as injuries from falls.

2. Outcomes
The study endpoint was neurological recovery evaluated with a change in AIS grade by at least one grade (i.e., from A to B or greater) and motor recovery evaluated with a change in lower extremity motor score (LEMS), upper extremity motor score (UEMS) and total motor scores (TMS) from baseline to follow-up between 12 to 52 weeks. The 52-week follow-up timepoint was selected as the end range as previous literature has shown that most of the recovery after acute SCI has occurred by this time, with minimal recovery observed afterwards.

3. Statistical Analysis
Descriptive statistics were calculated with means and standard deviations (SDs) for continuous variables and absolute numbers with proportions for discrete categorical variables. Baseline continuous variables were compared between the 2 groups using the independent samples t-test and baseline discrete variables were compared using the chi-square test. Missing outcomes data were imputed in 2 steps. First, a last-observation carry forward method was applied for subjects with nonmissing 3-month and 6-month scores, a previously validated imputation method in
SCI studies. Subsequently, a Markov chain Monte Carlo approach was used for remaining missing outcome data at 40 iterations. The prerequisite missing-at-random assumption was accepted to be plausible based on literature finding losses to follow-up in SCI to be related to baseline demographic and injury factors, which was accounted for in the dataset. Predictive mean matching was used for continuous variables and logistic regression for discrete variables.

We used propensity score matching to identify cohorts of patients with similar baseline characteristics for the HEMI and LEMI groups. The propensity score was estimated with the use of multivariable logistic regression models with the mechanism of injury as the dependent variable and baseline variables that were significantly different between the 2 groups during descriptive analyses as covariates. A 1-to-1 nearest-neighbor matching protocol without replacement was used to match with a caliper width of 0.03 of the SD of the logit of the propensity score. Covariate balance between comparison groups as deemed adequate if below an absolute standardized mean difference (SMD) of 0.1. In the matched cohorts, comparisons of outcomes were performed using a paired Student t-test for continuous variables, which was reported with mean differences (MDs) and p-values, and McNemar test for discrete variables, which was reported with proportions and p-values. A sensitivity analysis was conducted with a subgroup of patients from the NACTN registry and STASCIS trial with data on complications of shock (spinal, neurogenic, cardiogenic) and hypotension. These complications were included in a separate propensity score model as a covariate and outcomes were compared as mentioned above. All statistical analyses were performed using R, version 4.1.1, (The R Foundation for Statistical Computing, Vienna, Austria), at a significance level of 95% (p < 0.05; 2-sided).

RESULTS

1. Descriptive Statistics

A total of 2,452 acute traumatic SCI patients were identified in the combined dataset of 4 high-quality prospective, multicenter SCI databases (Fig. 1). After 1,785 patients were removed following the exclusion criteria, 667 patients were divided into 2

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**Fig. 1.** Flowchart of study population. NACTN, North American Clinical Trials Network; STASCIS, Surgical Timing in Acute Spinal Cord Injury Study; NASCIS III, National Acute Spinal Cord Injury Study; SCI, spinal cord injury; BMI, body mass index.
groups: HEMI (n = 523, 78.4%) and LEMI (n = 144, 21.6%). Prior to propensity score matching, HEMI patients were generally younger (32.8 ± 13.5 years vs. 47.9 ± 17.9 years, p < 0.001) and had a greater proportion of patients with associated fractures, subluxations, and dislocations with their tSCI compared to LEMI patients (91.6% vs. 75.0%, p<0.001). After admission, a greater proportion of LEMI patients received early surgical decompression ≤ 24 hours of initial injury (47.2% vs. 34.0%, p = 0.005). Descriptive statistics are detailed in Table 1.

2. Propensity Score Matching

The HEMI and LEMI groups were balanced with the covariates identified with a between-group difference threshold of p < 0.1: age, body mass index, baseline UEMS, early surgery, and associated fractures, subluxation, and dislocations. The match resulted in 118 pairs that were well balanced with an SMD of 0.1 or less for all variables (Table 1).

3. Primary Outcome

HEMI patients had a significantly worse motor recovery from baseline to follow-up based on their smaller change in upper extremity motor scores with a mean difference of 3.7 (12.0 ± 12.3 vs. 8.3 ± 12.0, p = 0.010). Change in TMS (17.8 ± 19.6 vs. 11.9 ± 17.5, p = 0.011) was significantly diminished in HEMI patients compared to LEMI patients with a mean difference of 5.9 (Table 2). We detected no significant differences between HEMI and LEMI patients on AIS grade conversion (LEMI: 41.5% vs. HEMI: 45.8%, p = 0.609) or change in LEMS (LEMI: 5.9 ± 12.6 vs. HEMI: 3.7 ± 9.6, p = 0.119).

4. Sensitivity Analysis

In a subgroup of 1,193 patients from the NACTN registry and STASCIS trial, cardiovascular complications were included as a covariate in the propensity score match algorithm. From a total of 199 patients that met our inclusion and exclusion criteria, 90 patients were matched (Supplementary Table 1). After matching, the remaining differences of p < 0.05 were no longer statistically significant.

Table 1. Descriptive statistics and between-group comparisons of LEMI and HEMI patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude cohort</th>
<th>Propensity score-matched cohort</th>
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<tbody>
<tr>
<td></td>
<td>LEMI (n = 144)</td>
<td>HEMI (n = 523)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.9 ± 17.9</td>
<td>32.8 ± 13.5</td>
</tr>
<tr>
<td>Female sex</td>
<td>27 (18.8)</td>
<td>98 (18.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 4.8</td>
<td>25.4 ± 4.7</td>
</tr>
<tr>
<td>Fractures, subluxations, dislocations (%)</td>
<td>108 (75.0)</td>
<td>479 (91.6)</td>
</tr>
<tr>
<td>Early surgery rate (≤24 hr from initial injury) (%)</td>
<td>68 (47.2)</td>
<td>178 (34.0)</td>
</tr>
<tr>
<td>Baseline upper extremity motor score</td>
<td>11.5 ± 11.0</td>
<td>13.5 ± 12.7</td>
</tr>
<tr>
<td>Baseline lower extremity motor score</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Baseline total motor score</td>
<td>11.6 ± 11.1</td>
<td>13.5 ± 12.7</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). HEMI, high-energy mechanism of injury; LEMI, low-energy mechanism of injury; BMI, body mass index; SMD, standardized mean difference. *p < 0.05, statistically significant differences.

Table 2. Paired comparisons between matched HEMI and LEMI cohorts from propensity score matching

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Propensity score-matched cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LEMI (n = 118)</td>
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<tr>
<td>Change in upper extremity motor score</td>
<td>12.0 ± 12.3</td>
</tr>
<tr>
<td>Change in lower extremity motor score</td>
<td>5.9 ± 12.6</td>
</tr>
<tr>
<td>Change in total motor score</td>
<td>17.8 ± 19.6</td>
</tr>
<tr>
<td>≥ 1 AIS grade improvement (%)</td>
<td>49 (41.5)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). HEMI, high-energy mechanism of injury; LEMI, low-energy mechanism of injury; AIS, American Spinal Injury Association Impairment Scale. *p < 0.05, statistically significant differences.
paired analysis, the results of the sensitivity analysis supported our findings (Supplementary Table 2). Compared to LEMI patients, HEMI patients had a significantly decreased recovery of UEMS (12.7 ± 10.6 vs. 8.2 ± 8.2, p = 0.010) and TMS (22.5 ± 25.1 vs. 13.2 ± 13.8, p = 0.025).

DISCUSSION

To the best of our knowledge, this is the first study to thoroughly investigate the role of mechanism of injury in long-term neurological outcomes after acute traumatic complete cervical SCI.

Mputu et al. and others suggest that neural tissue destruction in high-energy trauma resulted in complete thoracic level injuries and this, coupled with resultant dislocation and shear injuries, caused poorer outcomes in high-energy injury patients, though they did not find mechanism of injury to be significantly associated with outcome. Much of the existing literature is based on supposed correlations such as the decrease in severity of injury overtime with the greater prevalence of falls, suggesting a possible correlation with energy of injury and outcome severity. Other studies comparing high-energy falls and MVCs to low-energy falls comment on the former causing complete injuries compared to the latter allowing us to predict that injury severity is often greater in HEMIs, with additional studies suggesting a lower quality of life resulting from a more severe mechanism of injury. Several studies have found that there are poorer outcomes in patients with higher injury mechanisms due to concomitant other injuries but do not clarify whether the outcome is directly related to the injury to the spine. Qiu et al. found that high-energy mechanisms were associated with motor complete injuries (in noncompression flexion injuries)—although they did not conduct a subgroup analysis consisting of only complete injuries, this allows us to deduce that perhaps the outcomes would also be more severe. While the aforementioned studies either allow for speculation on the impact of energy or have found there to be no bearing of energy of injury on outcome, our study demonstrates clear, significant, difference between HEMI and LEMI groups in motor recovery at follow-up.

Our primary outcomes included AIS grade conversion of at least 1 grade and change in constituent motor and sensory scores between baseline and follow-up. Although our analysis did detect a significant difference between groups in the composite AIS grade conversion, with more granularity, a significant difference in motor outcomes as revealed. Notably, we found that HEMI patients had a significantly worse recovery TMS of an average of 5.9 points. Although minimum clinically important differences for neurological outcomes of acute traumatic SCI have not yet been established, motor recovery of even a single cervical segment could have significant impacts on a patient’s independence in activities of daily living and quality of life. Our results suggest a diminished recovery in the upper extremity motor scores. This is clinically relevant as patients with tetraplegia often rate restoration of hand and arm motor function as their priority. The aforementioned findings refute a previous study’s finding that the energy of initial trauma was not found to influence neurological outcome at 6-month follow-up in those with SCI. The previous study was limited to subgroup comparisons of less than 5 patients per group and defined high impact sports injuries as low-energy trauma. Another such study which did not see an impact on motor score was conducted by Dvorak et al., who prospectively assessed factors impacting ASIA Motor Score, functional status, and quality of life – none of which were found to be impacted by mechanism or energy of injury. Kay et al. studied the likelihood of walking at the time of discharge, which can be considered a surrogate for motor improvement, from rehab in various grade SCIs and found that ASIA C patients were more likely to walk than ASIA A or B, suggesting more severe grade results in worse long-term motor ability, allowing us to conclude this about HEMI compared to LEMI given that HEMIs are typically of higher grade. However, this was not studied specifically in the ASIA A group nor assessing the role of mechanism of injury, thus reinforcing the results of our group. Other studies have commented on higher energy falls resulting in ASIA A injuries, longer rehab stay and paraplegia, all outcomes in keeping with severe injury but no information regarding outcomes within one ASIA grade. Similarly, Higashi et al. did not find statistical significance in mechanism of injury and mortality across all grades of ASIA injury, however, they did not conduct a subgroup analysis for those only in the ASIA A cohort. There have been ample additional studies which comment on the lack of significant findings regarding the impact of mechanism/ etiology on outcomes.

Our findings on motor recovery were supported by our sensitivity analysis that included complications of neurogenic, cardiogenic, and spinal shock as well as hypotension in a subgroup of patients from the NACTN registry and STASCIS trial.

Our study has several limitations. First, the combined dataset did not contain explicit granularity of data to differentiate falls based on height. Falls from high heights would be plausibly categorized as high-energy mechanisms of injury compared to falls...
from low heights. A previous study found that patients with falls from greater heights resulted in more severe injuries and length of stay. This may underestimate the effect size between the HEMI and LEMI groups. However, we make a point that in our database, most high-altitude falls are from workplace and sports-related activities such as climbing, so this categorization effect may be small, and our fundamental conclusions are supported. The older mean age of our LEMI cohort also aligns to that characteristic of low-height falls. Future studies and registries should focus on recording the height of falls or the circumstances of falls, such as workplace injuries, which can be an indirect measure of a fall from high height. Another limitation of the study is its retrospective and nonrandomized nature. As our dataset is not randomized, we used propensity score matching to balance covariates between cohorts to create a quasi-experimental setting. Although this method can balance measured variables, unmeasured variables may be unbalanced between cohorts and may influence the results. These variables could include history of degenerative disc disease or spondylosis, which presents a focus for future studies. For future studies focusing on incomplete injuries, commentaries on the rates of central cord injury and incomplete cervical cord injury without fracture may indirectly measure the impact of degenerative disc disease and cervical spondylosis.

CONCLUSION

Our work presents a comprehensive analysis of the role of mechanism of injury on the long-term neurological recovery of complete cervical tSCI patients. Our findings suggest that patients with a HEMI, such as those from MVCs or sports, may have significantly lower motor recovery at one year compared to those that sustained tSCIs from falls. Future studies may choose to explore larger cohorts, changes in outcomes within ASIA B, C, and D, and specific function outcomes such as ambulating, eating, and writing. Similar to our findings, increasing literature is supporting the heterogeneity of outcomes following complete tSCI. To provide more precise care to these patients, mechanism of injury should be considered in efforts to prognosticate and understand the patient recovery trajectory.

NOTES

Supplementary Materials: Supplementary Tables 1-2 can be found via https://doi.org/10.14245/ns.2244518.259.

Supplementary Table 1. Descriptive statistics and between-group comparisons of LEMI and HEMI patients in sensitivity analysis subgroup.

Supplementary Table 2. Paired comparisons between matched HEMI and LEMI cohorts from propensity score matching of sensitivity analysis subgroup.

Conflict of Interest: MGF is supported by the Robert Campeau Family Foundation/Dr. C.H. Tator Chair in Brain and Spinal Cord Research. Other authors have nothing to disclose.

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Author Contribution: Conceptualization: ABB, Ali M, AM, MGF; Data curation: ABB, Ali M, AM; Formal analysis: ABB, Ali M, AM; Funding acquisition: ABB; Methodology: ABB, Ali M, AM, MGF; Project administration: MGF; Visualization: ABB; Writing - original draft: ABB, Ali M, AM, MGF; Writing - review & editing: ABB, Ali M, AM, MGF.

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### Supplementary Table 1. Descriptive statistics and between-group comparisons of LEMI and HEMI patients in sensitivity analysis subgroup

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude cohort</th>
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<td>LEMI (n = 67)</td>
<td>HEMI (n = 132)</td>
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<td>Age (yr)</td>
<td>55.07 ± 15.76</td>
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<td>BMI (kg/m²)</td>
<td>27.91 ± 5.42</td>
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</tr>
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<td>Female sex</td>
<td>18 (26.9)</td>
<td>23 (17.4)</td>
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<tr>
<td>Fractures, subluxations, dislocations</td>
<td>42 (62.7)</td>
<td>69 (52.3)</td>
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<td>Early surgery rate (≤ 24 hr from initial injury)</td>
<td>42 (62.7)</td>
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<td>Baseline upper extremity motor score</td>
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<tr>
<td>Baseline lower extremity motor score</td>
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<td>0.00 ± 0.00</td>
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<td>Baseline total motor score</td>
<td>11.44 ± 10.75</td>
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<tr>
<td>Complications</td>
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<td>Spinal shock</td>
<td>17 (25.4)</td>
<td>72 (54.5)</td>
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<tr>
<td>Neurogenic shock</td>
<td>18 (26.9)</td>
<td>63 (47.7)</td>
</tr>
<tr>
<td>Cardiogenic shock and hypotension</td>
<td>22 (32.8)</td>
<td>62 (47.0)</td>
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</table>

Values are presented as mean ± standard deviation or number (%).
HEMI, high-energy mechanism of injury; LEMI, low-energy mechanism of injury; BMI, body mass index; SMD, standardized mean difference. *p < 0.05, statistically significant differences.
**Supplementary Table 2.** Paired comparisons between matched HEMI and LEMI cohorts from propensity score matching of sensitivity analysis subgroup

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LEMI (n = 45)</th>
<th>HEMI (n = 45)</th>
<th>Mean difference</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Change in upper extremity motor score</td>
<td>12.7 ± 10.6</td>
<td>8.2 ± 8.2</td>
<td>4.5</td>
<td>0.010*</td>
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<td>Change in lower extremity motor score</td>
<td>9.8 ± 16.4</td>
<td>5.0 ± 10.4</td>
<td>4.8</td>
<td>0.104</td>
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<td>Change in total motor score</td>
<td>22.5 ± 25.1</td>
<td>13.2 ± 13.8</td>
<td>9.3</td>
<td>0.025*</td>
</tr>
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<td>≥ 1 AIS grade improvement (%)</td>
<td>27 (60.0)</td>
<td>30 (66.7)</td>
<td>-</td>
<td>0.606</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
HEMI, high-energy mechanism of injury; LEMI, low-energy mechanism of injury; AIS, American Spinal Injury Association Impairment Scale. *p < 0.05, statistically significant differences.
Relationship Between Syrinx Resolution and Cervical Sagittal Realignment Following Decompression Surgery for Chiari I Malformation Related Syringomyelia Based on Configuration Phenotypes

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Objective: Combined with different configuration types of syringomyelia, to analyze the correlation between syrinx resolution and changes in cervical sagittal alignment following Foramen magnum and Magendie dredging (FMMD) for syringomyelia associated with Chiari I malformation (CM-I), and to further explore the respective relationship with clinical outcome.

Methods: A consecutive series of 127 patients with CM-I and syringomyelia who underwent FMMD in our center met the inclusion criteria of this study. Their clinical records and radiologic data were retrospectively reviewed. The Japanese Orthopedic Association (JOA) scoring system and the Chicago Chiari Outcome Scale (CCOS) were used to evaluate the surgical efficacy. The phenotypes of syringomyelia and the clinical characteristics of the patients were analyzed according to grouping by cervical curvature at baseline.

Results: The preoperative straight or kyphotic cervical alignment is more common in the moniliform syrinx. After surgery, the syrinx resolution and cervical sagittal realignment in the moniliform group are more obvious, and the corresponding prognosis is relatively better. Spearman correlation analysis showed that the ΔS/C ratio (the change ratio of syrinx/cord) was positively correlated with the CCOS (p = 0.001, r = 0.897) and ΔC2–7A (the change of lower cervical angle) (p = 0.002, r = 0.560). There was also a correlation between the ΔJOA score (the change rate of the JOA score) and ΔC2–7A (p = 0.012, r = 0.467).

Conclusion: After decompression surgery, syrinx resolution may coexist with the changes in the subaxial lordosis angle, especially for syrinx in moniliform type, and the relationship between syrinx resolution and cervical sagittal realignment might be valuable for evaluating the surgical outcome.

Keywords: Cervical sagittal alignment, Syringomyelia, Chiari malformation, Decompression surgery, Prognosis

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INTRODUCTION

Syringomyelia is characterized by chronic dilation of the central canal of the spinal cord due to the abnormal accumulation of fluid caused by cerebrospinal fluid (CSF) circulation disorder. It is a disease often associated with Chiari malformation, trauma, tumor, inflammatory disease, or idiopathic etiologies.1-3 Chiari malformation type I (CM-I) is a kind of congenital dysplasia in the craniovertebral junction. Imaging often shows a small posterior fossa volume and syringomyelia located at the lower cervical and upper thoracic segments. For the pathogenesis of CM-I related syringomyelia, there has been a wide concern in the fluid dynamics, syrinx phenotypes, clinical symptoms, and imaging morphology of the posterior fossa and craniovertebral junction (CVJ) region.4,5

Surgical procedures have been generally recognized for improving the neurological status of CM-I patients, such as posterior fossa decompression (PFD) or with duraplasty (PFDD), or a more thorough intradural decompression for syringomyelia, such as Foramen magnum and Magendie dredging (FMMD).6-7 By integrating clinical and radiographic characteristics of both syringomyelia and spinal biomechanics, we could better evaluate the surgical outcome of the CM-I patients after decompression surgery.8-10 In particular, the relationship between CM-I related syringomyelia and scoliosis has been recognized.11-13 Some studies reported that scoliosis will improve after decompression surgery for syringomyelia.14,15 All of the above suggested that syringomyelia may be a relevant factor affecting the spinal alignment. However, there are few reports focused on the relationship between the changes in syringomyelia and cervical sagittal alignment parameters.

Previous researchers have proposed that the decrease of syrinx size after decompression surgery may restore cervical lordosis.16 But the correlation between syringomyelia and cervical sagittal alignment remains vague, especially among different kinds of syrinx configurations. Therefore, the purpose of this study was to further explore the correlation between syrinx resolution and changes in cervical sagittal alignment following FMMD in CM-I patients with syringomyelia and to further determine the respective relationship with clinical outcomes.

MATERIALS AND METHODS

1. Patient Selection

The study was approved by the institutional research ethics committee of Xuanwu Hospital (approval number: 2018030).

From January 2017 to January 2020, a consecutive series of 198 CM-I patients with syringomyelia confirmed by magnetic resonance imaging (MRI) were retrospectively analyzed including their clinical records and radiologic data from a prospectively maintained database in a single center. According to screening, 66 of 198 patients were excluded from this study due to the exclusion criterion, and 5 patients had incomplete imaging data or were lost to follow-up. The exclusion criteria are as follows: (1) age < 18 years old; (2) syringomyelia associated with trauma, tumor, inflammatory disease, or idiopathic etiologies; (3) patients with atlantoaxial dislocation, degenerative cervical spondylosis, congenital vertebral anomalies, severe scoliosis, myelomeningocele, or tethered cord; (4) a history of CVJ surgery with cervical or occipital fusion and instrumentation. Finally, a total of 127 patients diagnosed with CM-I and syringomyelia who underwent intradural decompression for syringomyelia in our center met the inclusion criteria of our study. The research flow chart is shown in Fig. 1.

2. Clinical Evaluation

The patients’ chief complaints on admission mainly include general symptoms such as headache or neck and back pain, spinal cord syndromes such as suspended sensory disorder, amyotrophy and weakness of limbs, dysfunction of urination and defecation, and other symptoms including cerebellar symptoms and cranial nerve dysfunction. Some patients had multiple clinical symptoms at the same time. The specific data were summarized in Table 1.

3. Radiographic Evaluation

MRI and lateral radiographs of x-ray in neutral position were taken pre- and postoperatively. A routine MRI and x-ray examination was taken within one week before surgery. Follow-up MRI was conducted regularly at 1 month, 3 months (± 1 month), 6 months (± 3 months), and 1 year after surgery. After that, it was performed every 6 months until the last follow-up. All measurements were made using computer-aided software called RadiAnt DICOM Viewer (ver. 4.6.9, Medixant, Poznan, Poland). All relative radiologic measurements were repeated at least 3 times, independently by one surgeon and another radiologist.

4. X-Ray Evaluation

X-ray evaluation of the above cervical sagittal alignment parameters were shown Supplementary Fig. 1. Cervical lordosis angles were measured successively accord-
ing to the 4-line method from the lateral radiographs in a neutral position before surgery and at the final follow-up evaluation: drawing a line parallel to the inferior endplate of the upper vertebral body, and another line parallel to the inferior endplate of the lower vertebral body. Perpendicular lines are then drawn from each of the 2 lines noted above, and the angle subtended between the crossing of the perpendicular lines is the cervical lordosis angle. A negative value of the angle meant lordosis and the positive value marked kyphosis.

Upper cervical angle (C0–2A): the included angle between the McGregor line and the line parallel to the lower endplate of the C2 body.

Lower cervical angle (C2–7A): the included angle between a line parallel to the lower endplate of the C2 body and a line parallel to that of the C7 body.

The sagittal vertical axis (C2–7 SV A): the horizontal distance between the C2 plumb line and the posterosuperior point of the C7 body.

T1 slope: The T1 slope can be used to predict the physiological curvature of the cervical spine, which was measured as the included angle between the upper endplate of T1 and the horizontal line.

5. MRI Evaluation

As proposed by Ono et al.,\textsuperscript{17} the cerebellar tonsillar descent could be divided into 3 grades in MRI: grade 1, the cerebellar tonsil descends beyond the foramen magnum but does not reach the C1 arch; grade 2, the cerebellar tonsil reaches the C1 arch; grade 3, the cerebellar tonsil descends beyond the C1 arch.

The following indicators were measured at the T2-weighted median sagittal and transverse positions of MRI before surgery and at the final follow-up: (1) Syrinx/spinal cord ratio (S/C ratio), the ratio of syrinx diameter to the spinal cord diameter at the same level. (2) Syrinx length: the number of vertebral seg-

Fig. 1. Research flow chart of this clinical research. CM-I, Chiari I malformation; MRI, magnetic resonance imaging; C2-7A, lower cervical angle; JOA, Japanese Orthopedic Association; CCOS, Chicago Chiari Outcome Scale; ΔC2–7A, the change of lower cervical angle; ΔS/C ratio, the change ratio of syrinx/cord.
ments spanned by the spinal syrinx. (3) A radiographic change ratio in the maximal S/C ratio or syrinx length was calculated using the following formula: (preoperative value-postoperative value)/preoperative value. A ratio value of zero means no improvement of the syrinx size, whereas 1 means the complete disappearance of the syrinx.

Table 1. The preoperative distribution of cervical curvature combined with the data of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hyperlordosis</th>
<th>Normal lordosis</th>
<th>Straight or kyphotic</th>
<th>H/F value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>71</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>5</td>
<td>45</td>
<td>38</td>
<td>3.263</td>
<td>0.071</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49.0 ± 9.3</td>
<td>48.9 ± 11.1</td>
<td>45.4 ± 9.9</td>
<td>1.591</td>
<td>0.208</td>
</tr>
<tr>
<td>Degree of cerebellar tonsillar descent</td>
<td></td>
<td></td>
<td></td>
<td>2.147</td>
<td>0.342</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>37</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>4</td>
<td>29</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>14</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of the syrinx (segment)</td>
<td>8.8 ± 4.5</td>
<td>9.0 ± 3.4</td>
<td>8.7 ± 4.0</td>
<td>0.030</td>
<td>0.971</td>
</tr>
<tr>
<td>Maximal S/C ratio (%)</td>
<td>60.1 ± 22.1</td>
<td>59.3 ± 18.9</td>
<td>66.5 ± 17.5</td>
<td>2.176</td>
<td>0.118</td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± standard deviation. The H-value is the statistic value for the Kruskal-Wallis H test, and the F-value is for the 1-way analysis of variance test.

S/C, change ratio of syrinx/cord; C0–2A, upper cervical angle; C2–7A, lower cervical angle; JOA, Japanese Orthopedic Association.

*p < 0.05, statistically significant differences. †The criteria for the judgment of hyperlordosis, normal lordosis, and straight or kyphotic cervical alignment. ‡Cerebellar symptoms: ataxia, dysarthria; cranial nerve dysfunction: diplopia, dysphagia.
Fig. 2. The specific surgical procedures of Foramen magnum and Magendie dredging. Illustrative case 1: The median sagittal and transverse positions of T2-weighted magnetic resonance imaging (MRI) before surgery show the syringomyelia and a detectable channel between the fourth ventricle and the syrinx (yellow arrow) (A, B, D), and the postoperative MRI shows effective reduction of the syrinx (C, E). (F) The departure of the tonsils shows arachnoid adhesions (black arrow) overlying the foramen of Magendie. (G) Dissolution of the arachnoid adhesions and exposure of the foramen of Magendie (asterisk). (H, I) Completely opening of the foramen of Magendie by microsurgical separation (black arrow) and cerebrospinal fluid (CSF) recirculation after dredging. Illustrative case 2: (J, L, M, N) The pre- and postoperative MRI shows the resolution of syringomyelia. (K) The preoperative x-ray radiograph shows a straight cervical alignment. (O) The foramen of Magendie is visible under the semitransparent veil (arrow). (P) Dissolution of the arachnoid adhesions and exposure of the foramen of Magendie (asterisk). (Q, R) Opening of the arachnoid veil and CSF recirculation after dredging. LT, left tonsil, RT, right tonsil, MO, medulla oblongata.
6. Operation Strategy

All operations in all of the 127 patients were performed via PFD with intradural exploration using FMMD to remove the factors causing CSF circulation obstruction, which was recorded via the operating microscope for all potential intradural pathology and factors (Fig. 2). The specific surgical procedures have been described in our previous study.6,7

7. Variable and Grouping Definition

The postoperative syrinx was reported to be either significantly resolved (syrinx decreased in size ≥ 20%, a more than 20% decrease in maximal S/C ratio on follow-up MRI) (Fig. 3) or unchanged (syrinx decreased in size less than 20% or remained the same size).

The physiological curvature of the cervical spine in men is between -16° to -22° and -15° to -25° in females.18 The negative value less than this range (the absolute value) is defined as a straight cervical spine, the positive value is kyphosis, and the larger value than this range (the absolute value) is defined as hyperlordosis.

Referring to the configuration of the syringomyelia, the syrinx can be defined into 4 types: A, distended type; B, moniliform type; C, slender type; D, circumscribed type (Fig. 4A–D).

8. Prognostic Evaluation

All patients completed the evaluation of the Japanese Orthopedic Association (JOA) scoring system to assess their neurological status before surgery and at the last follow-up. We calculated the neurologic improvement rate (ΔJOA score) according to the preoperative JOA score and the last follow-up JOA score by the following formula: (postoperative score – preoperative score) × 100%/(full score [17 points] – preoperative score).

The Chicago Chiari Outcome Scale (CCOS) was used to evaluate the surgical efficacy from 4 aspects: pain symptoms, nonpain symptoms, functionality, and complications, with scores from 1 to 4 for each item. The better the prognosis, the higher the score, with the CCOS score groupings presenting the prognosis as good between 13 and 16, no obvious improve-
ment between 9 and 12, and poor between 4 and 8.

9. Statistical Analysis
   IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. For continuous variables, the mean values are presented with standard deviations, and the differences between the 2 groups were analyzed using the Student t-test and 1-way analysis of variance test for ≥ 3 groups. A chi-square or Fisher exact test was used for dichotomous categorical variables, and the Kruskal-Wallis H test was for multiple categorical variables. P-value < 0.05 was considered statistically significant. The relationships between clinical and radiographic parameters were assessed using Spearman rank correlation coefficients. Intraclass correlation coefficient (ICC) was used to evaluate the intra-repeatability of different observers (interobserver reliability). One independent researcher blinded to the group allocation completed the evaluations.

RESULTS

There were 39 men and 88 women, the mean age of whom was 47.6 years (range, 23–73 years). The mean duration of follow-up was 2.7 ± 1.2 years (range, 1.5–4.5 years). Five postoperative complications happened caused by leakage of CSF in 2 cases and superficial wound infection in 3 cases, and all of them had disappeared at the last follow-up. In the present study, syringomyelia resolved (change ratio > 20%) in 108 patients (85.0%), and the average CCOS score was 13.5 ± 1.6 after surgery. The mean values of the JOA score before surgery and at the last follow-up evaluation were 12.2 ± 1.9 points (range, 7–15 points) and 15.1 ± 1.3 points (range, 12–17 points) respectively, and the mean improvement rate was 54.1% ± 33.0%. The difference between the pre- and postoperative JOA score was significant (p < 0.001).
1. The Preoperative Distribution of Cervical Curvature

Primarily, by comparing 127 CM-I patients with syringomyelia and 32 CM-I patients without syringomyelia in our center, the mean value of C2–7 angle in CM-I with syringomyelia was significantly less lordotic than that in CM-I without syringomyelia (-13.5 ± 7.5 vs. -20.7 ± 8.4, p < 0.05).

The distribution of preoperative cervical lordosis was different in various types of syringomyelia. Specifically, cervical alignment straight or kyphotic was more common in the moniliform type of syrinx. In addition, it was found that the preoperative symptom duration was significantly shorter in patients with cervical alignment straight or kyphotic than in patients in the other 2 groups. However, cervical curvature in patients with CM-I related syringomyelia was not related to age, gender, degree of cerebellar tonsil descent, C0–2A, syrinx length, S/C ratio, deviation, location, or the preoperative symptoms (Table 1).

2. Changes in Relevant Parameters Following the Decompression Surgery

We summarized various parameters, including changes in cervical sagittal alignment, syrinx resolution, JOA score, and CCOS (Table 2). The mean C2–7A was -13.5 ± 7.5 before surgery and -17.1 ± 6.0 at the last follow-up (ICC = 0.856, p < 0.001), and the difference was significant between them (p < 0.001). The mean pre-and postoperative syrinx length was 8.8 ± 3.7 and 5.8 ± 2.9 (ICC = 0.905, p < 0.001) and there was also a significant difference (p < 0.001). However, there was no difference between the preoperative and the last follow-up evaluation regarding C0–2A, C2–7 SV A, and T1-slope.

3. Intergroup Comparison of Changes in Key Parameters Before and After Surgery

Compared with other types of syringomyelia, the syrinx with moniliform type showed the most significant changes in ΔC2–7A (p = 0.010), ΔS/C ratio (p < 0.001), and its postoperative CCOS is relatively better (p = 0.031) (Table 3). The patients with normal lordosis and straight or kyphotic cervical alignment accounted for 28.6% and 67.8% before surgery, respectively. The rate of normal cervical lordosis increased to 57.1%, and the number of patients with straight or kyphotic cervical alignment decreased to 39.3%. The proportion of patients with hyperlordosis remained unchanged (3.6%) before and after surgery. Using McNemar exact test, there was a statistically significant difference between the pre- and postoperative rate of normal cervical lordosis and straight or kyphotic cervical alignment (p = 0.008) (Table 4). The reliability of the radiographic measurements 3 times showed excellent consistency from different observers.
Correlation of Syrinx Resolution With Clinical and Radiographic Parameters

We further analyzed the correlation between baseline factors and syrinx resolution, ΔC2–7A, ΔJOA score, and CCOS (Table 5). Spearman correlation analysis showed that the ΔS/C ratio was positively correlated with the change of CCOS (p = 0.001, r = 0.897) and ΔC2–7A (p = 0.002, r = 0.560). There was also a correlation between the ΔJOA score (the change rate of the JOA score) and ΔC2–7A (p = 0.012, r = 0.467) (Fig. 5C–E). However, there was no correlation between the improvement rate of the JOA score and the resolution ratio of the syrinx, and no correlation was seen between the ΔSyrinx length ratio and any other factors.

DISCUSSION

For syringomyelia associated with CM-I, patients are plagued by a series of neurological symptoms such as suspended sensory disorder, hypoesthesia, amyotrophy, or weakness of limbs. Quite a few studies have been carried out to explore the relationships between syringomyelia formation and CSF circulation obstruction in the subarachnoid space. However, its specific mechanism remains controversial.

Decompression surgery with or without duraplasty is commonly used to control the development of syringomyelia, which has been reported in previous studies. Although tra-

Table 5. Correlation of syrinx resolution with clinical and radiographic parameters in moniliform syringomyelia

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔS/C ratio (p-value)</th>
<th>ΔSyrinx length ratio (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.710</td>
<td>0.443</td>
</tr>
<tr>
<td>Sex</td>
<td>0.161</td>
<td>0.320</td>
</tr>
<tr>
<td>Tonsillar descent grade</td>
<td>0.092</td>
<td>0.215</td>
</tr>
<tr>
<td>Preoperative JOA</td>
<td>0.440</td>
<td>0.320</td>
</tr>
<tr>
<td>Preoperative C0–2A</td>
<td>0.124</td>
<td>0.747</td>
</tr>
<tr>
<td>Preoperative C2–7A</td>
<td>0.562</td>
<td>0.762</td>
</tr>
<tr>
<td>CCOS</td>
<td>0.001* (r = 0.897)</td>
<td>0.593</td>
</tr>
<tr>
<td>ΔJOA score</td>
<td>0.793</td>
<td>0.847</td>
</tr>
<tr>
<td>ΔC0–2A</td>
<td>0.145</td>
<td>0.300</td>
</tr>
<tr>
<td>ΔC2–7A</td>
<td>0.002* (r = 0.560)</td>
<td>0.751</td>
</tr>
</tbody>
</table>

Relationships between factors above were assessed using Spearman rank correlation coefficients.

S/C ratio, syrinx/spinal cord ratio; JOA, Japanese Orthopedic Association; C0–2A, upper cervical angle; C2–7A, lower cervical angle; CCOS, Chicago Chiari Outcome Scale.

*p < 0.05, statistically significant differences.
Syrinx Resolution and Cervical Sagittal Realignment

Lu C, et al.

Additional surgical methods, such as PFD or PFDD, show certain curative effects in controlling the development of syrinx, they are not beneficial for all patients with syringomyelia. However, intradural pathology in various forms may cause CSF circulation obstruction, which makes great significance in the pathogenesis and outcome of syringomyelia. Therefore, the key to surgical treatment for syringomyelia likely settles in to relieve the obstruction of the foramen magnum and foramen of Magendie.\textsuperscript{6,7}

There is a strong association between syringomyelia and scoliosis, but there does not seem to be a significant relationship between CM-I and scoliosis in the absence of syringomyelia.\textsuperscript{11-13} Syringomyelia is known to be frequently accompanied by scoliosis in some patients, possibly because of asymmetric spinal cord injury (SCI) due to chronic expansion of the central canal in the spinal cord, which means that syringomyelia may be an aggravating factor in spinal alignment. Similarly, cervical sagittal alignment reflects the cervical physiological curvature, syringomyelia as its possible aggravating factor, while there are few studies on the relationship between them.

The mean value of the C2–7A in 127 CM-I patients with syringomyelia was less lordotic than in 32 CM-I patients without syringomyelia in our center (-13.5 ± 7.5 vs. -20.7 ± 8.4, p < 0.05). We could initially infer that space occupying syrinx formation caused by the obstruction of CSF circulation might drive the loss of cervical physiological curvature as an adaptive response. Combined with the patients’ preoperative clinical and radiologic characteristics, we continued to explore the differences in the distribution of cervical curvature at baseline. The results showed that the distribution of preoperative cervical lordosis was different in various types of syringomyelia. Specifically, straight or kyphotic cervical alignment was more common in the moniliform group. After Foramen magnum and Magendie dredging, syrinx resolution may coexist with the cervical sagittal realignment, especially for moniliform syrinx. (A, B) Spearman correlation analysis for moniliform type showed that $\Delta S/C$ ratio was positively correlated with change of CCOS ($p = 0.001$, $r = 0.897$) (C) and $\Delta C2–7A$ ($p = 0.002$, $r = 0.560$) (D). (E) There was also a correlation between $\Delta$JOA score (the change rate of the JOA score) and $\Delta C2–7A$ ($p = 0.012$, $r = 0.467$). S/C ratio, syrinx/spinal cord ratio; CCOS, Chicago Chiari Outcome Scale; JOA, Japanese Orthopedic Association; C0–2A, upper cervical angle; C2–7A, lower cervical angle.

Fig. 5. Schematic drawing and the linear correlation diagram for moniliform group. After Foramen magnum and Magendie dredging, syrinx resolution may coexist with the cervical sagittal realignment, especially for moniliform syrinx. (A, B) Spearman correlation analysis for moniliform type showed that $\Delta S/C$ ratio was positively correlated with change of CCOS ($p = 0.001$, $r = 0.897$) (C) and $\Delta C2–7A$ ($p = 0.002$, $r = 0.560$) (D). (E) There was also a correlation between $\Delta$JOA score (the change rate of the JOA score) and $\Delta C2–7A$ ($p = 0.012$, $r = 0.467$). S/C ratio, syrinx/spinal cord ratio; CCOS, Chicago Chiari Outcome Scale; JOA, Japanese Orthopedic Association; C0–2A, upper cervical angle; C2–7A, lower cervical angle.

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form type of syrinx. Additionally, patients with cervical alignment straight or kyphotic tend to have a short natural history. However, cervical curvature in patients with CM-I related syringomyelia was not related to syrinx length, S/C ratio, deviation, location, or other clinical characteristics. Why the straight or kyphotic cervical alignment is more concentrated in the type of moniliform syrinx has aroused our interest in further exploration.

Although the relationship between CM-I related syringomyelia and scoliosis is not fully understood. Some scholars once speculated that the syringomyelia may affect or even damage neurons in the spinal cord responsible for muscle in charge of trunk balance, thereby influencing the spinal sagittal alignment. We speculated that the development of syringomyelia could also bring certain changes to the cervical sagittal alignment as the result of chronic central SCI, which was related to the faster progression of enlargement of the central canal. Usually, the cross-fibers in front of the central canal bear the brunt, which is presented as the typical suspended sensory disorder. During the further enlargement, the anterior horn neurons and longitudinal conduction tracts were then involved in appearing manifestations such as amyotrophy, hypoesthesia, or weakness of limbs. However, whether this process is reversible depends on the degree of disturbance in the internal environment of the SCI and the degree of neuronal damage.

The decreasing of the syringomyelia size is accompanied by the stabilization or improvement of scoliosis in most patients following decompression surgery, so neurosurgical decompression is recommended for patients with CM-I, SM, and scoliosis with its potential to treat all 3 conditions at the same time. Since early decompression could improve neurological status and scoliosis in patients with syringomyelia associated with CM-I, accordingly, intradural decompression for syringomyelia by FMMD may also help in restoring the cervical sagittal alignment. In our results, after FMMD, syringomyelia resolved in 108 patients (85.0%), along with significant improvements in cervical sagittal alignment and JOA score. The mean value of CCOS at the last follow-up was 13.1 ± 2.8 (about 80% of the patients got a score of CCOS ≥ 13). Therefore, FMMD was effective for CM-I patients with syringomyelia in terms of improving neurological symptoms in the current study and is considered to be an effective surgical technique for not only syringomyelia resolution but also helping in cervical sagittal realignment. We speculate that this benefits from the elimination of intradural obstruction through FMMD, which might be conducive to a more complete restoration of CSF circulation, thereby reversing the adverse effects of chronic SCI and sagittal alignment imbalance caused by unrestricted enlargement of the syrinx (Fig. 5A, B).

The above parameters with statistically significant differences before and after surgery were then compared among 4 groups of different syrinx types. Compared with other groups, the syrinx with moniliform type showed the most significant changes in ΔC2–7A, and ΔS/C ratio after surgery, and the postoperative CCOS of it is relatively better. In addition, the cervical sagittal realignment of the moniliform syrinx is the most obvious after surgery in the 4 different morphological kinds of syringomyelia (Fig. 4E).

Therefore, we propose that the moniliform type of syrinx may be a special kind of configuration. Its particularity lies in that the reactivity following the change of CSF circulation seems to be more sensitive, and it shows stronger adaptability and reducibility than other types of syringomyelia, which not only reflects in the greater changes in the cervical lordosis during the syrinx formation with a shorter natural history but also in the more obvious syrinx resolution and a relatively better prognosis after removing the intradural obstruction and dredging the circulation of CSF. In terms of syrinx width, both moniliform type and distended type belong to the category with a larger S/C ratio; from the perspective of syrinx morphology, syrinx separation is the typical imaging manifestation for moniliform type, and some studies have preliminarily confirmed syrinx separation might be related with the ependymal cells surrounding the central canal of the spinal cord, which would be a source of endogenous stem cells, heralding a potential endogenous approach to SCI repair. While it is still unknown the specific pathophysiological mechanism of syrinx separation in chronic SCI.

Correspondingly, further analysis suggested that the ΔS/C ratio was positively correlated with both ΔC2–7A and CCOS in the moniliform syrinx. With the restoration of the CSF circulation following FMMD, the resolution of syringomyelia also coexisted with the improvement of cervical lordosis angle. Our results proposed that some relationships exist among syringomyelia, cervical sagittal alignment, and neurological prognosis, revealing that both syrinx resolution and cervical sagittal alignment might be predictive factors for prognosis, especially in the typical moniliform type.

Given that musculoskeletal abnormalities are part of the initial presentations of intraspinal lesions in a significant proportion of cases, the pre- and postoperative multifactorial analysis should be taken into account in patients with syringomyelia,
especially for the sagittal plane presented on lateral plain radiographs of the spine. Spinal deformities may also serve as a certain reference value for spinal cord dysfunction in the pathogenesis and clinical manifestations. For example, Zhu et al. found the convexity of thoracic vertebrae in idiopathic syringomyelia patients associated with the deviated side of the syrinx. Ono et al. concluded that scoliosis could be a predictor of the prognosis in CM-I patients with syringomyelia. Ouellet et al. also proved that thoracic hyperkyphosis in the sagittal plane may be used as an indicator of the presence of syringomyelia. All of them reinforced the necessity of assessing sagittal plane deformity for the predisposition to syringomyelia. Therefore, from the overall prognosis of surgical decompression for syringomyelia in CM-I patients, the multivariate factors including CCOS, syrinx characteristics on MRI, and cervical sagittal alignment could evaluate the surgical outcome more comprehensively, especially for the specific syrinx phenotype.

In our opinion, the syringomyelia configuration on MRI and cervical sagittal alignment on x-ray radiographs might complement each other in the clinical diagnosis and treatment of CM-I with syringomyelia. To evaluate the prognosis of CM-I patients with syringomyelia following PFD, attention should be given only to the change of the intramedullary syrinx but also to the improvement of the cervical sagittal alignment.

Our findings have supplemented and improved based on the previous studies. Some of the propositions we put forward have a certain significance in clinical and mechanism research. On the one hand, we should pay attention to the significance of the cervical sagittal alignment in the process of syringomyelia development or disappearance after decompression, such as evaluating the prognosis of patients with syringomyelia through sagittal plane presented on lateral plain radiographs; in addition, for some patients with the cervical sagittal deformity (straight or lordotic), they may be able to return to normal on their own to a certain extent as the syrinx resolution following decompression surgery. On the other hand, we should attach importance to the special type of moniliform syringomyelia. It is characterized by typical syrinx separation on imaging morphology, which we have initially confirmed in rat models of syringomyelia. However, that still needs to be better understood whether it belongs to a transitional state of syringomyelia or a special configuration, which will certainly lead us to potential implications for the exploration of the hydrodynamics and biological mechanisms during syringomyelia formation and resolution.

But as a retrospective analysis, selection bias is hard to avoid in this study. The duration of clinical observation was not long enough, and the results cannot provide the relationship between the syringomyelia resolution and cervical sagittal alignment over a longer period of follow-up. In addition, it is necessary to conduct a more specific analysis for patients in different age groups. However, given the limited number of patients, it seems not realistic to conduct randomized controlled trials.

CONCLUSION

The preoperative straight or kyphotic cervical alignment is more common in the moniliform syrinx. After FMMD, the syringomyelia resolution may be accompanied by the lower cervical lordosis recovery accordingly. In addition, the relationship between syrinx resolution and cervical sagittal realignment might have a certain reference value for the prognosis of CM-I patients with syringomyelia following surgery, especially in the moniliform syrinx.

NOTES

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Supplementary Fig. 1. Schematic drawing (A) and x-ray evaluation (B) of the cervical sagittal alignment parameters. Upper cervical angle (C0–2A), lower cervical angle (C2–7A), the sagittal vertical axis (C2–7 SVA), and T1 slope.
Evaluation and Comparation of a Novel Surgical Technique and Hemivertebra Resection to the Correction of Congenital Cervical Scoliosis in Lower Cervical and Cervicothoracic Spine

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Objective: To report concave-side distraction technique to treat congenital cervical scoliosis in lower cervical and cervicothoracic spine. To evaluate and compare clinical and radiographic results of this procedure with classic hemivertebra resection procedure.

Methods: This study reviewed 29 patients in last 13 years. These patients were divided into convex-side resection group (group R) and concave-side distraction group (group D). Radiographic assessment was based on parameter changes preoperatively, postoperatively and at last follow-up. Demographic data, surgical data and complications were also evaluated and compared between the 2 groups.

Results: In group R, mean age was 8.9 ± 3.3 years and follow-up was 46 ± 18 months. Operation time and blood loss averaged 500 ± 100 minutes, 703 ± 367 mL. In group D, mean age was 9.9 ± 2.8 years and follow-up was 34 ± 14 months. Operation time and blood loss averaged 501 ± 112 minutes, 374 ± 181 mL. Structural Cobb angle was corrected from 29.4° ± 12.5° to 5.3° (2.1°–18.1°) (p = 0.001) and 33.7° ± 14.1° to 12.8° ± 11.4° (p < 0.001) in groups R and D. Compensatory Cobb angle had a spontaneous correction rate of 59.6% (40.0%–80.8%) and 59.7% ± 23.0% in groups R and D. Mandibular incline, clavicle angle and spine coronal balance were significantly improved at last follow-up in both groups. All correction rates were not statistically different between groups. However, group D had significant less blood loss (p < 0.001) and operation time (p = 0.004) per vertebra than group R. Seven patients developed C5 nerve root palsy and recovered by 6 months of follow-up.

Conclusion: Both surgical procedures are safe and effective in correcting congenital cervical scoliosis. But concave-side distraction technique has less blood loss and time-consuming during surgery, which provides a better option for the treatment of congenital cervical scoliosis.

Keywords: Congenital cervical scoliosis, Convex-side resection, Concave-side distraction, Spinal fusion

INTRODUCTION

Congenital cervical scoliosis is caused by multiple defects of segmentation or formation of vertebra, including hemivertebra, wedged vertebra, butterfly vertebra, block vertebrae, and unilateral bar. Major curve in cervical region usually associates with proximal thoracic compensatory curve. These deformities usually appear in children and adolescents with undesired appear-
ance, including head tilt, shoulder imbalance and asymmetrical facial development, which often trouble their patients and families. Pain or neurologic deficits due to the deformity are rare in the beginning and these symptoms usually occur later secondarily to instability and degenerative arthritis in the hypermobile segments adjacent to the anomaly. Deformed vertebra in cervical region is unusual and the incidence is low compared to that in the thoracic and lumbar regions. This anomaly is usually associated with additional deformities and the most common is congenital synostosis of 2 or more cervical vertebrae, known as Klippel-Feil syndrome. The potential of compensation in adjacent spine regions is low and conservative treatment, for example brace treatment, is unable to influence the unbalanced spinal growth. Because of the complex anatomy of deformed vertebra and adjacent structures, such as nerve roots and vertebral arteries, it greatly increases the difficulty of surgical correction. Thus, surgical treatment was limited to posterior fusion in situ without scoliosis correction for a long time. Until 2005, Ruf et al. reported a combined approach to resect hemivertebra to correct cervical scoliosis. Currently, hemivertebra resection is a widely accepted surgical technique to correct congenital cervical scoliosis and was adopted since 2009 in our department. Since 2016, we developed a novel surgical technique to treat congenital cervical scoliosis and was adopted since 2009 in our department. Since 2016, we developed a novel surgical technique to treat congenital cervical scoliosis. Instead of hemivertebra resection on convex side, we distract and fill the deficiency on concave side. The purpose of this study is (1) to report a novel surgical technique instead of hemivertebra resection and (2) to evaluate and compare the clinical and radiological outcomes between the 2 surgical techniques.

MATERIALS AND METHODS

1. Inclusion and Exclusion Criteria

Inclusion criteria was patients with the presence of torticollis caused by congenital cervical scoliosis (defined as a Cobb angle of > 10°) in lower cervical and cervicothoracic spine; Operation and follow-up were performed in our hospital. The indication for surgery is patients with severe disfiguring deformity or patients with proven or expected deterioration deformities.

Exclusion criteria included (1) Patients with congenital cervical scoliosis caused by deformed vertebra in cranial-cervical junction or other causes of torticollis appearance, such as muscular torticollis, ocular torticollis, neurogenic torticollis, etc.; (2) Patients with other spinal deformity or disease, such as cervical kyphosis or kyphoscoliosis, congenital deformity of middle and lower thoracic spine, lumbar spine, ankylosing spondylitis, severe ossification of cervical posterior longitudinal ligament, etc.; (3) Cervical infectious diseases, cervical primary, or metastatic tumor; (4) Have a history of spinal trauma or surgery; (5) Imaging data are incomplete or follow-up time less than 24 months.

2. General Data

We reviewed 76 cases from congenital cervical scoliosis database in our department from January 2009 till now. According to inclusion and exclusion criteria, 29 patients were included in this study. According to different surgical procedures, we divided these 29 patients into 2 groups, convex-side resection group (group R), which was performed before 2016, and concave-side distraction group (group D), which was performed after 2016. These 2 surgical procedures had same surgical indication. The details of patients’ demographic and operative data were recorded in Tables 1 and 2.

This study protocol was approved by the Medical Science Research Ethics Committee of the Peking University Third Hospital (approval number: 2015269) and written evidence of informed consent was obtained from patients’ parents.

3. Radiographic Assessment

Photos and radiographic images were captured on each patient at a relaxed standing position, with no correction of torticollis. Computed tomography (CT) was performed to provide the details of osseous malformation. Computed tomographic angiography (CTA) was used before operation to evaluate for vertebral and carotid artery malformations. Radiographic parameters were measured independently by 2 surgeons before surgery, 3 months after surgery, and at last follow-up. We recorded the average of each measurement.

On coronal reconstruction view of CT scan, we recorded structural Cobb angle, which is the large curve in the segments with vertebral deformities causing clinical asymmetry or head deviation and needs to be surgically corrected. It is shown as the angle between the lines drawn parallel to the superior endplate of the most cranial vertebra and to the inferior endplate of the most caudal vertebra in the curve.

On standing posteroanterior radiographs of the spine, we measured 4 parameters to describe scoliosis: (1) Compensatory Cobb angle, the small curve without vertebral deformities. It is compensatory to the structural curve and is shown as the angle between the lines drawn parallel to the superior endplate of the most cranial vertebra and to the inferior endplate of the most caudal vertebra in the curve; (2) Mandible incline, the angle between horizontal line and the line through mandibular angles.
Comparation of 2 Surgical Techniques to Correct Congenital Cervical Scoliosis

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on both sides; (3) Clavicle angle, the angle between horizontal line and the line through the clavicular distal end on both sides; and (4) Spine coronal balance, the distance between a vertical line drawn from the apex of the odontoid process and the vertical line through the midpoint of superior endplate of sacrum. The details are shown in Fig. 1.

All parameters were obtained from the PACS (picture archiving and communication system) of the hospital, with an accuracy of 0.1 mm or 0.1°. The postoperative correction rate was calculated using \( \frac{\text{preoperation parameter} - \text{postoperation parameter}}{\text{preoperation parameter}} \times 100\% \).

4. Surgical Techniques

In our department, convex-side resection and concave-side distraction procedure were used before and after 2016. The details of surgical techniques were introduced as follows.

Table 1. Demographic data for patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Deformity types</th>
<th>VA anomaly</th>
<th>Follow-up period (mo)</th>
</tr>
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<tbody>
<tr>
<td>R</td>
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<td>M</td>
<td>5</td>
<td>Left C5 fully segmented HVB; C2–3 right unilateral bar</td>
<td>None</td>
<td>54</td>
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<tr>
<td></td>
<td>2</td>
<td>F</td>
<td>10</td>
<td>Left T2 fully segmented HVB; C2–3, C5–T1 block vertebra</td>
<td>None</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>F</td>
<td>10</td>
<td>Left C3 semi segmented WVB; C2–3, C6–7 block vertebra</td>
<td>Right twisted VA</td>
<td>72</td>
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<tr>
<td></td>
<td>4</td>
<td>M</td>
<td>7</td>
<td>Right C6 fully segmented HVB; Occipitalization of atlas; C3–5 block vertebra</td>
<td>Right fine VA</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>F</td>
<td>12</td>
<td>Right T1 fully segmented HVB; C2–4, C5–6 block vertebra</td>
<td>Right fine VA</td>
<td>60</td>
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<tr>
<td></td>
<td>6</td>
<td>M</td>
<td>6</td>
<td>Left C4 fully segmented HVB</td>
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<td>24</td>
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<td>7</td>
<td>F</td>
<td>9</td>
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<td>Left fine VA</td>
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<td>M</td>
<td>9</td>
<td>Right C4 fully segmented HVB; C2–3 block vertebra; dysplasia of occipital condyle and atlas</td>
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<td>24</td>
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<td>Left fine VA</td>
<td>6</td>
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<td></td>
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<td>F</td>
<td>4</td>
<td>Left C4 non segmented butterfly VB; C2–5 block vertebra; C6–7 right unilateral bar</td>
<td>None</td>
<td>48</td>
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<td>Left C3 non segmented HVB; C1–4 block vertebra</td>
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<td>Left fine VA</td>
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<td>M</td>
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<td>24</td>
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<td>Left C3 nonsegmented WVB; C2–3–4 block vertebra</td>
<td>Right fine VA</td>
<td>26</td>
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<td>7</td>
<td>F</td>
<td>6</td>
<td>Right T1 fully segmented HVB; C5–7, T2–3 block vertebra</td>
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<td>60</td>
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<td>Left C3 semi segmented HVB; C2–3 right unilateral bar</td>
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<td>10</td>
<td>F</td>
<td>13</td>
<td>Left C3 nonsegmented WVB; C2–6 block vertebra; C2–3 right unilateral bar</td>
<td>Right fine VA</td>
<td>24</td>
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<td></td>
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<td>M</td>
<td>13</td>
<td>Left C3,C5 non segmented WVB; C2–6 block vertebra</td>
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<td>72</td>
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<td>12</td>
<td>M</td>
<td>13</td>
<td>Left C5 nonsegmented HVB, C2–3,C4–5–6 block vertebra</td>
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<td></td>
<td>13</td>
<td>M</td>
<td>14</td>
<td>Right C3 fully segmented HVB; left T2 fully segmented HVB</td>
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<td>13</td>
<td>Right C5 fully segmented HVB; C2–4, C6–7 block vertebra; T1 butterfly vertebra</td>
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</table>

Group R, convex-side resection group; group D, concave-side distraction group; VA, vertebral artery; HVB, hemivertebra; WVB, wedged vertebra; VB, vertebra.
Table 2. Surgical details for patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Surgical details</th>
<th>Resected VB or distracted segment</th>
<th>Fusion levels</th>
<th>VB of screw placement</th>
<th>Surgical time (min)</th>
<th>Blood loss (mL)</th>
<th>Complications</th>
</tr>
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<tbody>
<tr>
<td>R</td>
<td>1</td>
<td>A: C5 hemivertebrectomy P: C5 laminectomy; left C4–6 facetectomy; C4, C6 pedicle screw fixation and fusion A: C4–6 bone fusion with plate fixation</td>
<td>C5</td>
<td>C4–6</td>
<td>C4, C6</td>
<td>570</td>
<td>500</td>
<td>None</td>
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<tr>
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<td>2</td>
<td>A: T2 hemivertebrectomy P: T2 laminectomy; left T1-2–3 facetectomy; T1, T3 pedicle screw fixation and fusion A: T1–3bone fusion with plate fixation</td>
<td>T2</td>
<td>T1–3</td>
<td>T1, T3</td>
<td>550</td>
<td>900</td>
<td>None</td>
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<td>3</td>
<td>A: C3 partial wedged vertebrectomy P: C3 laminectomy; left C2–3 facetectomy; C2, C3 pedicle screw fixation and fusion A: C2–3 bone fusion with plate fixation</td>
<td>C3</td>
<td>C2–3</td>
<td>C2, C3</td>
<td>510</td>
<td>900</td>
<td>None</td>
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<td>A: C6 hemivertebrectomy P: C6 laminectomy; left C5–6 facetectomy; C5, T1 pedicle screw fixation and fusion A: C5–7 bone fusion with plate fixation</td>
<td>C6</td>
<td>C5–T1</td>
<td>C5, T1</td>
<td>670</td>
<td>600</td>
<td>None</td>
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<td>A: T1 hemivertebrectomy P: T1 laminectomy; left C7–T2 facetectomy; C7, T2 pedicle screw fixation and fusion A:C7–T2 bone fusion with plate fixation</td>
<td>T1</td>
<td>C7–T2</td>
<td>C7, T2</td>
<td>600</td>
<td>750</td>
<td>C5 verve root palsy on convex side</td>
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<td>6</td>
<td>A: C4 hemivertebrectomy P: C4 laminectomy; left C3–5 facetectomy; C3, C5 pedicle screw fixation and fusion A:C3–5 bone fusion with plate fixation</td>
<td>C4</td>
<td>C3–5</td>
<td>C3, C5</td>
<td>358</td>
<td>1,100</td>
<td>None</td>
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<td>7</td>
<td>A: C3 partial wedged vertebrectomy P: C3 laminectomy; right C2–4 facetectomy; C2, C4 pedicle screw fixation and fusion A: C2–4 bone fusion with plate fixation</td>
<td>C3</td>
<td>C2–4</td>
<td>C2, C4</td>
<td>500</td>
<td>700</td>
<td>None</td>
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<td></td>
<td>8</td>
<td>A: C3 wedged vertebrectomy P: C3 laminectomy; right C2–4 facetectomy; C2, C4 pedicle screw fixation and fusion A: C2–4 bone fusion with plate fixation</td>
<td>C3</td>
<td>C2–4</td>
<td>C2, C4</td>
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<td>1,500</td>
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<td>9</td>
<td>A: G6 partial wedged vertebrectomy P: G6 partial laminectomy; left C5–6 facetectomy; C5, C7 pedicle screw fixation and fusion A: C5–6 bone fusion with plate fixation</td>
<td>G6</td>
<td>C5–7</td>
<td>C5, C7</td>
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<td>100</td>
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<td>A: C3 partial wedged vertebrectomy P: Right C2–3 laminectomy and facetectomy; C2, C3 pedicle screw fixation and fusion A: C2–3 bone fusion with plate fixation</td>
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<td>C2–3</td>
<td>C2, C3</td>
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<td>C4</td>
<td>C2–6</td>
<td>C2, C6</td>
<td>360</td>
<td>700</td>
<td>C5 verve root palsy on convex side</td>
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<td>A: C4 partial wedged vertebrectomy P: C4 partial laminectomy; left C3–5 facetectomy; Occipital screws and C3, C5, C7 pedicle screw fixation and fusion A: C3–5 bone fusion with plate fixation</td>
<td>C4</td>
<td>C0–7</td>
<td>C3, C5, C7</td>
<td>572</td>
<td>850</td>
<td>C5 verve root palsy on concave side</td>
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<td>13</td>
<td>A: C4 butterfly vertebrectomy P: C4 laminectomy; left C3–5 facetectomy; C3, C5 pedicle screw fixation and fusion A: C3–5 bone fusion with plate fixation</td>
<td>C4</td>
<td>C3–5</td>
<td>C3, C5</td>
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<td>400</td>
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<td>14</td>
<td>A: C3 hemivertebrectomy P: C3 laminectomy; left C2–4 facetectomy; C2, C4 pedicle screw fixation and fusion A: C2–4 bone fusion with plate fixation</td>
<td>C3</td>
<td>C0–4</td>
<td>C2, C4</td>
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<td>400</td>
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<td>A: C4 hemivertebrectomy P: C4 laminectomy; left C3–5 facetectomy; C2, C6 pedicle screw fixation and fusion A: C3–6 bone fusion with plate fixation</td>
<td>C4</td>
<td>C2–6</td>
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<td>D</td>
<td>1</td>
<td>A: C4–5 discectomy, soft tissue release P: right C4–5 facetectomy and distraction, 3D spacer inserted; C4, C5 pedicle screw fixation and fusion A: C4–5 bone fusion with plate fixation</td>
<td>C4–5</td>
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<td>326</td>
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(Continued)
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<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Surgical details</th>
<th>Resected VB or distracted segment</th>
<th>Fusion levels</th>
<th>VB of screw placement</th>
<th>Surgical time (min)</th>
<th>Blood loss (mL)</th>
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<td>C5 vertebral root palsy on concave side</td>
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<td>A: C3–4 discectomy, soft tissue release P: C3 laminectomy; C3–4 facetectomy and right C3–4 distraction, cage inserted; C2, C4 pedicle screw fixation and fusion A: C2–4 bone fusion with plate fixation</td>
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<tr>
<td></td>
<td>8</td>
<td>A: C3–4 discectomy P: left C2–4 facetectomy and distraction, cage inserted; C2, C4 pedicle screw fixation and fusion A: C2–4 bone fusion with plate fixation</td>
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<td>C2–4</td>
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<td>A: C3–4–5 discectomy, soft tissue release P: right C3–4–5 facetectomy and distraction, two cages inserted; C2, C4, C5 pedicle screw fixation and fusion A: C3–4–5 bone fusion with plate fixation</td>
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<td>10</td>
<td>A: C4–5–6–7 discectomy, soft release P: right C5–6–7 facetectomy and distraction, two cages inserted; C4, C6, C7 pedicle screw fixation and fusion A: C4–5–6–7 bone fusion with plate fixation</td>
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<td>11</td>
<td>A: Osteotomy among C3–4–5, soft release P: Osteotomy among C3–4–5 lamina, right C2–4, C4–6 distraction, two cages inserted; C2, C4, C6 pedicle screw fixation and fusion A: C2–4–6 bone fusion with plate fixation</td>
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<td>A: C3–4–6–7 discectomy, soft tissue release P: right C3–4–6–7 facetectomy and distraction, 2 cages inserted; C3, C4, C6, C7 pedicle screw fixation and fusion A: C3–4–6–7 bone fusion with plate fixation</td>
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<td>13</td>
<td>A: C2–4–1–3 discectomy, soft tissue release P: left C2–4, right T1–3 facetectomy and distraction, two cages inserted; C2, C4, C7, T1, T3, T4 pedicle screw fixation and fusion A: C2–4–T1–3 bone fusion with plate fixation</td>
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<td>14</td>
<td>A: C4–5–6–7, C7–T1 discectomy P: left C4–6–7, C7–T1 facetectomy and distraction, 2 cages inserted; C2, C4, C6, C7, T1, T3 pedicle screw fixation and fusion A: C4–6–7, C7–T1 bone fusion with plate fixation</td>
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Comparation of 2 Surgical Techniques to Correct Congenital Cervical Scoliosis
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1) Preoperative preparation
A sterilized 3-dimensional (3D)-printed model was prepared to assist the surgeon to make preoperative surgical plan and recognize anatomical malformations during operation. Neurophysiological monitoring of the spinal cord was done throughout the procedure by measuring somatosensory evoked and motor-evoked potentials.

2) Convex-side resection technique
Resection of the cervical hemivertebra was performed using an anterior-posterior-anterior combined approach (Fig. 2). Detailed surgical procedures were shown in previous report. The main procedures consist of 3 steps. Step 1: The hemivertebra body and adjacent discs were entirely dissected and the anterior part of transverse process was removed through an anterior approach. The vertebral artery and nerve root were exposed. Pedicle screws and rods were placed and the gap between adjacent levels after resection was closed by bending the head to convex side under Mayfield traction. Step 3: A polyetheretherketone (PEEK) cage contained auto bone graft was placed into the intervertebral space and titanium plate was placed.

3) Concave-side distraction technique
Distraction and lateral opening on concave side to correct cervical scoliosis was also performed using an anterior-posterior-anterior combined approach (Figs. 3, 4).
Step 1: Patient was placed in supine position and then given general anesthesia. Conventional anterior cervical approach was used to reach prevertebral space. According to preoperative plan, the intervertebral discs and cartilage plate were removed by curettage and nucleus pulposus forceps. Musculi longus cervicis was dissected subperiosteally and released to the lateral side of uncovertebral joint. The upper or lower level disc was excised and the epiphyseal plates of the upper and lower segments were scraped off to the lateral side of uncovertebral joint. Posterior longitudinal ligament was released and drainage was placed and the incision was closed temporarily.
Step 2: Patient was then placed in the prone position. The lamina, lateral masses on both sides and facet joints were exposed. Pedicle screws were placed in the adjacent upper and lower segments under navigational guidance and fixation rods were placed. After pedicle screws were distracted on concave side under simultaneous Mayfield traction, a valley gap between facet joint on concave side was created. The cartilage of the facet joint was completely removed and cortical bone was roughened. According to the degree of distraction, a well-reshaped and polished PEEK cage or a 3D-printed customized titanium alloy spacer was placed between the upper and lower facet joints and make sure it was in close contact with the cortical bone of the facet joints. After satisfactory position was confirmed under fluoroscopy, nail rod system was locked. Allograft bone grafting was performed around cage, on facet joint, lateral mass, and lamina. Drainage was placed and the incision was closed.
Step 3: Then the patient was placed in supine position for anterior fusion with plate fixation. The upper and lower cartilage plates of the adjacent vertebral bodies were completely removed and the cortical bone was roughened. A PEEK cage or a 3D-printed customized titanium alloy spacer was grafted into the intervertebral space on concave side, above which a titanium plate and the posterior part of the transverse process were removed through a posterior approach. The spinal cord, vertebral artery and nerve root were exposed. Pedicle screws and rods were placed and the gap between adjacent levels after resection was closed by bending the head to convex side under Mayfield traction. Step 3: A polyetheretherketone (PEEK) cage contained auto bone graft was placed into the intervertebral space and titanium plate was placed.

Fig. 1. Radiographic assessment parameters. (A) On the coronal reconstruction view of computed tomography scan, structural Cobb angle (a) is the large curve with vertebral deformities and is shown as the angle between the lines drawn parallel to the superior endplate of the most cranial vertebra and to the inferior endplate of the most caudal vertebra in the curve. (B) On the standing posteroanterior radiographs of the spine, Compensatory Cobb angle (b) is the small curve without vertebral deformities and is compensatory to the structural curve; Mandible incline (c) is the angle between the horizontal line and the line through the mandibular angles on both sides; Clavicle angle (d) is the angle between the horizontal line and the line through the clavicular distal end on both sides; Spine coronal balance (e) is the distance between a vertical line drawn from the apex of the odontoid process and the vertical line through the midpoint of superior endplate of sacrum.
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Fig. 2. Photographs and radiographs from case 6, group R (convex-side resection group). A 6-year-old boy with left C4 fully segmented hemivertebra. (A) A preoperative photograph shows obvious torticollis and head tilt. (B, C, F) Posteroanterior radiographs and computed tomography (CT) scan on coronal reconstruction view show mandible incline angle is 6.1°, clavicle angle is 1.3° and spine coronal balance is 18.0 mm. Structural and compensatory Cobb angle are 31.6°, 25.4°. (D, E) Three-dimensional (3D) reconstruction on CT scan and 3D-printed model. (G) Photographs after surgery show obvious improved appearance. (H, I, L) Posteroanterior radiographs and CT scan show mandible incline angle is 0.4°, clavicle angle is 1.4° and spine coronal balance is 25.2 mm. Structural and compensatory Cobb angle are 7.7°, 14.7°. (J, K) Photographs show a sterilized 3D printed model is prepared to assist the surgeon in recognizing anatomical malformations during operation. A gap is showed after left C4 hemi lamina resection (green arrow) and intraoperative fluoroscopy.

plate was placed. At last drainage was placed and the incision was closed.

4) Postoperative management

After surgery, patients were given sufficient analgesia (intravenous nonsteroidal anti-inflammatory drugs and analgesic drugs combined with weak opioids) and prevention of infection (cephalosporin, intravenous infusion for 48 hours). When the drainage flow was less than 50 mL/24 hours, the drainage tube was removed. After the anterior and posterior drainage tubes were removed, the patient was able to move to the ground. Postoperative neck brace braking was not required but within 6 weeks after operation, collar protection should be applied when going out for activities.

5. Statistical Analysis

An adaptation of Shapiro-Wilk test was used to examine whether the data were normally distributed. Continuous variables with normal distribution were presented as mean ± standard deviation; nonnormal variables were reported as median (interquartile range). Categorical variables were analyzed by chi-square test. Mean of 2 continuous normally distributed variables between the 2 groups were compared by 2-independent samples t-test; nonnormal variables were assessed with the Mann-Whitney U-test. Mean of 2 continuous normally distributed variables before and after operation were compared by paired sample t-test in each group; nonnormal variables were assessed with Wilcoxon sign rank test. The data were analysed by IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). A p-value of < 0.05 was considered significant.

RESULTS

1. Demographic and Operative Data in Each Group

No patient presented neurologic deficit before surgery in these 2 groups. Convex-side resection group (group R) contained 15 patients (7 males and 8 females) with an average age of 8.9 ± 3.3 years (range, 4–15 years) at surgery. All cases in group R were resected one hemivertebra or wedged vertebra totally or partially. The mean operation time was 500 ± 100 minutes (range, 279–670 minutes) with an average blood loss of 703 ± 367 mL (range, 100–1,500 mL). The mean follow-up was 46 ± 18 months (range, 24–72 months) (Table 1). Concave-side distraction group (group D) contained 14 patients (8 males and 6 females) with an average age of 9.9 ± 2.8 years (range, 6–14 years) at surgery. Eight patients were distracted in 1 segment and 6 were distracted in 2 segments. The mean operation time was 501 ± 112 minutes (range, 326–660 minutes) with an average blood loss of...
Fig. 3. Photographs and radiographs from case 2, group D (concave-side distraction group). A 9-year-old girl with right C5 fully segmented hemivertebra and C2–3 block vertebra. (A) A preoperative photograph shows obvious torticollis and head tilt. (B–D) Posteroanterior radiographs and computed tomography (CT) scan on coronal reconstruction view show mandible incline angle is 6.3°, clavicle angle is 2.1°, spine coronal balance is 15.3 mm. Structural and compensatory Cobb angle are 35.4°, 11.0°. (D, E) Three-dimensional (3D) printed model and designed surgical plan show C5 right hemivertebra and 3D-printed metal spacers are placed between left C4–6 vertebral bodies and left C4–6 facet joint to distract concave side. (G) Photographs after surgery show obvious improved appearance. (H, I, J) Posteroanterior radiographs and CT scan show mandible incline angle is 0.1°, clavicle angle is 5.2°, spine coronal balance is 7.2 mm. Structural and compensatory Cobb angle are 4.9°, 1.7°. Two 3D-printed metal spacers between left C4–6 vertebral bodies and left C4–6 facet joint are placed as surgical plan.

374 ± 181 mL (range, 110–600 mL). The mean follow-up was 34 ± 14 months (range, 24–60 months) (Table 1).

Because of the different number of surgical segments in 2 groups, total operation time and total blood loss during surgery cannot make good comparison between groups. Except for the procedure of resection and distraction, pedicle screw placement is the most influential procedure for intraoperative bleeding and operation time. Thus, these 2 data were divided by the number of pedicle screw placed vertebra in each patient. The vertebral screw placement was shown in Table 2. Therefore, we obtained 2 new indicators to describe operation time and intraoperative blood loss. Operation time per vertebra was 243 ± 51 minutes (range, 140–335 minutes) and 181 ± 55 minutes (range, 101–302 minutes) in groups R and D, respectively. Blood loss per vertebra was 342 ± 183 mL (range, 50–750 mL) and 123 ± 55 mL (range, 55–250 mL) in groups R and D, respectively.
2. Correction Results in Each Group

In group R, the mean structural Cobb angle was 29.4° ± 12.5° before surgery and 5.3° (range, 2.1°–18.1°) after surgery (Z = -3.408, p = 0.001) with an average correction rate of 81.7% (range, 38.0%–90.3%) and 4.2° (range, 1.5°–14.6°) at the last follow-up (Z = -2.544, p = 0.057). The distal compensatory curve averaged 19.3° ± 11.6° before surgery and 8.7° ± 6.8° after surgery (t = 4.129, p = 0.001) with a mean spontaneous correction rate of 59.6% (range, 40.0%–80.8%) and it was 7.7° ± 6.3° at the last follow-up (t = 1.019, p = 0.325). In terms of head tilt and shoulder balance, mandibular incline was corrected from 7.4° ± 5.1° to 2.5° (range, 2.1°–4.3°) (Z = -2.386, p = 0.017) and clavicle angle was corrected from 4.8° ± 3.2° to 1.1° (range, 0.5°–2.3°) (Z = -1.875, p = 0.035). Spine Coronal balance changed from 30.3 mm (range, 18.0–46.4 mm) to 10.0 mm (range, 6.7–29.0 mm) (Z = -2.101, p = 0.036).

In group D, the mean structural Cobb angle was 33.7° ± 14.1° before surgery and 12.8° ± 11.4° after surgery (t = 11.979, p < 0.001) with an average correction rate of 66.7% ± 23.4% and 12.5° ± 11.0° at the last follow-up (t = 0.493, p = 0.630). The distal compensatory curve averaged 19.9° ± 8.6° before surgery and 8.9° ± 7.7° after surgery (t = 8.473, p < 0.001) with a mean spontaneous correction rate of 59.7% ± 23.0% and it was 8.7° ± 7.1° at the last follow-up (t = 0.819, p = 0.427). In terms of head tilt and shoulder balance, mandibular incline was corrected from 4.5° ± 2.6° to 1.6° (range, 0.3°–4.4°) (Z = -2.543, p = 0.011) and clavicle angle was corrected from 4.0° ± 2.0° to 2.0° ± 1.7° (t = 3.140, p = 0.008).

Table 3. Correction results for 2 groups

<table>
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<tr>
<th>Group</th>
<th>Correction rate at LFU (%)</th>
<th>Correction after operation (%)</th>
<th>Correction rate (preop vs. postop)</th>
<th>Correction rate (postop vs. LFU)</th>
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<tr>
<td>R</td>
<td>81.7 (38.0–90.3)</td>
<td>81.7 (46.7–92.2)</td>
<td>Z = -3.408, p = 0.001*</td>
<td>Z = -2.544, p = 0.057</td>
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<td>D</td>
<td>67.7 ± 22.3</td>
<td>67.7 ± 22.0</td>
<td>Z = 0.493, p = 0.650</td>
<td>Z = -0.056, p = 0.27</td>
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Values are presented as mean ± standard deviation or median (interquartile range).
Comparation of 2 Surgical Techniques to Correct Congenital Cervical Scoliosis

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Spine Coronal balance changed from 25.9 ± 15.4 mm to 8.5 mm (range, 6.3–22.1 mm) (Z = -3.006, p = 0.010). Details were shown in Table 3.

3. Comparasion Between Groups

In demographic and operative data, group D had less operation time per vertebra (t = 3.146, p = 0.004) and less blood loss per vertebra (t = 4.408, p < 0.001) than group R. The other data showed no statistical difference between the 2 groups. Meanwhile, there was no statistical difference in correction rate of each radiological parameter between the 2 groups (Table 4).

4. Complications

In group R, 3 of 15 patients developed a postoperative C5 nerve root palsy with a decrease in deltoid muscle strength. Two cases had palsy on convex side and the other one had it on concave side. In group D, 4 of 14 patients developed a postoperative C5 nerve root palsy. Two cases had palsy on convex side and the other 2 had it on concave side (Table 1). All patients were treated with conservative treatment and their symptoms were completely recovered by 6 months after the surgery. No vertebral artery injuries, dural sac tear, reoperation caused by pedicle screw malpositioning or other severe complications were observed either during surgery or the follow-up period. The bone fusion (infiltration of trabeculae in the bone grafting) was achieved in all patients at last follow-up.

DISCUSSION

Congenital cervical scoliosis is a rare but severe spinal deformity. It usually detected incidentally and radiographs are taken only when the patients develop decompensated head and neck tilt that proves recalcitrant to physical therapy. The prognosis depends on the type of the deformity. Patients with fully segmented hemivertebrae bode a poor prognosis, especially in combination with contralateral bar formation. Therefore, the main reason for medical consultations in our department was aesthetic asymmetries noticed by the patients' parents. The parents were concerned because exposure to undesired comments from children's peers about their appearance could lead to the development of psychosocial problems.

There is little possibility for compensation above the deformity region in cervical spine. In addition, congenital cervical scoliosis is usually associated with other deformities such as Klippel-Feil syndrome, which further reduce the number of flexible segments and the possibility for compensation in cervical spine. The result is an increasing tilt of head and neck. Patients with head tilt tend to have a horizontal binocular gaze and will develop compensatory curves in the cervicothoracic junction. If the flexibility of the upper thoracic spine is reduced due to additional congenital anomalies, the attempt to horizontalize gaze may produce trunk shift to the side of the cervical convexity and lead to shoulder imbalance.

Surgical treatment should be considered in patients with severe disfiguring deformity or poor prognosis. Posterior arthrodesis in situ of the affected part in spine is commonly recom-
mended surgical technique in last century. However, this maneuver has no effect on correcting existing scoliosis and a long period of immobilization is necessary to achieve a solid fusion. Thus, the resection of the hemivertebra seems a logical surgical technique. In thoracic and lumbar spine, a comparably less invasive posterior approach is sufficient for resection hemivertebra. However, the anatomic situation of cervical spine is complicated by the course of the vertebral arteries. Thus, to completely resect the hemivertebra requires a combined anterior and posterior approach with meticulous protection of the spinal cord, the nerve roots, and the vertebral arteries during surgery. After complete resection of the hemivertebra, the correction is achieved by closing the gap with anterior and posterior compression instrumentation. The first case of cervical hemivertebra resection with a combined approach was reported in 1981 by DeBurge and Briard. However, serial reports have been rare since then except for the one by Ruf et al. in 2005. We started using this surgical technique to treat our first patient in 2009 and reported our 5-year follow-up in 2019.

Although this technique can obtain satisfactory clinical outcome, it still has its disadvantages. Because of the presence of vertebral arteries, the procedure of cervical hemivertebra resection is not only difficult and risky, but also time and labor consuming. The operation is a great challenge to the skill, physical strength and energy of the surgical team. Meanwhile, hemivertebra resection and compression on convex side may lead to iatrogenic foraminal stenosis and increase the incidence of nerve root palsy at the corresponding segment after surgery. The shortening of the convex side may further aggravate the patient’s existing short neck deformity, which is not conducive to the recovery of patient’s appearance. Therefore, we developed a new surgical technique to avoid hemivertebra resection in 2016, which is concave-side distraction technique. This technique extends the concave side through intervertebral space where the concave apex locates or adjacent intervertebral space to achieve the purpose of scoliosis correction. The avoidance of hemivertebra resection and exposure of vertebral artery and nerve root significantly reduces the difficulty and risk of the operation. This procedure tries to make up for the patient’s congenital anatomical deficiency and lengthen the concave side. Although there is no need to expose vertebral artery, preoperative CTA should be performed routinely to determine whether there is abnormality in vertebral artery and whether it will interfere with the distraction on concave side and the placement of prosthesis and pedicle screws.

The principle of convex-side resection technique is to remove the hemivertebra or the triangle portion of unsegmented vertebrae. We named this procedure as “peak-cut” procedure because it can rebuild the parallel position of upper and lower vertebrae and correct the torticollis. The concave-side distraction technique can be named as “Valley-fill” procedure. Because this procedure creates a gap like a valley between 2 facets and fill this valley with a spacer, it easily rebuilds the parallel position of upper and lower vertebrae and correct the torticollis. To perform a “Valley-fill” procedure, we do not need to expose the neurovascular structure. All the process are carried out within the intervertebral space like disc and facet. Therefore it is easier, safer and faster than “peak-cut” procedure. One additional benefit that patient will obtain from this procedure is his/her body height will be taller immediately after the surgery.

As shown in Table 3, there are significant differences in each group’s parameters before and after operation, which means patients’ head tilt posture and shoulder imbalance are greatly ameliorated by surgery. Operation can also affect whole spine coronal balance as the parameter of trunk shift reduced significantly after surgery. Meanwhile, there are no significant differences between post operation and at last follow-up in each group’s parameters, which indicates these 2 surgical procedures have a stable effect and it’s especially important for adolescents. The results above show that each surgical technique is effective and stable to correct congenital cervical scoliosis.

Correction rates of all radiological parameters between the 2 groups have no statistical difference, which indicate these 2 methods have similar orthopedic effect (Table 4). Although 2 surgical techniques have some surgical indications, group D has less operation time per vertebra and less blood loss per vertebra than group R, which is the result of avoiding hemivertebra resection. Less blood loss and operation time means safer operation and faster postoperative recovery, especially for kids.

Regarding complications, all patients with postoperative C5 nerve root palsy completely recovered by 6 months of follow-up. Hence we believe that intraoperative traction or transient ischemia of the nerve root could be the main cause for this complication.

Our study has some limitations. First, it had a small sample size and included only certain types of deformities and thus was not fully representative of the complexity of congenital cervical scoliosis since this condition is extremely rare. However, to the best of our knowledge, this is the first study to introduce a novel technique to treat congenital cervical scoliosis. Second, given the young age of our patients, the follow-up duration is still relatively short. Thus, a long-term follow-up study should be conducted...
ducted in the future. Third, additional clinical results, like patients and parents satisfaction degree, are needed to better evaluate these 2 surgical techniques in the further studies.

CONCLUSION

By means of these 2 surgical techniques, a sufficient correction of cervical scoliotic deformity is achieved and the head tilt is corrected. Concave-side distraction technique has less operation time and blood loss during surgery and similar correction rates compared to hemivertebra resection procedure. It is a better and safer option to treat congenital cervical scoliosis.

NOTES

Conflict of Interest: The authors have nothing to disclose.
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Author Contribution: Conceptualization: XC, SP, YD, YZ, TX, WL, FZ, YS; Data curation: SC, YD, TX, WL, YS; Formal analysis: SC, XC, TX, WL, YS; Funding acquisition: XC, SP, YD, YZ, WL, FZ, YS; Methodology: SC, XC, TX, WL, YS; Project administration: SC, XC, SP, YZ, TX, FZ, YS; Visualization: SC, XC, SP, YZ, WL, FZ, YS; Writing - original draft: SC; Writing - review & editing: SC, YS

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REFERENCES


A Nomogram Model for Prediction of Tracheostomy in Patients With Traumatic Cervical Spinal Cord Injury

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Objective: To develop a nomogram for the prediction of tracheostomy in patients with traumatic cervical spinal cord injury (TCSCI).

Methods: A total of 689 TCSCI patients were included in our study. First, the variable selection was performed using between-group comparisons and LASSO regression analysis. Second, a multivariate logistic regression analysis (MLRA) with a step-by-step method was performed. A nomogram model was developed based on the MLRA. Finally, the model was validated on the training set and validation set.

Results: The nomogram prediction model incorporated 5 predictors, including smoking history, dislocation, thoracic injury, American Spinal Injury Association (ASIA) grade, and neurological level of injury (NLI). The area under curve in the training group and in the validation group were 0.883 and 0.909, respectively. The Hosmer-Lemeshow test result was p = 0.153. From the decision curve analysis curve, the model performed well and was feasible to make beneficial clinical decisions.

Conclusion: The nomogram combining dislocation, thoracic injury, ASIA grade A, NLI, and smoking history was validated as a reliable model for the prediction of tracheostomy.

Keywords: Nomogram, Risk forecasting model, Spinal cord injury, Tracheostomy

INTRODUCTION

Traumatic cervical spinal cord injury (TCSCI) is a devastating disease that leads to lifelong disability and long-term risk of medical complications. TCSCI often results in acute respiratory failure. Many researchers have demonstrated that early tracheostomy (≤ 7 days from intubation) can bring many benefits to patients with TCSCI. For example, early tracheostomy may reduce mechanical ventilation (MV) time and allow for more comfortable and efficient breathing. To take advantage of these benefits and allocate resources accordingly, it is important for surgeons to have a tool to predict whether a patient might need a tracheostomy.

Although several factors for tracheostomy have been identified through multivariate logistic regression analysis (MLRA) and classification and regression tree (CART) model early prediction of tracheostomy in TCSCI patients is still difficult.

The nomogram is an essential part of modern medicine and is considered a reliable and practical predictive tool. The nomogram can visually display the results of MLRA, and can also predict the probability through a simple picture representation. To the best of our knowledge, no nomogram prediction model of tracheostomy has been reported in TCSCI patients. The purpose of this study was to develop and validate a simple and convenient nomogram model for predicting tracheostomy after TCSCI.

MATERIALS AND METHODS

1. Study Design

This was a retrospective study. This study was based on data from a university hospital in Chongqing, China between January 2008 to December 2021. It was approved by the Ethics Committee of our hospital. TCSCI was diagnosed by taking into ac-
count a history of trauma, symptoms, consciousness, sensory and motor, complete neurological testing, and imaging findings such as computed tomography and/or magnetic resonance imaging. The decision to perform a tracheostomy was made by the spine surgeon in conjunction with the intensive care unit physician and was made when prolongation of the MV was expected, considering the patient’s neurologic function, respiratory function, age, concomitant injury, and other factors. Tracheostomy was performed if any of the following criteria were met: (1) the patient was retained in a transoral tracheal tube and failed to evacuate MV after several attempts; (2) the patient had a lot of sputum and poor coughing power, requiring retention of an artificial airway to drain sputum. All assessments were performed by experienced senior physicians on admission. The overall flow chart is shown in Fig. 1.

2. Study Participants
A total of 762 patients with TCSCI in the department of orthopedics were analyzed. The inclusion criteria were as follows: (1) clear history of trauma, (2) well-diagnosed cervical spinal cord injury, and (3) complete medical records. The exclusion criteria were as follows: (1) larynx injuries, (2) patients who underwent tracheostomy at other hospital, and (3) incomplete medical records. Finally, 689 patients were included in the study sample.

3. Data Collection
The relevant patient’s data were recorded, including sex, age, smoking history, dislocation, diabetes mellitus, hypertension, preexisting lung disease, brain injury, American Spinal Injury Association (ASIA) impairment scale grade, neurological level of injury (NLI), and thoracic injury. ASIA impairment scale grade was assessed using the ASIA standards. ASIA impairment scale grade was divided into grades A and B–D. NLI was divided into C1–4 and C5–8. The dislocation was defined as traumatic cervical facet dislocation confirmed by radiological examination. Preexisting lung diseases included chronic obstructive pulmonary disease, bronchial asthma, and restrictive lung disease. According to World Health Organization, smoking was defined as continuous or cumulative smoking for 6 months or more in a lifetime.

4. Statistical Analysis
All patients were randomized into training and validation groups, in a 7:3 ratio for nomogram construction and validation. Pearson chi-square test and LASSO regression analysis were used to screen variables. The screened variables were brought into MLRA in a step-by-step method to determine the independent predictors. Based on the MLRA, a nomogram prediction model of tracheostomy was constructed. The area under curve (AUC) was calculated in training and validation groups.
to measure the predictive accuracy of the nomogram model. The calibration curve and Hosmer-Lemeshow test were performed to assess the predictive ability of the nomogram. The decision curve analysis (DCA) was performed to evaluate the predictive model. All analyses and nomogram development were performed using R ver. 4.2.0 (R Foundation for Statistical

Table 1. Characteristics of patients with traumatic cervical spinal cord injury in the training and validation groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Training group (n = 482)</th>
<th>Validation group (n = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>382 (79.3)</td>
<td>167 (80.7)</td>
</tr>
<tr>
<td>Female</td>
<td>100 (20.7)</td>
<td>40 (19.3)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>145 (30.1)</td>
<td>54 (26.1)</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>337 (69.9)</td>
<td>153 (73.9)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>163 (33.8)</td>
<td>80 (38.6)</td>
</tr>
<tr>
<td>No</td>
<td>319 (66.2)</td>
<td>127 (61.4)</td>
</tr>
<tr>
<td>Dislocation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>195 (40.5)</td>
<td>86 (41.5)</td>
</tr>
<tr>
<td>No</td>
<td>287 (59.5)</td>
<td>121 (58.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (5.2)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>No</td>
<td>457 (94.8)</td>
<td>200 (96.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (7.5)</td>
<td>21 (10.1)</td>
</tr>
<tr>
<td>No</td>
<td>446 (92.5)</td>
<td>186 (89.9)</td>
</tr>
<tr>
<td>ASIA impairment scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>65 (13.5)</td>
<td>27 (13)</td>
</tr>
<tr>
<td>B–D</td>
<td>417 (86.5)</td>
<td>180 (87)</td>
</tr>
<tr>
<td>Neurological level of injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1–4</td>
<td>148 (30.7)</td>
<td>77 (37.2)</td>
</tr>
<tr>
<td>C5–8</td>
<td>334 (69.3)</td>
<td>130 (62.8)</td>
</tr>
<tr>
<td>Preexisting lung disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (8.3)</td>
<td>19 (9.2)</td>
</tr>
<tr>
<td>No</td>
<td>442 (91.7)</td>
<td>188 (90.8)</td>
</tr>
<tr>
<td>Brain injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>117 (24.3)</td>
<td>50 (24.2)</td>
</tr>
<tr>
<td>No</td>
<td>365 (75.7)</td>
<td>157 (75.8)</td>
</tr>
<tr>
<td>Thoracic injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81 (16.8)</td>
<td>32 (15.5)</td>
</tr>
<tr>
<td>No</td>
<td>401 (83.2)</td>
<td>175 (84.5)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74 (15.4)</td>
<td>28 (13.5)</td>
</tr>
<tr>
<td>No</td>
<td>408 (84.6)</td>
<td>179 (86.5)</td>
</tr>
</tbody>
</table>

Table 2. Comparison of data between patients with and without tracheostomy in the training group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tracheostomy (n = 74)</th>
<th>Without tracheostomy (n = 408)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.048</td>
</tr>
<tr>
<td>Male</td>
<td>65 (87.8)</td>
<td>317 (77.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (12.2)</td>
<td>91 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td>0.033</td>
</tr>
<tr>
<td>≥ 60</td>
<td>30 (40.5)</td>
<td>115 (28.2)</td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>44 (59.5)</td>
<td>293 (71.8)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>39 (52.7)</td>
<td>124 (30.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35 (47.3)</td>
<td>284 (69.6)</td>
<td></td>
</tr>
<tr>
<td>Dislocation</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>54 (73.0)</td>
<td>141 (34.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (27.0)</td>
<td>267 (65.4)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (5.4)</td>
<td>21 (5.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>70 (94.6)</td>
<td>387 (94.9)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>0.820</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (8.1)</td>
<td>30 (7.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68 (91.9)</td>
<td>378 (92.6)</td>
<td></td>
</tr>
<tr>
<td>ASIA impairment scale</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>A</td>
<td>38 (51.4)</td>
<td>27 (6.6)</td>
<td></td>
</tr>
<tr>
<td>B–D</td>
<td>36 (48.6)</td>
<td>381 (93.4)</td>
<td></td>
</tr>
<tr>
<td>Neurological level of injury</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>C1–4</td>
<td>49 (66.2)</td>
<td>99 (24.3)</td>
<td></td>
</tr>
<tr>
<td>C5–8</td>
<td>25 (33.8)</td>
<td>309 (75.7)</td>
<td></td>
</tr>
<tr>
<td>Preexisting lung disease</td>
<td></td>
<td></td>
<td>0.190</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (12.2)</td>
<td>31 (7.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65 (87.8)</td>
<td>377 (92.4)</td>
<td></td>
</tr>
<tr>
<td>Brain injury</td>
<td></td>
<td></td>
<td>0.138</td>
</tr>
<tr>
<td>Yes</td>
<td>23 (31.1)</td>
<td>94 (23.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>51 (68.9)</td>
<td>314 (77.0)</td>
<td></td>
</tr>
<tr>
<td>Thoracic injury</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (36.5)</td>
<td>54 (13.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>47 (63.5)</td>
<td>354 (86.8)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%). ASIA, American Spinal Injury Association.
Computing, Vienna, Austria). A p-value of < 0.05 was considered statistically significant.

RESULTS

1. Baseline Characteristics in Training Group

In the training group, 482 patients with TCSCI, and 74 patients (15.4%) underwent tracheostomy. The baseline characteristics of patients in the training group are shown in Table 1. A comparison of patients with and without tracheostomy is shown in Table 2. Compared with the nontracheostomy group, the tracheostomy group presents a significant difference in age ≥ 60 years, sex, smoking history, dislocation, ASIA impairment scale, NLI, and thoracic injury (p < 0.05).

2. LASSO Regression and MLRA

The variables screened by LASSO regression analysis were: age, smoking history, dislocation, ASIA impairment scale grade,
NLI, and thoracic injury (Fig. 2A, B). Their optimal coefficients were 0.029, 0.297, 0.847, 1.830, 1.097, and 0.535, respectively. These 6 variables selected by the LASSO regression with non-zero coefficients were included in the MLRA analysis. The results of the MLRA are given in Table 3. Five variables, including smoking history, dislocation, thoracic injury, ASIA impairment scale grade, and NLI, showed significant statistical differences.

3. Nomogram Model Development

Using these 5 variables, a nomogram model for predicting tracheostomy was developed (Fig. 3). Each factor corresponded to a score at the top of the nomogram, and the total score was calculated and compared to the bottom of the nomogram to predict tracheostomy risk. The AUC in the training group was 0.883. The best cutoff point was 0.124 (sensitivity, 0.838; specificity, 0.770) (Fig. 4A), which indicated that the discrimination of the nomogram model was good. The calibration curve of the nomogram model revealed satisfactory consistency (Fig. 5A).

4. Validation With Validation Set

Twenty-eight patients (13.5%) in the validation group underwent tracheostomy. The result of the Hosmer-Lemeshow test was $p = 0.153$. The AUC in the validation group was 0.909. The best cutoff point was 0.136 (sensitivity, 0.893; specificity, 0.777) (Fig. 4B), which indicated that the discrimination of the nomogram model was good. The calibration curve of the nomogram model revealed satisfactory consistency in the validation group (Fig. 5B).

Table 3. Multivariate logistic regression analysis performed in a step-by-step method for the tracheostomy in patients with traumatic cervical spinal cord injury in training group

<table>
<thead>
<tr>
<th>Intercept and variable</th>
<th>$\beta$</th>
<th>Wald</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-4.282</td>
<td>116.149</td>
<td>0.001</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Dislocation</td>
<td>1.408</td>
<td>17.899</td>
<td>0.001</td>
<td>4.089</td>
<td>2.130–7.862</td>
</tr>
<tr>
<td>ASIA A</td>
<td>2.139</td>
<td>37.412</td>
<td>0.001</td>
<td>8.490</td>
<td>4.278–16.849</td>
</tr>
<tr>
<td>NLI C1–4</td>
<td>1.630</td>
<td>25.690</td>
<td>0.001</td>
<td>5.104</td>
<td>2.717–9.586</td>
</tr>
<tr>
<td>Smoking history</td>
<td>0.806</td>
<td>6.288</td>
<td>0.012</td>
<td>2.238</td>
<td>1.192–4.201</td>
</tr>
<tr>
<td>Thoracic injury</td>
<td>1.028</td>
<td>8.248</td>
<td>0.004</td>
<td>2.796</td>
<td>1.386–5.639</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; ASIA, American Spinal Injury Association; NLI, neurological level of injury.

Fig. 3. The nomogram model for prediction of tracheostomy. ASIA, American Spinal Injury Association; NLI, neurological level of injury.
5. DCA of the Nomogram Model

The clinical validity of the nomogram model was assessed using DCA (Fig. 6A, B). From the DCA, the nomogram performed well, and was feasible to make beneficial clinical decisions.

Fig. 4. Receiver operating characteristic (ROC) curve of the nomogram model. The training group (A) and the validation group (B). AUC, area under the curve.

Fig. 5. Calibration curve to confirm the prediction performance stability of the nomogram. The training group (A) and the validation group (B).
DISCUSSION

The study presented 102 of 689 TCSCI patients who underwent tracheostomy to comprehensively screen the independent risk factors. In the MLRA analysis, dislocation, thoracic injury, ASIA grade A, NLI, and smoking history were associated with tracheostomy in TCSCI patients. Based on these results, a nomogram model was developed. Then, the model was validated on the training set and validation set. This nomogram model showed that dislocation, thoracic injury, ASIA grade A, NLI at C1–4, and smoking history were key predictors. This study provided a relatively reliable nomogram model. It exhibited relatively good discrimination and calibration capabilities.

The ASIA grade A has been regarded as an essential predictor for tracheostomy in TCSCI patients. In the results of Childs et al., they even suggested early tracheostomy in all patients with ASIA A. Consistent with previous research, the present MLRA results revealed that the ASIA grade A was a significant predictor of tracheostomy. In this nomogram prediction model, the score corresponding to ASIA grade A was the highest.

Due to diaphragm and/or intercostal muscle dysfunction, NLI was considered to be another important predictor for tracheostomy in TCSCI patients. Tanaka et al. suggested that tracheostomy may be required in patients with NLI C4 or above. The present study also classified NLI into C1–4 and C5–8. Consistent with previous studies, the score corresponding to NLI at C1–4 were also high in our nomogram prediction model.

This predictive model also included dislocation, smoking history, and thoracic injury. Cervical dislocations mostly cause spinal cord compression and dramatic neurological deficits. Mu
et al. also found that facet dislocation was a significant risk factor for tracheostomy in patients with TCSCI. Smoking increases susceptibility to pulmonary infection and the development of cigarette smoke-induced lung diseases. Similarly, Nakashima et al. found that one of the risk factors for tracheostomy was smoking history. One intriguing finding of the study was that thoracic injury was a predictor of tracheostomy. In the nomogram prediction model, thoracic injury corresponds to a score roughly around 50, between smoking history and dislocation.

Several risk variables associated with tracheostomy were presented in other studies, but not included in the present study. Some authors found that age was a statistically significant risk factor and that older age groups were more likely to undergo tracheostomy. Controversially, other authors argued that age is not a risk factor. Some scholars have introduced the forced vital capacity (FVC) variable in their prediction models. However, using FVC for the predicted predictions has some shortcomings. For example, those who suffer great injury had to receive a tracheostomy may not have acceptable and reproducible pulmonary function test results.

There are 3 limitations to this study. First, this study was based on retrospective data from a single-specialty spine injury center, so the level of evidence is limited. Second, indications for tracheostomy in patients with TCSCI varied between institutions. Third, although the population was relatively large, the patients were from a single hospital. So, representation needs to be further improved.

CONCLUSION

The present study developed and validated a nomogram model that can predict tracheostomy in TCSCI patients. The nomogram combining dislocation, thoracic injury, ASIA grade A, NLI, and smoking history was validated as a reliable model for tracheostomy prediction. The present nomogram prediction model can help clinicians take timely and more targeted medical interventions.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: YJ; Formal analysis: YJ; Methodology: YJ; Project administration: ZZ; Visualization: YJ; Writing - original draft: YJ; Writing - review & editing: DS, ZZ.

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Dawei Sun: 0000-0001-7147-4658
Zhengfeng Zhang: 0000-0001-9983-9540

REFERENCES


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Global Trends and Hotspots in Endoscopic Discectomy: A Study Based on Bibliometric Analysis

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¹Hunan University of Chinese Medicine, Changsha, China
²Guangzhou University of Chinese Medicine, Guangzhou, China

Objective: With the advancement of minimally invasive spine surgery, endoscopic discectomy (ED) has become a common technique for degenerative disease of the spine. The present study aimed to explore the knowledge structure, emerging trends, and future research hotspots in this field.

Methods: All relevant publications on ED from 2002 to 2021 were extracted from the Web of Science databases. Key bibliometric indicators, including countries/regions, institutions, authors, journals, references, and keywords were calculated and evaluated using VOSviewer and CiteSpace software.

Results: A total of 1,196 articles and reviews were included for analysis. The number of publications regarding ED increased yearly. From the quality and quantity viewpoint, China, South Korea, and the United States were the major contributors in this field. The most influential institution in the field of ED was Wooridul Spine Hospital. We identified 3,488 authors, among which Lee SH had the most significant number of papers, and Ruetten S was cocited most often. World Neurosurgery was the journal with the most papers, and Spine was the most commonly cocited journal. Keywords were stratified into 4 clusters by VOSviewer software: cluster 1 (clinical outcomes of ED in the treatment of lumbar disc herniation); cluster 2 (surgical technique of percutaneous endoscopic lumbar discectomy); cluster 3 (clinical outcomes of ED in the treatment of lumbar spinal stenosis); and cluster 4 (clinical outcomes of percutaneous endoscopic cervical discectomy). Several topics including lateral recess stenosis, spinal stenosis, and reoperation were considered as the next hotspot in ED research.

Conclusion: ED research has gained considerable attention over the last 2 decades. Our bibliometric findings illuminate the publication trends and research hotspots of the ED field, which may provide useful references for scholars and decision-makers interested in this field.

Keywords: Endoscopic discectomy, Bibliometric, VOSviewer, CiteSpace

INTRODUCTION

Since earlier work by Kambin¹ to adapt arthroscopy for lumbar disc herniation (LDH), endoscopic discectomy (ED) has experienced tremendous development in the past few decades. Multiple studies²⁻⁵ have suggested the ED provides equivalent clinical outcomes to conventional microdiscectomy with fewer postoperative pain, shorter hospitalizations, less local tissue injury, and faster recovery. With growing experience and technological innovation, the indications of ED have been extended from lumbar degenerative diseases to degenerative diseases of the thoracic and cervical spine.⁶⁻⁸

Bibliometrics is a multidisciplinary discipline that involves various disciplines such as mathematics, statistics, and philology.⁹⁻¹⁰ It can not only quantitatively analyze the current state of a certain research domain through data visualization, but also...
identify current research hotspots and predict future research trends.\textsuperscript{11,12} However, to our knowledge, there is currently no bibliometric analysis assessing the relevant status quo and trends regarding ED research have been performed.

In this study, we aimed to visually analyze publications about ED in the Web of Science (WoS) database over the past 20 years. We presented a statistical analysis of the current status of the ED field, including the annual publication, countries/regions, institutions, authors, journals, funding sources, citation frequency, and Hirsch index (H-index). In addition, the journal impact factor (IF) and quartile ranks were extracted from the Journal Citation Reports 2021. The information extraction process was performed by 2 researchers independently, and any discrepancies were resolved through consensus.

Then, the VOSviewer 1.6.18 (Leiden University, Leiden, The Netherlands) and CiteSpace 5.8.R3 (Drexel University, Philadelphia, PA, USA) were applied to perform the bibliometric and visualization analysis. VOSviewer was applied to generate knowledge maps of the identified influential authors, contributing countries and institutions, core journals, high-quality papers, co-occurring keywords and cocited references. CiteSpace was used to extract keywords and references from publications with high-citation bursts and generate a dual-map overlay for journals. The flow diagram of literature search and analysis are presented in Fig. 1.

**MATERIALS AND METHODS**

1. **Data Sources and Search Strategies**

A comprehensive online search was performed using the Science Citation Index Expanded in the Web of Science Core Collection database on April 29, 2022. The search formula was “TS = (endoscop*) AND ((TS = (discectomy)) OR TS = (diskectomy)).” The search was limited to the English language with a publication date restricted from January 1, 2002 to December 31, 2021. For literature types, only articles and reviews were included. Ultimately, 1,196 records were identified.

2. **Data Extraction and Bibliometric Analysis**

Records retrieved from WoS were extracted and downloaded in “plain text” format with “Full Record and Cited References” for subsequent bibliometric analysis.

WoS was applied to describe the characteristics of the publications, including annual publications, countries/regions, institutions, authors, journals, references, and keywords. We also analyzed the trends and hotspots of ED to provide a reference for scholars and decision-makers interested in this field.
RESULTS

1. The Publication and Citation Trends

A total of 1,196 publications were identified from WoS, including 1,038 articles and 158 reviews. Fig. 2 shows the publications and citations in the field of ED between 2002 and 2021. In general, the annual number of publications and citations showed an overall increasing trend over the years. The evolution of the annual number of publications in the ED field can be separated into 2 stages: a slow and steady growth phase from 2002–2015, followed by a rapid and high-yield growth phase from 2016–2021. As of the search date, these publications received 20,633 citations, an average of 17.25 citations per publication, and an H-index of 66.

2. Countries/Regions, Institutions, and Funding Agencies

The ED is a research hotspot worldwide, with a total of 53 countries/regions contributed to this field. The top 10 most productive countries/regions in ED are shown in Table 1 and Fig. 3A. China published the largest number of papers (521), followed by South Korea (241), and the United States (181). South Korea accounted for 5,409 citations with an H-index of 40, which both ranked first among all involved countries/regions. The number of citations of publications from the United States was 5,013 with an H-index of 37, which both ranked second. Notably, though the number of citations and H-index from China both ranked third, the average number of citations ranked last in the top 10 countries/regions. The VOSviewer was employed to analyze the network visualization of coauthorship between countries/regions. The United States and China occupied the central place of the network, and there were active collaborations among these countries/regions (Fig. 3B).

As for institutions, the top 10 most productive institutions are listed in Table 2. Among the top 10 most productive institutions, 5 were from China, 4 from South Korea, and 1 from the United States. Wooridul Spine Hospital contributed the most publications with 57 papers published, followed by the Tongji University (48 publications), and The Catholic University of Korea (31 publications). In terms of other parameters, the H-index of Wooridul Spine Hospital ranked first (32), followed by that of Army Medical University (15) and Tongji University.

Table 1. Top 10 largest contributing countries/regions in the field of endoscopic discectomy research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country/region</th>
<th>No.</th>
<th>Citations</th>
<th>Average article citations</th>
<th>H-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>China</td>
<td>521</td>
<td>3,985</td>
<td>7.565</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>South Korea</td>
<td>241</td>
<td>5,409</td>
<td>22.44</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>USA</td>
<td>181</td>
<td>5,013</td>
<td>27.7</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Germany</td>
<td>65</td>
<td>2,408</td>
<td>37.05</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>Japan</td>
<td>63</td>
<td>721</td>
<td>11.44</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>Taiwan</td>
<td>44</td>
<td>623</td>
<td>14.16</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Turkey</td>
<td>31</td>
<td>316</td>
<td>10.19</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>India</td>
<td>26</td>
<td>271</td>
<td>10.42</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>Netherlands</td>
<td>20</td>
<td>671</td>
<td>33.55</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>Italy</td>
<td>19</td>
<td>264</td>
<td>13.89</td>
<td>8</td>
</tr>
</tbody>
</table>
Fig. 3. (A) The annual number of publications in the top 10 countries/regions from 2002 to 2021. (B) The coauthorship map of countries/regions involved in percutaneous endoscopic discectomy research (generated by VOSviewer). (C) The coauthorship map of institutions involved in endoscopic discectomy research (generated by VOSviewer); The size of the node indicates the number of documents in the countries/regions or institutions, and the thickness of the line between the nodes indicates the collaborative intensity between countries/regions or institutions. (D) The top 10 most active funding agencies involved in endoscopic discectomy research.
The citation frequency of papers from Wooridul Spine Hospital ranked first (2,895 times), followed by that from The Catholic University of Korea (673 times) and Army Medical University (526 times). The Wooridul Spine Hospital had the highest average citations of 50.79 per paper, followed by Leon Wiltse Memorial Hospital (22.86) and The Catholic University of Korea (21.71). The institutional coauthorship network map was conducted by VOSviewer and illustrated in Fig. 3C. There was an active collaboration among leading institutions.

The top 10 most active funding agencies are shown in Table 3 and Fig. 3D. 7 were from China, and the other 3 were from South Korea. The National Natural Science Foundation of China financed 96 studies in the ED field (ranked first, 8.027%), followed by the Wooridul Spine Foundation (16 studies, 1.338%) and the Korea Health Technology R D Project through the Korea Health Industry Development Institute Khidi Ministry of Health Welfare Republic of Korea (8 studies, 0.669%).

### 3. Authors and Cocited Authors
A total of 3,488 authors contributed to the publications on ED research. The top 10 most productive authors and the top 10 cocited authors are presented in Table 4. Among the top 10 authors, 5 were from South Korea, 4 from China, and 1 from the United States. Lee SH published the most papers (66) and ranked first, followed by Ahn Y (43) and Kim HS (41). The co-authorship network of authors was performed by VOSviewer and illustrated in Fig. 4A. In this network, different colors represent different clusters. It found that authors in the same cluster have relatively close cooperation. Nevertheless, the collaboration between authors from different clusters was weak, indicating little cooperation between different research teams. Additionally, we also use VOSviewer to perform author cocitation

### Table 2. Top 10 most productive institutions in the field of endoscopic discectomy research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Institutions</th>
<th>Country</th>
<th>No.</th>
<th>Citations</th>
<th>Average no. of citations</th>
<th>H-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wooridul Spine Hospital</td>
<td>South Korea</td>
<td>57</td>
<td>2,895</td>
<td>50.79</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Tongji University</td>
<td>China</td>
<td>48</td>
<td>461</td>
<td>9.6</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>The Catholic University of Korea</td>
<td>South Korea</td>
<td>31</td>
<td>673</td>
<td>21.71</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Army Medical University</td>
<td>China</td>
<td>30</td>
<td>526</td>
<td>17.53</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Brown University</td>
<td>USA</td>
<td>27</td>
<td>408</td>
<td>15.11</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Southern Medical University</td>
<td>China</td>
<td>24</td>
<td>101</td>
<td>4.21</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Chongqing Medical University</td>
<td>China</td>
<td>23</td>
<td>244</td>
<td>10.61</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>Leon Wiltse Memorial Hospital</td>
<td>South Korea</td>
<td>22</td>
<td>503</td>
<td>22.86</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>Capital Medical University</td>
<td>China</td>
<td>21</td>
<td>54</td>
<td>2.57</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>Gachon University</td>
<td>South Korea</td>
<td>21</td>
<td>206</td>
<td>9.81</td>
<td>8</td>
</tr>
</tbody>
</table>

### Table 3. Top 10 most active funding agencies in the field of endoscopic discectomy research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Funding Source</th>
<th>Country</th>
<th>No.</th>
<th>% of 1,196</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>National Natural Science Foundation of China</td>
<td>China</td>
<td>96</td>
<td>8.027</td>
</tr>
<tr>
<td>2</td>
<td>Wooridul Spine Foundation</td>
<td>South Korea</td>
<td>16</td>
<td>1.338</td>
</tr>
<tr>
<td>3</td>
<td>Korea Health Technology R D Project Through The Korea Health Industry Development Institute Khidi Ministry of Health Welfare Republic of Korea</td>
<td>South Korea</td>
<td>8</td>
<td>0.669</td>
</tr>
<tr>
<td>4</td>
<td>China Postdoctoral Science Foundation</td>
<td>China</td>
<td>5</td>
<td>0.502</td>
</tr>
<tr>
<td>5</td>
<td>Natural Science Foundation of Zhejiang Province</td>
<td>China</td>
<td>6</td>
<td>0.502</td>
</tr>
<tr>
<td>6</td>
<td>Chinese Ministry of Health</td>
<td>China</td>
<td>5</td>
<td>0.418</td>
</tr>
<tr>
<td>7</td>
<td>Foundation for Leading Talent in Traditional Chinese Medicine of Jiangsu Province</td>
<td>China</td>
<td>5</td>
<td>0.418</td>
</tr>
<tr>
<td>8</td>
<td>Ministry of Education Science and Technology Republic of Korea</td>
<td>South Korea</td>
<td>5</td>
<td>0.418</td>
</tr>
<tr>
<td>9</td>
<td>National Key R D Program of China</td>
<td>China</td>
<td>5</td>
<td>0.418</td>
</tr>
<tr>
<td>10</td>
<td>National Key Research and Development Program of China</td>
<td>China</td>
<td>5</td>
<td>0.418</td>
</tr>
</tbody>
</table>
Table 4. Top 10 most productive authors and the top 10 cocited authors in the field of endoscopic discectomy research

<table>
<thead>
<tr>
<th>Rank</th>
<th>Author</th>
<th>Country</th>
<th>No.</th>
<th>Total citations</th>
<th>H-index</th>
<th>Cocited author</th>
<th>Country</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lee SH</td>
<td>South Korea</td>
<td>66</td>
<td>2,916</td>
<td>32</td>
<td>Ruetten S</td>
<td>Germany</td>
<td>1,113</td>
</tr>
<tr>
<td>2</td>
<td>Ahn Y</td>
<td>South Korea</td>
<td>43</td>
<td>1,816</td>
<td>24</td>
<td>Ahn Y</td>
<td>South Korea</td>
<td>850</td>
</tr>
<tr>
<td>3</td>
<td>Kim HS</td>
<td>South Korea</td>
<td>41</td>
<td>459</td>
<td>14</td>
<td>Kambin P</td>
<td>USA</td>
<td>675</td>
</tr>
<tr>
<td>4</td>
<td>Kim JS</td>
<td>South Korea</td>
<td>38</td>
<td>948</td>
<td>15</td>
<td>Yeung AT</td>
<td>USA</td>
<td>494</td>
</tr>
<tr>
<td>5</td>
<td>He SS</td>
<td>China</td>
<td>31</td>
<td>302</td>
<td>11</td>
<td>Choi G</td>
<td>South Korea</td>
<td>485</td>
</tr>
<tr>
<td>6</td>
<td>Zhou Y</td>
<td>China</td>
<td>27</td>
<td>520</td>
<td>15</td>
<td>Choi KC</td>
<td>South Korea</td>
<td>407</td>
</tr>
<tr>
<td>7</td>
<td>Jang IT</td>
<td>South Korea</td>
<td>26</td>
<td>286</td>
<td>8</td>
<td>Lee SH</td>
<td>South Korea</td>
<td>294</td>
</tr>
<tr>
<td>8</td>
<td>Telfeian AE</td>
<td>USA</td>
<td>25</td>
<td>397</td>
<td>12</td>
<td>Hoogland T</td>
<td>Germany</td>
<td>256</td>
</tr>
<tr>
<td>9</td>
<td>Gu X</td>
<td>China</td>
<td>23</td>
<td>242</td>
<td>10</td>
<td>Kim CH</td>
<td>South Korea</td>
<td>247</td>
</tr>
<tr>
<td>10</td>
<td>Fan GX</td>
<td>China</td>
<td>23</td>
<td>235</td>
<td>10</td>
<td>Kim HS</td>
<td>South Korea</td>
<td>240</td>
</tr>
</tbody>
</table>

4. Journals and Cocited Journals

A total of 174 journals published papers on ED research. The top 10 journals with the greatest number of publications are listed in Table 5 and Fig. 5A. Among the top 10 journals, 7 were from the United States, and the other 3 were from Germany, England, and South Korea. World Neurosurgery published the most papers (179), followed by Pain Physician (75) and Medicine (53). Spine has the largest number of total citations (3,406 times) and highest value of H-index (27), and Pain Physician has the highest IF (2021 IF, 4.396). The journal cocitation analysis was conducted via VOSviewer. As shown in Fig. 5B, the top 5 cocited journals were Spine (6,326 times), European Spine Journal (2,097 times), Neurosurgery (1,528 times), World Neurosurgery (1,336 times), and Journal of Neurosurgery-Spine (1,269 times).

Fig. 4. The network visualization map of authors’ coauthorship (A) and cocitation (B). In the authors’ coauthorship map, the node’s 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 authors’ cocitation map, the size of the node represents the citation frequency, and the line between 2 nodes means that both were cited by one author.

A dual-map overlay of journals was generated using CiteSpace (Fig. 5C). We found that there were 3 main citation paths. The published articles were mainly focused on journals in the field of neurology, sports, and ophthalmology, whereas most of the cited articles were published in journals in the field of health, nursing, medicine, sports, rehabilitation, sport, psychology, education, and social.

5. Cocited Reference and Reference Burst

We used VOSviewer to analyze the cocited references and create a network map (Fig. 6A). The top 10 most cocited refer-
Table 5. Top 10 journals with the greatest number of publications in the field of endoscopic discectomy research

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>World Neurosurgery</td>
<td>179</td>
<td>USA</td>
<td>1,578</td>
<td>18</td>
<td>2.210</td>
<td>Q3/Q4</td>
</tr>
<tr>
<td>2</td>
<td>Pain Physician</td>
<td>75</td>
<td>USA</td>
<td>1,293</td>
<td>21</td>
<td>4.396</td>
<td>Q2</td>
</tr>
<tr>
<td>3</td>
<td>Medicine</td>
<td>53</td>
<td>USA</td>
<td>187</td>
<td>7</td>
<td>1.817</td>
<td>Q3</td>
</tr>
<tr>
<td>4</td>
<td>Spine</td>
<td>47</td>
<td>USA</td>
<td>3,406</td>
<td>27</td>
<td>3.241</td>
<td>Q2/Q3</td>
</tr>
<tr>
<td>5</td>
<td>European Spine Journal</td>
<td>46</td>
<td>Germany</td>
<td>1,511</td>
<td>22</td>
<td>2.721</td>
<td>Q2/Q3</td>
</tr>
<tr>
<td>6</td>
<td>Journal of Neurosurgery-Spine</td>
<td>38</td>
<td>USA</td>
<td>1,143</td>
<td>18</td>
<td>3.467</td>
<td>Q1/Q2</td>
</tr>
<tr>
<td>7</td>
<td>Neurospine</td>
<td>35</td>
<td>South Korea</td>
<td>259</td>
<td>9</td>
<td>3.374</td>
<td>Q2/Q3</td>
</tr>
<tr>
<td>8</td>
<td>Journal of Neurological Surgery Part A-Central European Neurosurgery</td>
<td>34</td>
<td>USA</td>
<td>180</td>
<td>8</td>
<td>0.984</td>
<td>Q4</td>
</tr>
<tr>
<td>9</td>
<td>Biomed Research International</td>
<td>29</td>
<td>USA</td>
<td>260</td>
<td>10</td>
<td>3.246</td>
<td>Q3</td>
</tr>
<tr>
<td>10</td>
<td>Journal of Orthopaedic Surgery and Research</td>
<td>26</td>
<td>UK</td>
<td>177</td>
<td>9</td>
<td>2.677</td>
<td>Q2</td>
</tr>
</tbody>
</table>

IF, impact factor; JCR, Journal Citation Report; Q, quartile.

Fig. 5. (A) The top 10 journals with the greatest number of publications. (B) The network visualization map of journal cocitation analysis using VOSviewer. 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 on endoscopic discectomy research was generated by CiteSpace. The labels represent different disciplines covered by the journals. The citing journals are on the left half, the cited journals are on the right half, and the colored path represents the citation relationship.
Fig. 6. (A) The cocitation network map of references on endoscopic discectomy. The size of the node represents the citation frequency, and the line between 2 nodes means that both were cited by 1 paper. (B) The top 25 references with the highest burst value (generated by CiteSpace). The blue bars indicate the time interval, and the red bars indicate the active time.
ences are presented in Table 6. The most cocited reference was an article published in *Spine* by Yeung and Tsou with 308 citations in 2002, entitled “Posterolateral endoscopic excision for lumbar disc herniation: surgical technique, outcome, and complications in 307 consecutive cases.” Among the top 10 references, 9 articles focused on the surgical technique and outcome of ED.

The ‘Burstness’ tool of the Citespace software was used to identify the publications that received widespread attention from related researchers during a certain period of time. Fig. 6B presents the top 25 references with the strongest citation bursts. The strongest burst reference was an article published in *Spine* by Ruetten et al. (2010–2013, strength 19.2), entitled “Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: a prospective, randomized, controlled study.” In addition, the articles of Liu et al. and Komp et al. were the most recent high-citation reference with a citation burst.

### Table 6. Top 10 cocited references in the field of endoscopic discectomy research

<table>
<thead>
<tr>
<th>Rank</th>
<th>First author</th>
<th>Title</th>
<th>Year</th>
<th>Source</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yeung AT</td>
<td>Posterolateral endoscopic excision for lumbar disc herniation: surgical technique, outcome, and complications in 307 consecutive cases</td>
<td>2002</td>
<td><em>Spine</em></td>
<td>308</td>
</tr>
<tr>
<td>2</td>
<td>Ruetten S</td>
<td>Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: a prospective, randomized, controlled study</td>
<td>2008</td>
<td><em>Spine</em></td>
<td>274</td>
</tr>
<tr>
<td>3</td>
<td>Mayer HM</td>
<td>Percutaneous endoscopic discectomy: surgical technique and preliminary results compared to microsurgical discectomy</td>
<td>1993</td>
<td><em>Journal of Neurosurgery</em></td>
<td>143</td>
</tr>
<tr>
<td>5</td>
<td>Hoogland T</td>
<td>Transforaminal posterolateral endoscopic discectomy with or without the combination of a low-dose chymopapain: a prospective randomized study in 280 consecutive cases</td>
<td>2006</td>
<td><em>Spine</em></td>
<td>137</td>
</tr>
<tr>
<td>6</td>
<td>Ahn Y</td>
<td>Percutaneous endoscopic lumbar discectomy for recurrent disc herniation: surgical technique, outcome, and prognostic factors of 43 consecutive cases</td>
<td>2004</td>
<td><em>Spine</em></td>
<td>133</td>
</tr>
<tr>
<td>7</td>
<td>Ruetten S</td>
<td>Use of newly developed instruments and endoscopes: full-endoscopic resection of lumbar disc herniations via the interlaminar and lateral transfornaminal approach</td>
<td>2007</td>
<td><em>Journal of Neurosurgery</em></td>
<td>132</td>
</tr>
<tr>
<td>8</td>
<td>Hermantin FU</td>
<td>A prospective, randomized study comparing the results of open discectomy with those of video-assisted arthroscopic microdiscectomy</td>
<td>1999</td>
<td><em>The Journal of Bone and Joint Surgery</em></td>
<td>129</td>
</tr>
<tr>
<td>9</td>
<td>Choi G</td>
<td>Percutaneous endoscopic approach for highly migrated intracanal disc herniations by foraminoplasty technique using rigid working channel endoscope</td>
<td>2008</td>
<td><em>Spine</em></td>
<td>110</td>
</tr>
<tr>
<td>10</td>
<td>Ruetten S</td>
<td>A new full-endoscopic technique for the interlaminar operation of lumbar disc herniations using 6-mm endoscopes: prospective 2-year results of 331 patients</td>
<td>2006</td>
<td><em>Minimally Invasive Neurosurgery</em></td>
<td>108</td>
</tr>
</tbody>
</table>

### 6. Keywords Analysis of Research Hotspots

Research hotspots and frontiers of the ED field can be revealed through keyword co-occurrence analysis and burst detection. In this study, VOSviewer was applied to present the keyword co-occurrence and cluster analysis (Fig. 7A). We merged some keywords with the same meaning to get a better perspective. According to the criteria that the co-occurrence of the keywords was at least 15 times, we totally introduced 84 keywords into the analysis. The top 5 keywords identified were “discectomy,” “surgery,” “disc herniation,” “lumbar disc herniation,” and “endoscopy,” which is consistent with our research topic. In addition, the inclusion keywords could be classified into 4 clusters: (1) clinical outcomes of ED in the treatment of LDH, green frames; (2) clinical outcomes of ED in the treatment of LDH, blue frames; (3) clinical outcomes of ED in the treatment of lumbar spinal stenosis (LSS), yellow frames; (4) clinical outcomes of percutaneous endoscopic cervical discectomy (PECD), red frames.
Fig. 7. (A) Keyword co-occurrence analysis on endoscopic discectomy research using the VOSviewer. The size of the node represents the occurrence times of keywords, the line between 2 nodes represents the co-occurrence of keywords, and different colors represent different clusters. (B) The top 25 keywords with the highest burst value (generated by CiteSpace). The blue bars indicate the time interval, and the red bars indicate the active time.
We also used CiteSpace to detect burst keywords (Fig. 7B). Among these words, “surgical technique” (2008–2012, strength 7.49) was the strongest burst keyword. Notably, the citation burst time of keywords including “lateral recess stenosis” (2018–2021), “spinal stenosis” (2019–2021), and “reoperation” (2019–2021) has continued to 2021, and the bursts are still ongoing, indicating that these research directions have received great attention recently.

**DISCUSSION**

In the past 20 years, ED has been extensively researched, and the overall number of publications has also increased yearly. From 2002 to 2015, the relatively small amount of paper in this period suggests that the study of ED is in its infancy. From 2016 to 2021, the number of papers showed rapid growth, demonstrating that the ED has been attracting increasing interest from scholars in the last years. Therefore, the topic of ED possibly remains a research hotspot in the field of spinal surgery, and the number of publications on ED may increase in the upcoming years.

From the current study, China had the largest number of publications in the ED field, followed by South Korea. Of course, this is closely associated with the local funding agencies, and the top ten funding agencies were all from China and South Korea. South Korea, the United States, and China ranked in the top three regarding the total number of citations and H-index. Of note, China ranked first for the number of publications, while it ranked third for the total number of citations and H-index. This suggests that although China has an advantage in the number of publications, the quality of the publication is relatively low, resulting in a low average article citation. The possible reasons might be (1) The research on ED started late in China, with only 32 papers published from 2002–2015 (South Korea, 79 papers; United States, 75 papers). It is only since 2016 that China has gradually become a leading country in terms of the annual number of publications. (2) The type of studies published in China is primarily case-control studies and case series, while there are relatively few high-quality randomized control trials. (3) There may be certain language barriers, and China has less cooperation with top countries such as South Korea and the United States. Thus, it is urgent to promote the quality of papers for Chinese scholars in the future. Among the top 10 productive institutions, 5 were from China, and 4 were from South Korea. This may be the reason why China and South Korea have published most papers on the ED field. It is noteworthy that Wooridul Spine Hospital ranks first regarding the number of publications, the total number of citations, and H-index. This indicates that Wooridul Spine Hospital might be the top research institution in this field, and scholars interested in ED may cooperate with this institution.

According to the authors and cocited authors in Table 4, the top 3 most prolific authors were all from South Korea (Lee SH, Ahn Y, and Kim HS). This indicates that scholars from South Korea is leading in the field of ED, and there will be more papers on this field to be published on these scholars and their teams in the future. As for cocited authors, the publications of 3 authors were cocited more than 500 times, with Ruetten S having the highest citation frequency, followed by Ahn Y, and Kambin P. Notably, Ahn Y was ranked second in both the number of publications and cocitation frequency, indicating that the papers published by him and his team are excellent in both quantity and quality. The chief contribution of Ruetten S was first proposing the use of percutaneous endoscopic interlaminar discectomy for the treatment of LDH, and his team subsequently had done a lot of investigations for clinical promotion and application of this technique.16,19–21

Professor Kambin P is one of the top experts in the ED field from the United States. Through extensive clinical and cadaver studies, he proposed “safe working zone” for the transformaminal approach, which has been robustly cited and widely utilized in percutaneous transformaminal endoscopic discectomy (PTED).22,23

As for journal analysis, the journals with the most papers about ED were *World Neurosurgery*, followed by *Pain Physician, Medicine*. Thus, it suggests that more studies on this field would also be preferentially published in the listed journals. From the perspective of cocited journals, *Spine* was the journal with the highest citations, followed by the *European Spine Journal, Neurosurgery*, indicating the important influence of these journals in this field. Subsequently, researchers interested in ED should pay more attention to these journals as mentioned above.

As shown in Table 6, the most cocited article in this field was Yeung and Tsou13 published in 2002, which mainly introduced ‘inside-out’ technique of posterolateral endoscopic lumbar discectomy, called YESS technique. Subsequently, a substantial number of novel techniques based on the YESS technique have constantly emerged, which vastly promotes the development of PTED. Of note, a total of 3 publications within the list of top 10 cocited papers were reported by Ruetten S, which also explained why he was the author with the highest cocitation frequency. Burst references are those that are frequently cited over a period of time.14,15 Among these references, the references

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www.e-neurospine.org 1103
with the strongest citation bursts are published by Ruetten et al. with burst duration from 2010 to 2013. In this study, Ruetten et al. used a prospective randomized controlled trial design to compare the clinical results of lumbar discectomies in full-endoscopic transforaminal and interlaminar approach with the conventional microdiscectomy. They concluded that the full-endoscopic technique is equivalent in efficacy to conventional microdiscectomy, with the advantage of operation technique and reduced traumatization. More importantly, among the top 25 references with the strongest citation burst, 2 references are still in burstness, indicating that this topic has received sustained attention in recent years.

In bibliometrics, the analysis of frequently appearing keywords is used to identify the research direction. As illustrated in the keywords clustering map in Fig. 7A, all the included keywords in the ED research could separate into 4 main clusters.

(1) Clinical outcomes of ED in the treatment of LDH: At the beginning of the development of the ED technique, most of the studies focused on exploring whether the percutaneous endoscopic lumbar discectomy (PELD) was effective. At present, many studies have shown that PELD has the same effect as conventional microdiscectomy with the advantages of minimal trauma, fast recovery, and less pain. For example, Ao et al. designed a novel targeted foraminaloplasty device with the specially designed double-cannulas for PELD; their results showed that this novel technique is a safe and effective procedure for LDH, and provides more advantages than the traditional TESSYS technique in reducing the difficulty of PELD learning, minimizing radiation exposure, and decreasing intraoperative pain associated with foraminaloplasty.

(2) Surgical technique of PELD: As the PELD technique has been gradually accepted by surgeon and patient, some scholars have started to focus on improving surgical techniques. Recently, numerous attempts have been made to simplify the operation, reduce the procedure time, and shorten the learning curve. For example, Ao et al. designed a novel targeted foraminaloplasty device with the specially designed double-cannulas for PELD; their results showed that this novel technique is a safe and effective procedure for LDH, and provides more advantages than the traditional TESSYS technique in reducing the difficulty of PELD learning, minimizing radiation exposure, and decreasing intraoperative pain associated with foraminaloplasty.

(3) Clinical outcomes of ED in the treatment of LSS: LSS is a common spinal disorder in the elderly, which is classified into central spinal stenosis, lateral recess stenosis, and foraminal stenosis. In the past, the indication for ED was mainly soft disc herniation, and only a few physicians could use ED to manage LSS. With the rapid developments of surgical techniques and instruments, the indication of ED has expanded from soft disc herniation to LSS. Various studies have confirmed the safety and efficacy of ED in the treatment of LSS. Study carried out by Li et al. showed that ED is a safe and effective technique for the treatment of LSS in the elderly, with the advantages of less traumatic, fewer anesthesia-related complications, and fast postoperative recovery.

(4) Clinical outcomes of PECD: Currently, PECD has been developed as an effective surgical alternative for cervical disc herniation or radiculopathy. PECD can be performed using an anterior or posterior approach, which depends on the localization of pathology. With the aid of laser and high-speed drills, PECD can complete the resection of central, paracentral, or foraminal soft disc herniations. Compared with anterior cervical discectomy and fusion or posterior microdiscectomy, the most significant benefits of PECD are clearer surgical field, less tissue damage, and quicker recovery.

As shown in the keyword burst detection results, lateral recess stenosis, spinal stenosis, and reoperation are the latest burst terms in recent years, which indicate that these research topics might be considered as the next hotspot in ED research. Additionally, it identifies promising directions for research, which is of interest to scholars and funding agencies. Therefore, it suggests that scientific breakthroughs regarding these research topics may be possible within the next few years.

Publications on ED research evaluated in the current study are reviewed from the WoS database. To our knowledge, this is the first-ever bibliometric study to analyze publications of ED around the world, providing a valuable reference for further exploration in this field. Despite our comprehensive and systematic analysis of ED research in this study, there are some limitations that require discussion. First of all, the bibliometric analysis was limited to English language publications, and thus we may have missed some important papers published in other languages. As far as we know, most of the non-English papers lack English abstract or references, unable to meet the requirements of bibliometric analysis. Secondly, the data analyzed in this study originated only from the WoS database, and some papers from other databases might have been missed. However, it should be noted that the WoS database is the most commonly used tool for bibliometric analysis. Finally, the publications in 2022 were not included in our study as the WoS database is constantly updated, and the data for this year is incomplete. Nevertheless, we believe that this study has included the vast majority of publications from 2002, and our conclusions would not be affected even with these updated data.

CONCLUSION

In conclusion, the annual number of publications regarding ED has been constantly growing since 2002. From the quality
and quantity viewpoint, China, South Korea, and the United States were the major contributors in this field. According to keywords analysis, 4 research directions were identified: (1) clinical outcomes of ED in the treatment of LDH, (2) surgical technique of PELD, (3) clinical outcomes of ED in the treatment of LSS, (4) clinical outcomes of PECD. More focus will be placed on lateral recess stenosis, spinal stenosis, and reoperation, which may be the next hotspot in ED research.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: BW, HX; Data curation: CF, YZ; Formal analysis: LY, XF; Funding acquisition: HX; Methodology: CF; Visualization: YZ, XF; Writing - original draft: BW, LY; Writing - review & editing: BW, HX.

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REFERENCES


Prevalence, Distribution, and Concomitance of Whole-Spine Ossification of the Posterior Longitudinal Ligament and Ossification of the Ligament Flavum in South Koreans: A Whole-Spine-CT-Based Cross-Sectional Study

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Objective: No studies assessing the prevalence of ossification of the spinal ligament were conducted using whole-spine positron emission tomography and computed tomography (PET-CT) in healthy Koreans. We aimed to determine the prevalence of ossification of the posterior longitudinal ligament (OPLL) and ossification of the ligament flavum (OLF) in healthy Koreans using whole-body PET-CT.

Methods: We reviewed whole-body PET-CT images captured during general health check-ups at the General Health Promotion Center of our institution from January 2015 to 2020. OPLL and OLF were identified by the presence of heterotopic ossification in the posterior longitudinal ligament and ligament flavum on axial and sagittal PET-CT images.

Results: A total of 1,934 adults (1,645 men, 289 women) were included. The mean age was 48.05 years (range, 28–86 years). Among the 1,934 patients, 173 had OPLL (8.9%). The most commonly involved cervical vertebra levels arranged according to frequency were C4, C5, C3, and C6. OLF was observed in 125 patients (6.5%). The most commonly involved thoracic levels were T10, T11, and T5. The prevalence of OPLL and OLF was the highest in patients aged 60–69 years. Among the C-OPLL patients, 15.1% had T-OPLL, 5.0% had L-OPLL, and 25.8% had T-OLF.

Conclusion: Our study revealed the prevalence of OPLL and OLF in healthy Korean subjects. It was consistent with that in other Asian countries. The presence of OPLL and OLF at most locations correlated with the presence or absence of spinal ossification at other locations.

Keywords: Ossification, Longitudinal ligament, Prevalence, Flavum, Distribution, Computed tomography

INTRODUCTION

Ossification of the spinal ligament is characterized by heterotopic bone formation in the posterior longitudinal ligament, which results in the compression of the spinal cord and possibly leads to neurological deterioration; this condition is often associated with other forms of paravertebral ligament ossification. Traditionally, many studies on the ossification of the spinal ligament were performed using radiographs; however, the diagnostic accuracy associated with this method was relatively low. Recently, with the developments in radiographic diagnostic technology, studies on the prevalence of this condition were con-
ducted using computed tomography (CT) or magnetic resonance imaging (MRI).

Two studies conducted in other countries evaluated the prevalence of ossification of the spinal ligament using whole-body positron emission tomography and CT (PET-CT). Fujimori et al. reported that the prevalence of cervical ossification of the posterior longitudinal ligament (C-OPLL) is 6.3% and that of thoracic ossification of the ligamentum flavum (T-OLF) is 12% in Japan. Liang et al. reported that the prevalence of C-OPLL is 4.1% and that of T-OLF is 37.65% in China. In South Korea, a few studies on the prevalence of C-OPLL and T-OLF were conducted using various diagnostic imaging modalities. Sohn et al. reported on the prevalence of C-OPLL (5.7%) using thyroid CT. Moon et al. reported on the prevalence of T-OLF (16.9%) using whole-spine sagittal MRI. Kim et al. reported on the prevalence of T-OLF (21.8%) using chest CT. However, no studies assessing the prevalence of ossification of the spinal ligament were conducted at the whole-spine level based on CT images in healthy Korean people. For these reasons, in this study, we aimed to determine the prevalence, distribution, and concomitance of OPLL and OLF based on whole-spine CT images in randomized Korean populations.

MATERIALS AND METHODS

1. Subjects
This study was conducted on adults who underwent PET-CT (Discovery PET/CT 710, GE Healthcare, Chicago, IL, USA) scans as part of health checkups during the period from January 2015 to January 2020. Research data were provided by the General Health Promotion Center of Dong-A University Hospital, Busan, Korea. No patient consent was required for the use of images and records because the anonymity of the participants was ensured. The exclusion criteria were cancer, inflammation, infection diagnosed by PET-CT, history of spine surgery, and foreign ethnicity. As a result, 1,934 participants were enrolled: 1,645 men and 289 women. The age range was 28-86 years, with a mean age of 48.05 ± 8.49 years.

2. Image Assessment
We obtained whole-body CT data from participants who underwent PET-CT scans. Slice thickness was 2.5 mm in axial CT images. Automatic exposure control was used (range, 100–240 mA) at 120 kV. The scan range was from the head to the pelvis. PACS software (PACS, INFINITT PACS M6, INFINITT Healthcare Co, Seoul, Korea) was used to confirm the presence of ossification of the spinal ligament. OPLL was identified through the presence of heterotopic ossification in the posterior longitudinal ligament. OLF was identified through the presence of heterotopic ossification in the ligamentum flavum. OPLL was evaluated based on the levels of the vertebral bodies exhibiting ossification. OLF was evaluated based on the levels of the laminae involved in ossification. First, reconstruction sagittal images were examined to assess the presence and level of ossification, and ossification was confirmed by rechecking the axial PET-CT image (Fig. 1). All the PET-CT images were reviewed by 2 experienced spine surgeons. To obtain more reliable results, the image review was performed twice, and any disagreements were resolved through a discussion.

3. Statistical Analysis
IBM SPSS Statistics ver. 28.0 (IBM Co., Armonk, NY, USA) was used to perform the statistical analysis. The difference in the prevalence of ossification according to sex was analyzed using the chi-square test or Fisher exact test. The increase in the prevalence of ossification with age was analyzed using the linear-by-linear association test. Concomitance of OPLL and OLF

Fig. 1. Positron emission tomography and computed tomography image of a 44-year-old man. The patient had cervical ossification of the posterior longitudinal ligament (yellow arrow), and thoracic ossification of the ligamentum flavum (white arrow).
was analyzed using the chi-square test or Fisher exact test. p-values less than 0.05 were regarded as statistically significant.

RESULTS

1. Prevalence of OPLL and OLF

Table 1 presents the prevalence rate of ossification of the spinal ligament. A total of 1,934 patients (1,645 men and 289 women) were included in this study. The mean age of these patients was 48.05 ± 8.49 years (range, 28–86 years). Among the 1,934 patients, 257 patients exhibited ossification of the spinal ligament (228 men and 29 women). The prevalence rate of spinal ligament ossification was 13.3% (men, 13.9%; women, 10.0%). A total of 173 patients had OPLL (151 men and 22 women). The prevalence rate of OPLL was 8.9% (men, 9.2%; women, 7.6%). A total of 159 patients had C-OPLL (144 men and 15 women). The prevalence rate of C-OPLL was 8.2% (men, 8.8%; women, 5.2%). A total of 35 patients had thoracic (T)-OPLL (26 men and 9 women). The prevalence rate of T-OPLL was 1.8% (men, 1.6%; women, 3.1%). A total of 35 patients had lumbar (L)-OPLL (26 men and 9 women). The prevalence rate of L-OPLL was 0.6% (men, 0.5%; women, 1.0%). The prevalence of OPLL was significantly different between men and women at the cervical (p < 0.042) and lumbar (p < 0.004) levels.

A total of 133 patients had OLF (125 men and 8 women). The prevalence rate of OLF was 6.5% (men, 7.1%; women, 2.8%). In total, only one patient had C-OLF (1 man and 0 women). The prevalence rate of C-OLF was 0.1% (men, 0.1%; women, 0%). A total of 121 patients had T-OLF (113 men and 8 women). The prevalence rate of T-OLF was 6.3% (men, 6.9%; women, 2.8%). A total of 4 patients had L-OLF (3 men and 1 woman). The prevalence rate of L-OLF was 0.2% (men, 0.2%; women, 0.3%). The prevalence of OLF was significantly different between men and women at the whole-spine (p < 0.006) and thoracic (p < 0.008) levels.

2. Segmental Distribution of OPLL and OLF

Fig. 2 shows the segmental distribution of OPLL. The most common location of C-OPLL was C4 (106 cases), followed by C5 (103 cases), C3 (85 cases), and C6 (85 cases). The most common location of T-OPLL was T6 (13 cases), followed by T1 (11 cases), T5 (10 cases), and T7 (10 cases). In men, the prevalence of OPLL was remarkably high at the cervical spine level in the following order: C4 (100 cases), C5 (95 cases), and C3 (79 cases); however, there was no significant difference in the distribution at the cervical and thoracic levels in women. The prevalence of OPLL in women was the highest in C6 (9 cases), followed by C5 (8 cases) and C3, C4, T7 (6 cases). Fig. 3 shows the segmental distribution of OLF. In most cases, OLF was located at the thoracic level. Bimodal distribution was observed in the case of whole-spine OLF. OLF was most commonly seen in T10 (54 cases of OLF).
Prevalence of OPLL and OLF in South Koreans

Choi YH, et al.

2.7 ± 1.1
68.6*
0
15.1*
1,023
3.3*
41.7*
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used chest CT and reported a T-OLF
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rates were found based on whole-body CT: C-OPLL, 5.12%; T-OPLL, 0.56%; and T-OLF, 9.90% (Table 4). The prevalence of spinal ligament ossification in this study was consistently similar to that in previous studies based on CT and MRI. However, the prevalence of T-OLF in our study was relatively lower than that in other studies involving the Korean population and other Asian populations. Moon et al. did not report the age distribution in detail, and Kim et al. included patients suffering from pulmonary disease; therefore, it is thought that there was selective bias in the patient groups. Moreover, there is a difference in the age distribution of the population. The average ages were 56 years and 60.9 years in the studies by Moon et al. and Kim et al., respectively, which were higher than that of this study. In both studies, the age distribution of the population was high; thus, the proportion of the elderly population would have been relatively higher than in this study. For this reason, the T-OLF prevalence seemed relatively low in this study. Although Fujimori et al. did not report the age distribution in detail, the average age and standard deviation in their study were higher than in this study, suggesting that the prevalence was higher. It is unclear why Liang et al. have a higher prevalence compared to this study. It is believed that there may be a genetic or lifestyle-related cause for the difference in the prevalence rate in each country; however, more detailed research is needed.

In this study, the prevalence of C-OPLL was approximately twice as high in men than in women, and this finding corresponded to that in previous studies. The prevalence of T-OPLL was higher in women than in men, which was consistent with the findings of previous studies. However, the difference in the prevalence of T-OLF among men and women was inconsistent with that in previous studies. In some studies, the prevalence of T-OLF was higher in women than in men.

### Table 4. Prevalence of spinal ligament ossification in other studies

<table>
<thead>
<tr>
<th>Type</th>
<th>Study</th>
<th>Prevalence of spinal ligament ossification</th>
<th>Modality</th>
<th>Country</th>
<th>Mean age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total (%)</td>
<td>Male (%)</td>
<td>Female (%)</td>
<td></td>
</tr>
<tr>
<td>C-OPLL</td>
<td>Sohn et al. (2014)</td>
<td>5.7</td>
<td>8.8</td>
<td>4.2</td>
<td>Thyroid CT</td>
</tr>
<tr>
<td></td>
<td>Fujimori et al. (2016)</td>
<td>6.3</td>
<td>8.3</td>
<td>3.4</td>
<td>PET-CT</td>
</tr>
<tr>
<td></td>
<td>Liang et al. (2019)</td>
<td>4.10</td>
<td>4.12</td>
<td>4.06</td>
<td>PET-CT</td>
</tr>
<tr>
<td></td>
<td>Singh et al. (2021)</td>
<td>5.12</td>
<td>5.66</td>
<td>3.93</td>
<td>Whole-body CT</td>
</tr>
<tr>
<td></td>
<td>Present study</td>
<td>8.2</td>
<td>8.8</td>
<td>5.2</td>
<td>PET-CT</td>
</tr>
<tr>
<td>T-OPLL</td>
<td>Mori et al. (2014)</td>
<td>1.9</td>
<td>1.0</td>
<td>3.1</td>
<td>Chest CT</td>
</tr>
<tr>
<td></td>
<td>Fujimori et al. (2016)</td>
<td>1.6</td>
<td>1.4</td>
<td>2.0</td>
<td>PET-CT</td>
</tr>
<tr>
<td></td>
<td>Liang et al. (2019)</td>
<td>2.25</td>
<td>1.57</td>
<td>3.61</td>
<td>PET-CT</td>
</tr>
<tr>
<td></td>
<td>Singh et al. (2021)</td>
<td>0.56</td>
<td>0.53</td>
<td>0.63</td>
<td>Whole-body CT</td>
</tr>
<tr>
<td></td>
<td>Present study</td>
<td>1.8</td>
<td>1.6</td>
<td>3.2</td>
<td>PET-CT</td>
</tr>
<tr>
<td>L-OPLL</td>
<td>Fujimori et al. (2016)</td>
<td>0.7</td>
<td>0.8</td>
<td>0.5</td>
<td>PET-CT</td>
</tr>
<tr>
<td></td>
<td>Liang et al. (2019)</td>
<td>0.80</td>
<td>0.75</td>
<td>0.90</td>
<td>PET-CT</td>
</tr>
<tr>
<td></td>
<td>Present study</td>
<td>0.6</td>
<td>0.5</td>
<td>1.0</td>
<td>PET-CT</td>
</tr>
<tr>
<td>T-OLF</td>
<td>Moon et al. (2015)</td>
<td>16.9</td>
<td>13.7</td>
<td>19.0</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>Kim et al. (2018)</td>
<td>21.8</td>
<td>23.0</td>
<td>20.1</td>
<td>Chest CT</td>
</tr>
<tr>
<td></td>
<td>Fujimori et al. (2016)</td>
<td>12.0</td>
<td>15.0</td>
<td>7.7</td>
<td>PET-CT</td>
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<tr>
<td></td>
<td>Liang et al. (2019)</td>
<td>37.65</td>
<td>36.1</td>
<td>40.75</td>
<td>PET-CT</td>
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<td>Singh et al. (2021)</td>
<td>9.9</td>
<td>11.86</td>
<td>5.58</td>
<td>Whole-body CT</td>
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<td></td>
<td>Present study</td>
<td>6.3</td>
<td>6.9</td>
<td>2.8</td>
<td>PET-CT</td>
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<tr>
<td>L-OLF</td>
<td>Fujimori et al. (2016)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>PET-CT</td>
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<tr>
<td></td>
<td>Liang et al. (2019)</td>
<td>1.45</td>
<td>1.04</td>
<td>2.26</td>
<td>PET-CT</td>
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<tr>
<td></td>
<td>Present study</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>PET-CT</td>
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</table>

Values are presented as mean ± standard deviation unless otherwise indicated.

OPLL, ossification of the posterior longitudinal ligament; OLF, ossification of the ligamentum flavum; C, cervical; T, thoracic; L, lumbar; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging.
while in others, it was higher in men than in women. In this study, the prevalence of T-OLF was approximately twice as high in men than in women, and this difference was significant (men, 6.9%; women, 2.8%; p < 0.008). It remains unclear whether T-OLF is more prevalent in men or women.

The prevalence of C-OPLL was the highest in C4 (19.2%), followed by C5 (18.7%), C3 (15.4%), and C6 (15.4%). In other studies, the overall prevalence of C-OPLL was the highest in C5, followed by C6 and C4. It is presumed that the prevalence of OPLL was high in C3 in this study compared to other studies due to the relatively high number of male patients. Sohn et al. reported that the prevalence of OPLL was significantly higher at the C3, C4, C5, and C6 levels in men. Therefore, in this study, the prevalence at the C3 level was relatively high compared with previous studies.

In previous studies based on plain radiographs, it was reported that T-OPLL occurred most frequently in T6. However, in recent studies based on CT images, T-OPLL occurred most frequently in T1. On plain radiographs, many bony structures, such as the shoulders and ribs, were found to mask upper thoracic OPLL; therefore, OPLL was not detected at the upper level of the thoracic spine. In this study, the prevalence of T-OPLL was the highest in T6, followed by T1, and there was little difference in the values: the prevalence was 2.4% in T6 and 2.0% in T1. These results are somewhat consistent with those of recent studies on T-OPLL. The distribution pattern of OPLL was roughly consistent with that in previous studies.

The distribution pattern of OLF in this study was similar to that in previous studies. The distribution of OLF exhibited a bimodal pattern. OLF occurs most frequently in T10 and T11, followed by T5 and T4. The true ribs transition to the floating ribs at the T10 and T11 level, and the kyphotic curve changes to the lordotic curve; therefore, stability is lost at this level. It is considered that this characteristic causes repetitive and high tensile stress, thereby leading to ossification.

The second peak in the segmental distribution of OLF was consistent with that in previously published reports. However, there was a difference in the level of the second peak, and most previous studies reported a second peak at the T3 level. Liang et al. reported a second peak at T4, and Mori et al. reported a second peak at T4/5. The presumed reason for the occurrence of the second peak is that the kyphotic curve angle is high at T5, and thus, the mechanical stress is also high. Kim et al. reported that T-OLF patients had more pronounced thoracic kyphosis. The reason for the occurrence of the second peak at the upper level of the thoracic spine is still unclear, and further research is needed on this subject.

The prevalence of OPLL and OLF increases with age. The number of lesions with OPLL and OLF also tends to increase with age. We found a significant relationship between age and the prevalence of OPLL. This finding was consistent with the results of previous reports. The prevalence of OLF tended to increase with age. On the other hand, there was no significant relationship between age and the prevalence of OLF in this study. This tendency was consistent with that in previous studies, but the statistical significance was different. Kim et al. reported that the relationship between age and the prevalence of T-OLF was not significant, whereas Moon et al. reported that there was a positive correlation between age and T-OLF prevalence. Further data and studies are warranted for investigating the statistical correlation between age and the prevalence of OLF.

This study shows that the coexistence of spinal ligament ossification at different levels was high. Several past studies have reported that patients with C-OPLL also have ossification in other areas of the spine. Fujimori et al. reported that T-OPLL patients have a systemic tendency to develop ossification. In this study, even in healthy people, the presence of OPLL and OLF in all the locations was correlated with the presence or absence of spinal ossification in other locations. Prior to treating patients with locally observed OPLL or OLF, it should be determined whether ossification in other areas may become symptomatic. Additionally, we recommend performing an evaluation through whole-spine CT to determine whether ossification is present at any other level.

This study has several limitations. First, PET-CT performed at this institute did not provide data related to the bone setting view. The resolution of the PET-CT fusion image was relatively lower than that of the bone setting view; therefore, we could only check for the presence or absence of ligament ossification. It is also possible that we were not able to identify cases with subtle ossification. Therefore, there is a possibility that the reported prevalence rate is lower than the actual prevalence rate. Second, the male to female ratio was not uniform. There were many more men than women in the subject group. In addition, since treatment agreements were made between heavy industry and electric companies and this hospital, bias resulting from occupations must be considered. Despite these limitations, this is the first study of the prevalence of ossification in healthy Koreans, and we believe that the results of this study sufficiently reflect the prevalence of OPLL and OLF in the general Korean population.
CONCLUSION

This is the first study to confirm the prevalence of OPLL and OLF in healthy Korean subjects. The results were consistent with those of previous studies on Koreans. The prevalence and distribution were consistent with those in other East Asians. The prevalence and number of lesions with spinal ligament ossification tended to increase with age. Ossification of the spinal ligament is likely to be seen across more than one level. If necessary, we recommended the use of whole-spine CT for differentiating other ossified lesions.

NOTES

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Author Contribution: Conceptualization: YMK; Data curation: YHC, JHL; Formal analysis: YHC; Methodology: YMK; Visualization: YHC; Writing - original draft: YHC; Writing - review & editing: YHC, YMK

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REFERENCES


Freehand Juxtapedicular Screws Placed in the Apical Concavity of Adult Idiopathic Scoliosis Patients: Technique, Computed Tomography Confirmation, and Radiographic Results

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Objective: The purpose of this study is to highlight our technique for freehand placement of juxtapedicular screws along with intraoperative computed tomography (CT) and radiographic results.

Methods: Consecutive patients with adult idiopathic scoliosis undergoing primary surgery by the senior author were identified. All type D (absent/slit like channel) pedicles were identified on preoperative CT. Three-dimensional visualization software was used to measure screw angulation and purchase. Radiographs were measured by a fellowship trained spine surgeon. The freehand technique was used to place all screws in a juxtapedicular fashion without any fluoroscopic, radiographic, navigational or robotic assistance.

Results: Seventy-three juxtapedicular screws were analyzed. The most common level was T7 (9 screws) on the left and T5 (12 screws) on the right. The average medial angulation was 20.7° (range, 7.1°–36.3°), lateral vertebral body purchase was 13.4 mm (range, 0–28.9 mm), and medial vertebral body purchase was 21.1 mm (range, 8.9–31.8 mm). More than half (53.4%) of the screws had bicortical purchase. Two screws were lateral on CT scan, defined by the screw axis lateral to the lateral vertebral body cortex. No screws were medial. There was a difference in medial angulation between screws with (n = 58) and without (n = 15) lateral body purchase (22.0 ± 4.9 vs. 15.5 ± 4.5, p < 0.001). Three of 73 screws were repositioned after intraoperative CT. There were no neurovascular complications. The mean coronal cobb corrections for main thoracic and lumbar curves were 83.0% and 80.5%, respectively, at an average of 17.5 months postoperative.

Conclusion: Freehand juxtapedicular screw placement is a safe technique for type D pedicles in adult idiopathic scoliosis patients.

Keywords: Spine surgery, Pedicle screw, Thoracic instrumentation, Lumbar instrumentation, Juxtapedicular screw placement, Extrapedicular screw placement

INTRODUCTION

Pedicle screw instrumentation of the thoracolumbar spine is a critical component of modern spinal surgery and facilitates powerful correction of spinal deformities. Freehand placement of thoracolumbar pedicle screws has been shown to be a safe and reproducible technique. The purchase for transpedicular screws relies on the screw traversing the cancellous channel of
the pedicle.\textsuperscript{4}

Juxtapedicular, or extrapedicular, screw placement is a previously described method for screw fixation in the case of small or absent pedicles.\textsuperscript{5,6} Watanabe et al.\textsuperscript{4} identified 4 pedicle types in scoliosis patients based upon the size of the cancellous channel. Type A pedicles have a “large cancellous channel,” type B a “small cancellous channel,” type C a “cortical channel” that a pedicle probe can be inserted with a mallet, and type D is a “slit/absent channel,” that warrants a juxtapedicular screw position. The technique for freehand juxtapedicular screw placement has been inconsistently described. In addition, several publications recommend a starting point at the tip of the transverse process.\textsuperscript{6,7} Due to this lateral starting point, the resulting screw would require an offset connector to be in-line with the rest of the transpedicular screws. Moreover, the dorsal position of the tip of the transverse process increases the distance to vertebral body making freehand instrumentation more challenging.\textsuperscript{8} The purpose of this study is to highlight the freehand technique for juxtapedicular screw placement along with intraoperative CT and radiographic results in a retrospective series of adult idiopathic scoliosis patients.

MATERIALS AND METHODS

Consecutive patients (n = 25) with adult idiopathic scoliosis undergoing primary surgery by the senior author were identified. All type D pedicles with absent channels were identified on preoperative CT. Operative notes and instrumentation logs were reviewed to identify screw sizes. Intraoperative CT scan images obtained after screw placement were analyzed with 3-dimensional visualization software was used to measure screw angulation and purchase (Figs. 1, 2). Postoperative radiographs were used to analyze curve correction.

1. Surgical Technique

Our technique is similar to the previously published freehand placement of juxtapedicular pedicle screws (Fig. 3):

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Visualization software for pedicle instrumentation determination. Red line, dorsal limit of vertebral body; yellow line, screw axis; green line, medial vertebral body purchase; blue line, lateral vertebral body purchase.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Pre- and intraoperative computed tomography (CT) images were measured to determine screw placement.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Step-by-step illustration of the juxtapedicular screw placement technique. (A) Creation of pilot hole with matchstick burr, using traditional anatomical landmarks. (B) Insertion of slightly curved gearshift down the lateral pedicle with the curved tip directed medially. (C) Following palpation of competent lateral vertebral body wall and screw length measurement using a flexible ball tip probe, placement of K-wire into pathway. (D) Undertap by 1mm with an open cannulated tap to visualize that the K-wire is not advancing. (E) Screw placement.}
\end{figure}

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www.e-neurospine.org 1117
(1) Meticulous exposure of the dorsal bony surface
(2) Creation of ventral starting point creation by removing the dorsal transverse process bone to the depth of the superior articulating facet
(3) Starting point on the transverse process is in-line with the lateral edge of the superior articular facet in the thoracic spine and 1 mm lateral to the ascending pars in the lumbar spine
(4) Create pilot hole into juxtapedicular space using a match- stick burr
(5) Glide down lateral pedicle using a 1mm “baby” slightly curved gearshift with the curved tip directed medially to depth of 15 mm in the thoracic spine and 20 mm in the lumbar spine
(6) Enter lateral vertebral body at the pedicle-body junction
(7) Palpation of competent lateral vertebral body wall and screw length measurement using a flexible ball tip probe
(8) Place K-wire into pathway and undertap by 1mm with an open cannulated tap to visualize that the K-wire is not advancing
(9) Re-palpation of the bony tract ventrally in the vertebral body
(10) Screw placement

RESULTS

1. Instrumentation Characteristics
A total of 73 juxtapedicular screws were analyzed with intraoperative computed tomography (CT). The most common level for juxtapedicular screw placement was T7 (9 screws) on the left and T5 (12 screws) on the right, with 8 screws placed in the upper lumbar region (Table 1, Fig. 4). Screw widths had the following distribution: 15.1% of screws were 5.5 mm, 68.5% were 6.0 mm, 15.1% were 6.5 mm, and 1.4% were 7.0 mm. The average screw length was 35 mm (range, 30–45 mm) (Table 2).

2. Screw Placement
The average medial angulation of screw placement was 20.7° (range, 7.1°–36.3°), lateral vertebral body purchase was 13.4 mm (range, 0–28.9 mm), and medial vertebral body purchase was 21.1 mm (range, 8.9–31.8). More than half (53.4%) of the screws had bicortical purchase, without significant anterior breach (< 3

Table 1. Distribution of type D pedicles

<table>
<thead>
<tr>
<th>Type D pedicle level</th>
<th>Count (n)</th>
</tr>
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<tbody>
<tr>
<td>T2</td>
<td>1</td>
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<tr>
<td>T3</td>
<td>9</td>
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<tr>
<td>T4</td>
<td>12</td>
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<td>T5</td>
<td>14</td>
</tr>
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<td>T6</td>
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<td>1</td>
</tr>
<tr>
<td>T11</td>
<td>1</td>
</tr>
<tr>
<td>T12</td>
<td>0</td>
</tr>
<tr>
<td>L1</td>
<td>4</td>
</tr>
<tr>
<td>L2</td>
<td>3</td>
</tr>
<tr>
<td>L3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 2. Screw characteristics

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Count (n)</th>
<th>Length (mm)</th>
<th>Count (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td>11</td>
<td>30</td>
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</tr>
<tr>
<td>6.5</td>
<td>11</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>7.0</td>
<td>1</td>
<td>45</td>
<td>9</td>
</tr>
</tbody>
</table>

Fig. 4. Distribution of juxtapedicular screw placement by instrumented level. Yellow areas signify the most common levels in the patient cohort.
mm). Two screws had a lateral breach on CT scan, defined by the screw axis lateral to the lateral vertebral body cortex. No screws were medially breached. There was a difference in medial angulation between screws with (n = 58) and without (n = 15) lateral body purchase (22.0 ± 4.9 vs. 15.5 ± 4.5, p < 0.001). Thoracic (n = 65) and lumbar (n = 8) screws showed significant differences in screw length (37.5 ± 3.2 mm vs. 44.4 ± 1.8 mm, p < 0.001) and vertebral body purchase (16.4 ± 15 mm vs. 23.8 ± 20.0 mm, p = 0.0007), but no difference in screw angulation (20.7° ± 5.6° vs. 20.4° ± 3.9°, p = 0.871).

3. Surgical Outcomes

Three of seventy-three screws were repositioned after intraoperative CT. There were no neurovascular complications. The mean coronal cobb corrections for main thoracic and lumbar curves were 83.0% and 80.5%, respectively, at an average follow-up of 17.5 months postoperative. A representative case is shown in Fig. 5.

DISCUSSION

In scoliosis and spinal deformity surgery, pedicle screw fixation is a hallmark of achieving segmental stabilization. Transpedicular instrumentation achieves fixation in all 3 columns, allowing for rigid fixation and improved deformity correction.9-11 In adult idiopathic scoliosis (AdIS), differences in pedicle morphology on the convex versus concave sides of a spinal deformity have been well documented with narrower pedicle widths on the side of the concavity, creating additional challenges for transpedicular instrumentation.12-16 Juxtaapedicular, or extrapedicular, screw placement is a previously described method for screw fixation in the case of small or absent pedicles.5,7 The purpose of this manuscript is to describe our technique and radiographic results for freehand juxtaapedicular screw placement in AdIS patients.

In this study, we found that 70 of 73 (95.8%) of screws were placed successfully using our freehand technique with confirmation on intraoperative CT scan after screw placement. There were no neurovascular complications, as has been shown in previous similar studies.2,9 The most common screw diameter was 6.0 mm and the most commonly instrumented levels were at T4, T5, and T7.

Freehand pedicle screw placement without the guidance of intraoperative fluoroscopic, radiographic navigation or robotics, has been shown to be safe and reproducible. In a retrospective study of 3,204 freehand thoracic pedicle screws, Kim et al.1 found that out of 577 screws randomly assigned for CT analysis, only 10 (1.7%) violated the medial wall, and no screws had caused neurovascular compromise with up to 10-year follow-up.1 In a retrospective series of 115 consecutive patients receiving 1,035 thoracic pedicle screws for scoliosis correction, Di Silvestre et al.16 found a screws misplacement rate of 1.7%, with no occurrence of neurovascular complication. The use of intraoperative navigation and robotic assistance has been gaining popularity and has demonstrated high levels of accuracy as well.17,18 However, we believe it remains critical for spine deformity surgeons to understand the technique for freehand juxtaapedicular screw placement.

Juxtaapedicular screw placement has been previously described in several papers but with a very dorsal and lateral starting point over the tip of the transverse process. In a cadaveric study of extrapedicular screw placement at T3–10 levels, Husted et al.6 determined that extrapedicular screws can be safely and effectively placed throughout the thoracic spine using the transverse process starting point. In a comparative study between transpedicular and extrapedicular instrumentation, White et al.5 demonstrated in a cadaver model that while transpedicular screws were stronger in both axial and sagittal loading methods, the difference was small, suggesting that juxtaapedicular placement provides an acceptable alternative method for instrumentation.

In this study, juxtaapedicular screws were frequently placed at T3–5 on the right and T6–9 on the left, corresponding to the concavity of the proximal and main thoracic curves in idiopathic
scoliosis. These findings are in agreement with previous studies which show type C and D pedicles are most often found in the concavity of scoliotic curves. Our technique differs from previous descriptions in that that starting point is more ventral and medial. We have previously shown that a more ventral starting point generates a 51% increase in maximal insertional arc, allowing for safer freehand pedicle screw placement. This shortens the distance from the starting point to the target vertebral body in juxtapedicular screw placement, thereby minimizing the margin for error. In addition, by starting only 1 mm more lateral than a transpedicular screw, the screw heads can be well-aligned with the rest of the construct.

The current study has several limitations. Longitudinal patient data to assess outcomes and fusion rates were not available due to the short length of follow-up. However, the main purpose of this study was to assess the technical considerations and accuracy for instrumentation of small apical concave type D pedicles. There was no biomechanical testing as part of this study, and therefore the strength and pullout assessment of juxtapedicular screws (versus conventional pedicle screws) cannot be determined. However, the excellent overall coronal cobb correction rates speak to adequate vertebral purchase to allow for this amount of correction. Future studies are necessary to analyze long term patient outcomes, fusion rates, and biomechanical properties of juxtapedicular screws in the AdIS population.

CONCLUSION

The freehand technique for juxtapedicular screw placement of type D pedicles in AdIS is a safe and effective technique. Careful preoperative analysis, intraoperative technical execution with CT scan verification and appropriate instrumentation techniques can provide adequate deformity correction in these adult patients.

NOTES

Conflict of Interest: The authors have nothing to disclose.
Funding/Support: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contribution: Conceptualization: JDL, RAL, LGL; Data curation: JDL, JAO, NJL, JML; Formal analysis: AJS, NJL; Methodology: AJS, JDL, RAL, LGL; Project administration: JDL, NJL, JMS, LGL; Writing - original draft: AJS, JDL; Writing - review & editing: AJS, JDL, JAO, JMS, RAL, LGL.


Description of the Diversity in Surgical Indication and Surgical Strategies for Primary Spinal Cord Tumors: A Nationwide Survey by the Neurospinal Society of Japan

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Objective: To assess the current management of primary spinal cord tumors (PSCTs) and determine whether and to what extent there are differences in surgical strategies for PSCTs.

Methods: The Neurospinal Society of Japan conducted a survey between April 1 and 30, 2021. Certified spine surgeons were requested for information on the frequency of surgeries in 2020 and the surgical strategies adopted for each PSCTs. The following tumor histologies were focused: schwannoma, meningioma, and cauda equina tumor as extramedullary tumors; and ependymoma, hemangioblastoma, astrocytoma, and cavernoma as intramedullary tumors. The participants were divided according to their response as follows: experts, who had experienced ≥ 100 surgeries for PSCTs, and nonexperts.

Results: Among 308 participants (63%), 35 (11%) were experts. The total number of PSCTs in 2020 was 802 of which 564 tumors were extramedullary and 223 were intramedullary. Schwannoma accounted for 53% of the extramedullary tumors, and ependymoma accounted for 39% of the intramedullary tumors. Surgical strategies significantly differed among both the experts and nonexperts groups. Some discrepancies in the adopted surgical strategies were observed between groups. Some of the nonexperts, and none of the experts, resected the entire dura for meningiomas.

Conclusion: A nationwide survey revealed that a sufficient consensus did not exist regarding surgical strategies for PSCTs. A disease-specific registry for PSCTs is necessary in academic societies.

Keywords: Spinal cord neoplasms, Surgical strategy, General surgery, Surveys and questionnaires, Registries
INTRODUCTION

Generally, primary spinal cord tumors (PSCTs) are uncommon and are approximately 5% of all the diagnosed primary central nervous system tumors. PSCTs arise from the meninges, spinal cord, and cauda equina, with annual incidence of 0.35, 0.59, and 0.03 per 100,000 persons, respectively. Approximately 70% of PSCTs are reported to be benign or unknown, suggesting that most PSCTs can be cured by total resection.

Postoperative worsening of neurological symptoms is not common in PSCTs, which has been reported to be 2.2%. However, the removal of PSCTs, especially intramedullary tumors that originate in the spinal cord, inevitably involves invasion of normal nerve tissues, and the procedure requires a sensitive technique based on extensive experience. Nevertheless, accumulating sufficient experience in PSCT removal can be difficult as PSCTs are rare and extremely diverse in histology. Some reports have suggested that conservative treatment is better than surgery, and when physicians should recommend resection of benign PSCTs with slow progression is controversial.

Since the pathogenesis and prognosis of PSCTs are different in each histology and genotype, generating evidence to support the strategy for each PSCT can be difficult. Clinical decision may largely depend on the individual experience of each physician, and the existence of divergence regarding indications for surgery and extent of resection for PSCTs in actual clinical practice. However, no reports have demonstrated the actual degree of divergence to date.

If indeed a divergence in treatment strategy is observed, 2 issues become apparent. The first is the necessity to promote shared decision making in which decisions are made based on a bidirectional exchange of information, including patients’ values and preferences. The second is an urgency of accumulating information for shared decision-making, regarding prognosis associated with surgical strategies. Generating evidence to address these issues in rare diseases such as PSCTs, consolidating and sharing treatment experiences are essential, and establishing an academic society-initiated disease-specific registry would be highly desirable.

Thus, this study aimed to assess the current management of PSCTs by neurosurgeons in Japan and to determine whether and to what extent there are differences in surgical strategies for PSCTs.

MATERIALS AND METHODS

This study was conducted as a survey of the Neurospinal Society of Japan (NSJ), an academic society that consists mainly of neurosurgeons involved in the treatment of spinal diseases and has approximately 1,300 members and 500 certified spine surgeons. The survey was launched on April 1, 2021, and responses were collected until April 30, 2021. All certified spine surgeons listed in the NSJ membership directory with a valid email address were eligible to participate in the study and were asked to complete the web-based questionnaire. Those who refused to participate in the survey were excluded. This study was approved by certified local Institutional Review Boards of Katano Hospital (20210215-1), and all participants provided electronic informed consent.

1. Data Collection

The questionnaire consisted of 3 topics that included the characteristics of participants, surgical experience in PSCTs, and treatment strategies for each tumor histology. The characteristics of participants included age, sex, clinical experience as a spine surgeon, type of the institution. For surgical experience in PSCTs, the information on the total cases and the cases for each tumor histology in lifetime and 2020 were collected. The participants were reminded to register only the surgical cases that they had performed as the primary surgeon. The focus was on 7 types of tumor histology as representative of PSCTs for this study: schwannomas, meningiomas, and cauda equina tumors as intradural extramedullary tumors, whereas ependymomas, hemangioblastomas, astrocytomas, and cavernomas as intramedullary tumors. Although cavernoma is classified as a vascular malformation, it was included in this study because its treatment was comparable to that of intramedullary tumors.

Additionally, information was sought on surgical strategies, such as indication for surgery and extent of resection. To investigate the indication for surgery, both the experts (with ≥ 100 cases of experience) and the nonexperts were asked to select one of the following 6 items that was close to their preference, assuming the patient to be a healthy 50-year-old without any comorbidities: (1) at the time of diagnosis, (2) worsening imaging findings, (3) mild neurological symptoms (e.g., mild numbness), (4) moderate or more neurological symptoms (e.g., motor paralysis), (5) progressive neurological symptoms, and (6) do not recommend surgery. For cavernoma, an additional question was asked, “At what time point do you think resection should be indicated for a bleeding-onset cavernoma?” To investigate the extent of resection, a set of questions with 3 to 4 items specific to each tumor histology was prepared. Regarding the extent of resection, information only on intradural extramedul-
lary tumors was asked, and the responses were limited to those who were performing surgery for each tumor at the institution. For schwannomas and cauda equina tumors, no background disease such as neurofibromatosis was assumed. An English translation of the questionnaire is presented in Supplementary Table 1.

2. Statistical Analysis

The background characteristics of the participants were first described. Continuous variables were summarized by median and interquartile range, and dichotomous or categorical variables by absolute and relative frequencies. Second, the number of surgeries performed for each tumor histology in 2020 was described. Finally, the distribution of responses to each question by the experts and the nonexperts was illustrated. Data were managed using Stata 17 (StataCorp LLC; College Station, TX, USA).

RESULTS

Altogether, 321 participants (66%) responded to the questionnaire, of which 13 refused to participate, primarily because they did not treat for PSCTs (Supplementary Fig. 1). For 308 participants, the median age was 50 years, median clinical experience as a spine surgeon was 15 years, and 46% were physicians working in university or public hospitals (Table 1). Of the included participants, 35 (11%) who had performed ≥ 100 surgeries for PSCTs were in the experts group; they were older, and many of them worked at university or public hospitals.

1. Surgical Experience in PSCTs

The total frequency of PSCTs cases among the study participants in 2020 was 802 cases, which included 564 cases of intradural extramedullary tumors, 223 cases of intramedullary tumors, and 15 cases of others. Among intradural extramedullary tumors, schwannomas accounted for half of the cases, and meningiomas and cauda equina tumors accounted for one quarter each. Among intramedullary tumors, ependymomas accounted for 39%, hemangioblastomas and cavernomas were almost equal in number and accounted for > 20%, and astrocytomas accounted for < 20% (Table 2).

Table 1. Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 308)</th>
<th>Experts (n = 35)</th>
<th>Nonexperts (n = 273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50 (45–58)</td>
<td>60 (52–66)</td>
<td>49 (44–57)</td>
</tr>
<tr>
<td>Male sex</td>
<td>302 (98.1)</td>
<td>35 (100)</td>
<td>267 (97.8)</td>
</tr>
<tr>
<td>Clinical experience as a spine surgeon (yr)</td>
<td>15 (10–20)</td>
<td>23 (16–32)</td>
<td>14 (10–20)</td>
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<tr>
<td>Type of institution</td>
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<tr>
<td>Private hospital</td>
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<tr>
<td>&lt; 200 Beds</td>
<td>73 (23.7)</td>
<td>4 (11.4)</td>
<td>69 (25.3)</td>
</tr>
<tr>
<td>200–399 Beds</td>
<td>56 (18.2)</td>
<td>4 (11.4)</td>
<td>52 (19.0)</td>
</tr>
<tr>
<td>≥ 400 Beds</td>
<td>37 (12.0)</td>
<td>5 (14.3)</td>
<td>32 (11.7)</td>
</tr>
<tr>
<td>University hospital</td>
<td>74 (24.0)</td>
<td>17 (48.6)</td>
<td>57 (20.9)</td>
</tr>
<tr>
<td>Public hospital</td>
<td>68 (22.1)</td>
<td>5 (14.3)</td>
<td>63 (23.1)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).

Table 2. Frequency of surgeries for primary spinal cord tumors in 2020

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 308)</th>
<th>Experts (n = 35)</th>
<th>Nonexperts (n = 273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>802</td>
<td>364</td>
<td>438</td>
</tr>
<tr>
<td>Intradural extramedullary tumors</td>
<td>n = 564</td>
<td>n = 235</td>
<td>n = 329</td>
</tr>
<tr>
<td>Schwannomas</td>
<td>297 (52.7)</td>
<td>124 (52.8)</td>
<td>173 (52.6)</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>129 (22.9)</td>
<td>41 (17.4)</td>
<td>88 (26.7)</td>
</tr>
<tr>
<td>Cauda equina tumors</td>
<td>138 (24.5)</td>
<td>70 (29.8)</td>
<td>68 (20.7)</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>n = 223</td>
<td>n = 125</td>
<td>n = 98</td>
</tr>
<tr>
<td>Hemangioblastomas</td>
<td>49 (22.0)</td>
<td>26 (20.8)</td>
<td>23 (23.5)</td>
</tr>
<tr>
<td>Astrocytomas</td>
<td>36 (16.1)</td>
<td>23 (18.4)</td>
<td>13 (13.3)</td>
</tr>
<tr>
<td>Cavernomas</td>
<td>52 (23.3)</td>
<td>28 (22.4)</td>
<td>24 (24.5)</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
2. Treatment Strategies for Each Tumor Histology

1) Intradural extramedullary tumors

Indication for surgery for schwannomas (Eden types 1–3) are presented in Fig. 1. Although the experts were more aggressive than the nonexperts (57% vs. 45% for surgery at the time of diagnosis or mild neurological symptom), a large divergence in indication for surgery was observed in both groups. Similar trends were observed in schwannomas (Eden type 4; Supplementary Fig. 2), meningiomas (Supplementary Fig. 3), and cauda equina tumors (Supplementary Fig. 4). For schwannomas (Eden type 4), 12 of 273 (4.4%) of the nonexperts answered, “Do not recommend surgery,” while none of the experts selected that answer. The answers to the questions on the extent of resection for intradural extramedullary tumors are presented in Table 3. The extent of resection and indication for surgery varied in both the groups. None of the expert answered, “Resection of the entire dura” or “Preserve the dura, no coagulation” in the response regarding the extent of resection for meningiomas.

2) Intramedullary tumors

Indication for surgery for ependymomas are illustrated in Fig. 2. In comparison to intradural extramedullary tumors, both the groups had a higher percentage of indication for surgery at the time of diagnosis (14% of the experts and 15% of the nonexperts). As in the case of intradural extramedullary tumors, the experts were more aggressive than the nonexperts, and differences in the indication for surgery were observed among both groups. Similar trends were observed in hemangioblastomas (Supplementary Fig. 5), astrocytomas (Supplementary Fig. 6), and cavernomas (Supplementary Fig. 7). Compared to other tumor histologies, a high rate of surgical recommendations at diagnosis was noted for astrocytomas (23% of the experts and 28% of the nonexperts), while the rate was lower for cavernomas (5.7% of the experts and 4% of the nonexperts). Some of

![Fig. 2. Indication for surgery of the experts (≥ 100 cases) and the nonexperts (< 100 cases) for healthy 50-year-old patients with ependymomas without any comorbidities. Data are presented as absolute and relative frequencies (%).](image-url)

Table 3. Preferences of the extent of resection for each intradural extramedullary tumors

<table>
<thead>
<tr>
<th>Intradural extramedullary tumor</th>
<th>Experts</th>
<th>Nonexperts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwannomas*</td>
<td>n = 34</td>
<td>n = 229</td>
</tr>
<tr>
<td>Resect the origin of the tumor, regardless of the results of nerve stimulation</td>
<td>7 (20.6)</td>
<td>30 (13.1)</td>
</tr>
<tr>
<td>Resect the origin of the tumor, if unresponsive to nerve stimulation</td>
<td>23 (67.6)</td>
<td>173 (75.5)</td>
</tr>
<tr>
<td>Perform subcapsular resection, regardless of the results of nerve stimulation</td>
<td>4 (11.8)</td>
<td>26 (11.4)</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>n = 35</td>
<td>n = 230</td>
</tr>
<tr>
<td>Resection of the entire dura</td>
<td>0 (0)</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>Shave off as much of the dura as possible</td>
<td>16 (45.7)</td>
<td>66 (28.7)</td>
</tr>
<tr>
<td>Preserve the dura and coagulate</td>
<td>19 (54.2)</td>
<td>155 (67.4)</td>
</tr>
<tr>
<td>Preserve the dura, no coagulation</td>
<td>0 (0)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Cauda equina tumors*</td>
<td>n = 35</td>
<td>n = 223</td>
</tr>
<tr>
<td>Resect the origin of the tumor, regardless of the results of nerve stimulation</td>
<td>6 (17)</td>
<td>34 (15.2)</td>
</tr>
<tr>
<td>Resect the origin of the tumor, if unresponsive to nerve stimulation</td>
<td>26 (74)</td>
<td>168 (75.3)</td>
</tr>
<tr>
<td>Perform subcapsular resection, regardless of the results of nerve stimulation</td>
<td>3 (8.6)</td>
<td>21 (9.4)</td>
</tr>
</tbody>
</table>

Values are presented as absolute and relative frequencies (%). The number of respondents differs for each tumor histology because each question was limited to those who perform surgery for each tumor at their own institution.

*Assuming no background disease such as neurofibromatosis.
the nonexperts did not recommend surgery for astrocytomas and cavernomas (3 of 273 [1.1%] and 3 of 273 [1.1%], respectively). In an additional question for cavernoma, the majority of participants in both the groups refrained from surgery at initial bleeding (54% of the experts and 53% of the nonexperts; Supplementary Table 2).

**DISCUSSION**

A survey of NSJ certified neurosurgeons revealed the frequency of surgery for each PSCT in 2020, providing a roadmap for tumor histology to prioritize for generating evidence in the field of neurosurgery. Furthermore, a divergence in the surgical strategy for PSCTs (i.e., surgical indication and extent of resection) was observed among both the experts and the nonexperts, and the experts and the nonexperts had different preferences in some areas. Duong et al.\(^7\) have reported that the number of new diagnoses of PSCTs in the United States (US) was 0.97 per 100,000. It should be noted that their study included only 3.3% of Asian/Pacific Islanders. However, if this rate is applied to the Japanese population,\(^10\) the estimated number of people diagnosed with PSCT per year will be 1,217. The Japan Neurosurgery Registry, which covers 74.2% of the annual predicted number of surgical cases, registered 1,200 (400 cases/yr) surgeries for extramedullary tumors, 798 (266 cases/yr) surgeries for intramedullary tumors, and 713 (238 cases/yr) surgeries for extramedullary tumors with extradural or paravertebral extension, from 2015 to 2017, that is 904 cases on average per year.\(^11\) Considering these estimated incidence rates and the number of registered surgeries, the present data in this study (802 cases in total) has the potential to be representative. Therefore, this study would provide valuable information on how evidence should be accumulated and what kind of education should be implemented on an academic society basis.

1. **Indications for Surgery**

In a study including 430 PSCTs in the US, meningiomas, ependymomas, and schwannomas were reported to be the most commonly treated PSCTs, each accounting for approximately 20% of all PSCTs.\(^5\) Another study including 2,355 PSCTs conducted in China in 1982 showed a different distribution, with meningiomas accounting for 14%, ependymomas for 4%, and schwannomas for 47%.\(^12\) The 151 cases reported in Korea had the largest proportion of schwannomas (37%), followed by meningiomas (24%) and ependymomas (12%).\(^13\) In this study, the percentage of surgeries per tumor histology according to all surgeries performed (802) was 129 (16%) for meningiomas, 86 (11%) for ependymomas, and 297 (37%) for schwannomas. This shows that surgical rates in Japan for meningiomas and ependymomas are lower and those for schwannomas are higher than those in the US, and these rates are similar to those in other Asian countries. While this discrepancy may be due to racial differences in tumor prevalence, it also suggests that indications for surgery, which are defined by various factors, including the rate of tumor growth, impact of symptoms, curability, and difficulty and invasiveness of surgery, may differ between Asia and US. Furthermore, this survey revealed that there is no consistency in the indications for surgery according to tumor histology even within the same country, regardless of surgeon's experience.

Regarding cavernoma as a specific example, 35% (108 of 305) of the participants recommended surgery at the initial bleeding, 53% (163 of 305) forwent surgery, and the rest did not consider the presence of bleeding as an indication for surgery (Supplementary Table 2). One of the key studies on the treatment of cavernoma was reported by Badhiwala in 2014, a meta-analysis of 632 patients, including approximately 10% conserved cases.\(^14\) They have reported valuable findings, such as an annual bleeding rate of 2.1% and an association between resection within 3 months of symptom onset and improved neurological outcome (odds ratio, 2.1). However, meta-analyses of small retrospective studies have limitations, such as the restricted precision and number of variables that can be used for analysis, and the small number of conserved cases. Existing evidence does not resolve the specialized clinical question of “Should we recommend resection at initial bleeding?” and clinical decisions are based on individual beliefs and experience, leading to divergence in indication for surgery.

There were some discrepancies in the indications for surgery between the experts and the nonexperts. Some of the nonexperts responded that they would not recommend surgery for schwannomas (Eden type 4), astrocytomas, and cavernomas, but none of the experts responded similarly. To establish whether surgery should be recommended for these tumors is challenging because it requires rigorous comparative studies with nonoperative groups. Expert opinion is meaningful considering the difficulty in generating high-quality evidence. Thus, we should raise awareness of the fact that these tumors may be indicated for surgery on the academic society basis.

2. **Extent of Resection**

Nakamura et al.\(^15\) have reported on 75 surgical cases of cervical schwannomas, of which 13 involved subtotal resections and
5 involved partial resections, with 2 recurrences each; further, 23% had postoperative denervation symptoms and 8% had residual symptoms. Kuo et al. noted that for acoustic neurinoma, the tumor is encapsulated, although the capsule is not sufficiently thick for the surgeon to recognize. These studies have suggested a trade-off between denervation and recurrence in the extent of tumor resection. Complete amputation of the schwannoma with anatomical nerve preservation should be the ideal surgical goal. Although nerve stimulation has been proposed as an adjunct device that could solve this problem, it is not sufficiently trusted, as 32% of the experts in this study did not refer to the results of nerve stimulation when determining the extent of schwannoma resection (Table 3). Electromyography has been reported to be useful for predicting denervation after total resection, and there is a need to establish a method for predicting denervation using nerve stimulation or a combination of these methods. Careful dissection of the origin of schwannomas is also crucial for surgeons.

Regarding the extent of resection for meningiomas, 2.2% of the nonexperts answered that they would resect the entire dura, while none of the experts provided the same answer. As reported by Naito et al. and Saiwai et al., meticulous Simpson grade II resection may be the first choice in actual clinical practice. A case of spinal cord herniation secondary to entire dura resection for meningioma has been reported. However, a previous study has reported that in approximately 30% of patients who underwent grade II resection, the tumor recurred after approximately 12 years. Thus, accumulating evidence from long-term observation of a larger number of cases that are appropriately treated by the meticulous Simpson grade II resection is necessary.

### 3. Generation of High-Quality Evidence

Data from large population-based sources have provided accurate descriptive statistics on benign and malignant central nervous system tumors. However, the establishment of an academic society-initiated disease-specific registry is essential to generate evidence to support specialized clinical decisions around PSCTs, such as the appropriate indication for surgery and the optimal extent of resection. Furthermore, there is an urgent need to train researchers who can manage the registry, design scientifically valid studies, and conduct valid analysis and interpretation.

Ideally, a randomized controlled trial is the best approach to examine the causal relationship between each clinical decision and prognosis. However, in PSCTs, the rarity and ethical considerations make it impractical to conduct randomized controlled trials. Therefore, the establishment of a comprehensive registry and high-quality observational studies using the data are required. Recently, target trial emulation, a method of causal inference using observational data, has been proposed, and high-quality observational studies using this method have been reported. A registry of all surgical cases would enable generating evidence on the extent of resection using these modern epidemiological methods. If a registry of all cases, including conservative cases, could be established, to generating evidence for surgical indication would be possible.

### 4. Study Limitations

This study had several limitations. First, the survey collected data for the year 2020, when coronavirus disease 2019 began to threaten the world. Hence, surgeries for patients with mild symptoms may have been counted in the following year, resulting in fewer surgeries than in previous years. Second, since it is a self-reported questionnaire survey, the accuracy of the information obtained is not guaranteed. Third, because the survey did not include case presentations with imaging information indicating localization and size of the tumor, the severity of the PSCTs evoked by the participants may have differed, leading to variability in the responses. Therefore, the observed divergence in surgical strategy may have been overestimated. Finally, there is the issue of generalization. This survey was intended for neurosurgeons, and many orthopedic surgeons did not respond. Additionally, although the response rate was high for a web-based survey, 34% of the participants did not respond. However, most of the experienced surgeons in Japan are likely to have participated in this study, so the negative impact might be minimal.

### CONCLUSION

In various PSCTs, the decision-making regarding the surgical indication and extent of tumor resection differed even among the experts. The least consensus was on the surgical issues such as the extent of resection of schwannomas, meningiomas, and cauda equina tumors, as well as the timing of cavernoma resection. These results indicate that the consensus on indications for surgery and extent of resection for each PSCT is insufficient and an evidence-based consensus is urgently needed. It is necessary to establish a detailed disease-specific registry of PSCTs managed by academic societies and high-quality observational studies conducted using data from these registries.
Surgical Strategies for Primary Spinal Cord Tumors

Hijikata Y, et al.

https://doi.org/10.14245/ns.2244686.343

NOTES

Supplementary Materials: Supplementary Tables 1-2 and Figs. 1-7 can be found via https://doi.org/10.14245/ns.2244686.343.

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Author Contribution:
Conceptualization: YH, SU, TY, DU, TT, MM, MH; Data curation: YH, SU, TY, DU, TE, TT, MM, MH; Formal analysis: YH; Methodology: YH, SU, TY, DU; Project administration: TT, MM, KH, MH; Visualization: YH, SU, MH; Writing - original draft: YH; Writing - review & editing: SU, TY, DU, TE, TT, MM, KH, MH.

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REFERENCES

ment of solitary nerve sheath tumors originating around the epiconus or conus medullaris: a retrospective case analysis based on neurological function. Neurosurg Rev 2018;41:275-83.
### Supplementary Table 1. English translation of the questionnaire with excerpts from the section on the results of this study (original in Japanese)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section 2 Basic information and affiliation</strong></td>
<td></td>
</tr>
<tr>
<td>Q2-1 Indicate the year of birth.</td>
<td></td>
</tr>
<tr>
<td>Q2-2 What is your gender?</td>
<td>Male, female</td>
</tr>
<tr>
<td>Q2-3 Indicate the year of clinical experience as a spine surgeon.</td>
<td></td>
</tr>
<tr>
<td>Q2-4 Select one answer that applies to your facility.</td>
<td>University hospital, public hospital, private hospital 200 &lt; beds, private</td>
</tr>
<tr>
<td></td>
<td>hospital 200–399 beds, private hospital ≥ 400 beds</td>
</tr>
<tr>
<td><strong>Section 3 Surgical experience for intradural primary spinal cord tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Q3-1 Indicate the number of surgeries for intradural primary spinal cord</td>
<td>No experience, 1–9 cases, 10–29 cases, 30–49 cases, 50–99 cases, more than</td>
</tr>
<tr>
<td>tumors you have performed as a primary surgeon.</td>
<td>100 cases</td>
</tr>
<tr>
<td>*Do not include teaching assistants or assistants.</td>
<td></td>
</tr>
<tr>
<td>*Do not include spinal cord lipomas.</td>
<td></td>
</tr>
<tr>
<td>*Include cauda equina tumors.</td>
<td></td>
</tr>
<tr>
<td>Q3-2 Indicate the number of surgeries for intradural primary spinal</td>
<td></td>
</tr>
<tr>
<td>cord tumors you have performed as a primary surgeon during the 1-year</td>
<td></td>
</tr>
<tr>
<td>period from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Do not include teaching assistants or assistants.</td>
<td></td>
</tr>
<tr>
<td>*Do not include spinal cord lipomas.</td>
<td></td>
</tr>
<tr>
<td>*Include cauda equina tumors.</td>
<td></td>
</tr>
<tr>
<td>Q3-3 Indicate the number of surgeries for ependymoma as a primary</td>
<td></td>
</tr>
<tr>
<td>surgeon during the year from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
<tr>
<td>Q3-4 Indicate the number of surgeries for hemangioblastoma as a primary</td>
<td></td>
</tr>
<tr>
<td>surgeon during the year from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
<tr>
<td>Q3-5 Indicate the number of surgeries for astrocytoma as a primary</td>
<td></td>
</tr>
<tr>
<td>surgeon during the year from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
<tr>
<td>Q3-6 Indicate the number of surgeries for cavernoma as a primary surgeon</td>
<td></td>
</tr>
<tr>
<td>during the year from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
<tr>
<td>Q3-7 Indicate the number of surgeries for schwannoma (nerve root origin)</td>
<td></td>
</tr>
<tr>
<td>as a primary surgeon during the year from January 1 to December 31, 2020</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
<tr>
<td>Q3-8 Indicate the number of surgeries for meningioma as a primary</td>
<td></td>
</tr>
<tr>
<td>surgeon during the year from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
<tr>
<td>Q3-9 Indicate the number of surgeries for cauda equina tumor as a primary</td>
<td></td>
</tr>
<tr>
<td>surgeon during the year from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
<tr>
<td>Q3-10 Indicate the number of surgeries for other tumors as a primary</td>
<td></td>
</tr>
<tr>
<td>surgeon during the year from January 1 to December 31, 2020.</td>
<td></td>
</tr>
<tr>
<td>*Confirm that the total of the breakdown of all 7 histologies matches</td>
<td></td>
</tr>
<tr>
<td>the total number of surgeries in Q3-2.</td>
<td></td>
</tr>
</tbody>
</table>

*Continued*
**Supplementary Table 1.** English translation of the questionnaire with excerpts from the section on the results of this study (original in Japanese) (Continued)

<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Answer options</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>If you suspect ependymoma, at what point do you recommend surgery?</td>
<td>At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery.</td>
</tr>
<tr>
<td></td>
<td>*Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Do not include myxopapillary ependymoma.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>If you suspect hemangioblastoma, at what point do you recommend surgery?</td>
<td>At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery.</td>
</tr>
<tr>
<td></td>
<td>*Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Assume no background disease such as von Hippel-Lindaw disease.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>If you suspect astrocytoma, at what point do you recommend surgery?</td>
<td>At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery.</td>
</tr>
<tr>
<td></td>
<td>*Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Include biopsy.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>If you suspect cavernoma, at what point do you recommend surgery?</td>
<td>At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery.</td>
</tr>
<tr>
<td></td>
<td>*Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td></td>
</tr>
<tr>
<td>7-2</td>
<td>For bleeding-onset cavernomas, at how many bleeds would you recommend surgery?</td>
<td>Initial bleeding, bleeding after the second, bleeding not considered</td>
</tr>
<tr>
<td></td>
<td>*Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Assume that the symptom caused by bleeding is mild numbness.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>If you suspect schwannoma (Eden type 1-3), at what point do you recommend surgery?</td>
<td>At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery.</td>
</tr>
<tr>
<td></td>
<td>*Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Assume no background disease such as neurofibromatosis.</td>
<td></td>
</tr>
<tr>
<td>8-2</td>
<td>If you suspect schwannoma (Eden type 4), at what point do you recommend surgery?</td>
<td>At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery.</td>
</tr>
<tr>
<td></td>
<td>*Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Assume no background disease such as neurofibromatosis.</td>
<td></td>
</tr>
<tr>
<td>8-3</td>
<td>If you suspect a schwannoma (nerve root origin) and perform surgery, to what extent do you resect the tumor?</td>
<td>Resect the origin of the tumor regardless of the results of nerve stimulation, resect the origin of the tumor if unresponsive to nerve stimulation, perform subcapsular resection regardless of the results of nerve stimulation.</td>
</tr>
<tr>
<td></td>
<td>*Assume no background disease such as neurofibromatosis.</td>
<td></td>
</tr>
</tbody>
</table>
**Supplementary Table 1.** English translation of the questionnaire with excerpts from the section on the results of this study (original in Japanese) (Continued)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section 9</strong> Surgical strategies for meningioma</td>
<td></td>
</tr>
<tr>
<td>Q9-1 If you suspect meningioma, at what point do you recommend surgery? Please select one answer that is closed to your preference. *Assume the patient to be a healthy 50-year-old without any comorbidities.</td>
<td>At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery</td>
</tr>
<tr>
<td>Q9-2 If you suspect a meningioma and perform surgery, to what extent do you resect the tumor?</td>
<td>Resection of the entire dura, shave off as much of the dura as possible, preserve the dura and coagulate, preserve the dura no coagulation</td>
</tr>
</tbody>
</table>

| **Section 10** Surgical strategies for cauda equina tumor | |
| Q10-1 If you suspect cauda equina tumor, at what point do you recommend surgery? Please select one answer that is closed to your preference. *Assume the patient to be a healthy 50-year-old without any comorbidities. *Include myxopapillary ependymoma. | At the time of diagnosis, mild neurological symptoms (e.g., mild numbness), moderate neurological symptoms (e.g., motor paralysis), worsening imaging findings, progressive neurological symptoms, do not recommend surgery |
| Q10-2 If you suspect a cauda equina tumor and perform surgery, to what extent do you resect the tumor? *Assume no background disease such as neurofibromatosis. | Resect the origin of the tumor regardless of the results of nerve stimulation, resect the origin of the tumor if unresponsive to nerve stimulation, perform subcapsular resection regardless of the results of nerve stimulation |
Supplementary Table 2. Indication for surgery in bleeding-onset cavernomas

<table>
<thead>
<tr>
<th>Variable</th>
<th>Experts (n = 35)</th>
<th>Nonexperts (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial bleeding</td>
<td>12 (34)</td>
<td>96 (36)</td>
</tr>
<tr>
<td>Bleeding after the second</td>
<td>19 (54)</td>
<td>144 (53)</td>
</tr>
<tr>
<td>Bleeding not considered</td>
<td>4 (11)</td>
<td>30 (11)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
Supplementary Fig. 1. Flowchart of the study participants.
NSJ, Neurospinal Society of Japan.
Supplementary Fig. 2. Indication for surgery of the experts (≥ 100 cases) and the nonexperts (< 100 cases) for healthy 50-year-old patients with schwannomas (Eden type 4) without any comorbidities. Data are expressed as absolute and relative frequencies (%).
Supplementary Fig. 3. Indication for surgery of the experts (≥ 100 cases) and the nonexperts (< 100 cases) for healthy 50-year-old patients with meningiomas without any comorbidities. Data are expressed as absolute and relative frequencies (%).
Supplementary Fig. 4. Indication for surgery of the experts (≥ 100 cases) and the nonexperts (<100 cases) for healthy 50-year-old patients with cauda equina tumors without any comorbidities. Data are expressed as absolute and relative frequencies (%).
Supplementary Fig. 5. Indication for surgery of the experts (≥ 100 cases) and the nonexperts (< 100 cases) for healthy 50-year-old patients with hemangioblastomas without any comorbidities. Data are expressed as absolute and relative frequencies (%).
Supplementary Fig. 6. Indication for surgery of the experts (≥100 cases) and the nonexperts (<100 cases) for healthy 50-year-old patients with astrocytomas without any comorbidities. Data are expressed as absolute and relative frequencies (%).
Supplementary Fig. 7. Indication for surgery of the experts (≥100 cases) and the nonexperts (<100 cases) for healthy 50-year-old patients with cavernomas without any comorbidities. Data are expressed as absolute and relative frequencies (%).
Commentary on “Sacral Nerves Reconstruction After Surgical Resection of a Large Sacral Chordoma Restores the Urinary and Sexual Function and the Anal Continence”

Chordoma is a rare tumor originating from the residue of the notochord which usually occurs in the sacrum, skull base and spine, and has the characteristics of local invasiveness and poor prognosis. The clinical onset of chordoma is usually insidious and the symptoms are atypical. Therefore, at the time of diagnosis, the tumor has grown to a large volume, often involving important nerves and blood vessels, and has a tendency to recur and metastasize, bringing difficulties and challenges to surgical resection. Nowadays, the options of treatment for sacral chordoma include surgical resection, radiotherapy, chemotherapy, targeted drug therapy, and so on. However, surgery is still the main management modality for sacral chordoma.

In the paper, the authors described a new technique, which is used for the first time in the field of sacral chordoma resection, that is, bulk resection of sacral chordoma, and then sacral nerve reconstruction with peripheral nerve transplantation. The 54-year-old patient diagnosed with sacral chordoma, the authors marked the nerve roots in the proximal and distal part of the lesion with sutures, separated the proximal and distal sacral nerves, and resected the chordoma involving bilateral lower S1 sacral nerves (14 cm × 8 cm × 7 cm) through the posterior approach. After operation, the sural nerve of the bilateral leg was grafted, and the epineural microsuture technique was used to connect the stump and the distal end of S2-S3-S4. During the follow-up of 3 months, 6 months, and 1 year after operation, the bilateral limb discomfort of the patients began to improve, the residue after micturition gradually decreased to basically normal, the bladder could be emptied spontaneously, and the sensitivity and sexual function of Sellar and genital areas were gradually restored.

The surgical treatments of sacral chordoma were the mass resection of extensive surgical margin. Previous clinical trials have shown that negative surgical margin was the single most important predictor of tumor recurrence and long-term survival. Although recurrent sacral chordoma can be performed by revision surgery, its surgical risks and recurrent mortality were high. In a meta-analysis of 436 patients, the recurrence rate in the wide margin group was lower than that in the insufficient margin group, but the recurrence mortali-
In this study, postoperative sacral nerve reconstruction can make up for the intestinal and bladder dysfunction caused by total resection of the sacral nerve. But the autologous nerve transplantation used by the authors also had many disadvantages, such as increased surgical trauma, donor skin scar, sensory disturbance, nerve structure mismatch, and so on, which limited its clinical application to a certain extent. Therefore, the nerve transplantation is more suitable for the reconstruction of sacral nerve in cases where mass and sacral nerve have to be removed as a whole. The surgical strategy of transferring new axon sources was to restore the function of denervated bladder after nerve injury has never been used in the clinical environment, and it was obvious that the authors have taken an important step in the field of sacral nerve repair. Zheng et al. reported that 5 cases of sacral nerve root anastomosis were performed after block resection of sacral tumor, and only 2 cases showed improvement in limb, bladder and intestinal function. However, in the author's article, only one case of functional improvement after nerve transplantation after tumor resection was described, which may be related to the surgeon's experience, body healing ability etc. It does not have extensive maneuverability and outstanding representativeness. We need more clinical cases to support this method and conduct further research in the field of human nerve repair and reconstruction. In the clinical application of nerve transplantation and reconstruction, the surgeons, the patients and patients' families urgently hoped that the surgery could greatly improve the emptying and storage function of the bladder, so in the absence of a standard scoring system for the recovery of sacral nerve function, the patients may be likely to exaggerate the improvement of postoperative function, and the surgeons may overestimate the success of the operation. Based on this, it was found that the authors lacked a standardized scale for preoperative and postoperative evaluation of sacral nerve function. In addition, the postoperative follow-up time of the case was too short, which requires at least 2–3 years of long-term follow-up and evaluation to rule out the possibility of being overinterpreted as a permanent good index.

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

**REFERENCES**


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Letter to the Editor

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See the article "Sacral Nerves Reconstruction After Surgical Resection of a Large Sacral Chordoma Restores the Urinary and Sexual Function and the Anal Continence" via https://doi.org/10.14245/ns.2142724.362.

See the commentary on "Sacral Nerves Reconstruction After Surgical Resection of a Large Sacral Chordoma Restores the Urinary and Sexual Function and the Anal Continence" via https://doi.org/10.14245/ns.2244872.436.

Dear Editor,

We appreciate the interest in our article “Sacral nerves reconstruction after surgical resection of a large sacral chordoma restores the urinary and sexual function and the anal continence.”1 The sacrifice of sacral nerves is often a necessary step if a benefit is to be given to the progression free survival rate, which results in a severe burden and deterioration of quality of life for patients with sacral chordoma.

The authors of the commentary emphasize that the technique we have adopted opens up a new treatment perspective and is an important technical innovation.

We welcome the suggestion of using standardization of sphincter function, which we will adopt in future studies in this regard.2

Regarding the possibility that the patient may have overestimated improvements, we can state that we have instrumental data such as electromyography and, most importantly, rectal manometry and uroflowmetry that demonstrate the absence of significant postminctional residual (which was present after surgery and required intermittent catheterization) and the reappearance of effective anal sphincter tone. At the time of writing, the patient has passed 2 years since surgery and is continuing follow-up clinical and instrumental checks that show no new findings, and the clinical status is characterized by an excellent quality of life.

In conclusion, we welcome the opportunity to use sphincter disability scales recognized by the scientific community, with the goal of verifying and validating this reconstructive technique.

Conflict of Interest: The author has nothing to disclose.

REFERENCES

Instructions for Contributors

Revised: January 1, 2022

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3) Manuscript format may vary in review articles. There should be no more than 100 references in review articles.
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1) Objective, Methods, Results, and Conclusion sections should be included in abstract of clinical or laboratory research, but are not necessary in other types of studies.
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4) A list of key words, with a minimum of two items and maximum of six items, should be included at the end of the abstract.
5) The selection of Key Words should be based on Medical Subject Heading (MeSH) of Index Medicus and the web site (http://www.nlm.nih.gov/mesh/MBrowser.html).

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The introduction should address the purpose of the article concisely, and include background reports mainly relevant to the purpose of the paper. Detailed review of the literature should be addressed in the discussion section.

5. Materials and Methods
1) The article should record research plans, objective, and methods in order, as well as the data analysis strategies and control of bias in the study. Enough details should be furnished for the reader to understand the method(s) without reference to another work in the study described.
2) When reporting experiments with human subjects, the authors must document the approval received from the local Institutional Review Board. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by the research board of the affiliated institution or such. Approved number of IRB must be noted.
3) Photographs disclosing patients must be accompanied by a signed release form from the patient or family permitting publication.
4) Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

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1) The authors should logically describe their results of observations and analyses performed using methodology given in the previous section and provide actual data.
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3) While an effort should be made to avoid overlapping descriptions by Tables and by main text, important trends and points in the Table should be described in the text.

7. Discussion
Discussions about the findings of the research and interpretations in relation to other studies are made. It is necessary to emphasize the new and critical findings of the study, not to repeat the results of the study presented in the previous sections. The meaning and limita-
tion of observed facts should be described, and the conclusion should be related to the objective of the study only when it is supported by the results of the research.

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The conclusion section should include a concise statement of the major findings of the study in accordance with the study purpose.

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Do not link the references to the text. Cite unpublished data, such as papers submitted but not yet accepted for publication or personal communications, in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at https://www.nlm.nih.gov/archive/20130415/tsd/serials/lji.html. Sample references are given below:

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- **Entire book**

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1) Tables should be created using the table formatting and editing feature of Microsoft Word. The title of the table must be noted. Tables cannot be submitted in a picture format.
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1) Figures should have resolution of 300 dpi or above and should be submitted individually (Namely, if Figure 1 is divided into A, B, C, and D, do not combine them into one, but submit each of them separately). Allowable file format for figures are JPG or TIF (TIFF) only.
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Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Minimum standards are as follows: First, it shall publish a correction notice as soon as possible, detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing; Second, it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; Third, it shall archive all prior versions of the article. This archive can be either directly accessible to readers; and Fourth, previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

8. Handling Complaints and Appeals

The policy of the journal is primarily aimed at protecting the authors, reviewers, editors, and the publisher of the journal. If not described below, the process of handling complaints and appeals follows the guidelines of the Committee of Publication Ethics available from: https://publicationethics.org/appeals

Who complains or makes an appeal?

Submitters, authors, reviewers, and readers may register complaints and appeals in a variety of cases as follows: falsification, fabrication, plagiarism, duplicate publication, authorship dispute, conflict of interest, ethical treatment of animals, informed consent, bias or unfair/inappropriate competitive acts, copyright, stolen data, defamation, and legal problem. If any individuals or institutions want to inform the cases, they can send a letter to editor through https://www.e-neurospine.org/about/contact.php. For the complaints or appeals, concrete data with answers to all factual questions (who, when, where, what, how, why) should be provided.

Who is responsible to resolve and handle complaints and appeals?

The Editor, Editorial Board, or Editorial Office is responsible for them.

What may be the consequence of remedy?

It depends on the type or degree of misconduct. The consequence of resolution will follow the guidelines of the Committee of Publication Ethics (COPE).

9. Postpublication Discussions and Corrections

The postpublication discussion is available through letter to the editor. If any readers have a concern on any articles published, they can submit letter to the editor on the articles. If there founds any errors or mistakes in the article, it can be corrected through errata, corrigenda, or retraction.

10. Policies on data sharing and reproducibility

Until 2020, authors will be encouraged to share their data openly, but starting in 2021, they will be mandated to do so. The related regulation follows the open data sharing policy outlined below.

1) Open data sharing policy

For clarification on result accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository, for example, Harvard Dataverse (https://dataverse.harvard.edu/) after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data, authors should contact the editorial office.

2) Clinical data sharing policy

This journal follows the data sharing policy described in “Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors” (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018 manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing state-
Table. Examples of Data Sharing Statements That Fulfill These ICMJE Requirements*

<table>
<thead>
<tr>
<th>Will individual participant data be available (including data dictionaries)?</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
<th>Example 4</th>
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<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>What data in particular will be shared?</td>
<td>All of the individual participant data collected during the trial, after deidentification.</td>
<td>Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).</td>
<td>Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).</td>
<td>Not available</td>
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<td>When will data be available (start and end dates)?</td>
<td>Immediately following publication. No end date.</td>
<td>Beginning 3 months and ending 5 years following article publication.</td>
<td>Beginning 9 months and ending 36 months following article publication.</td>
<td>Not applicable</td>
</tr>
<tr>
<td>With whom?</td>
<td>Anyone who wishes to access the data.</td>
<td>Researchers who provide a methodologically sound proposal.</td>
<td>Investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.</td>
<td>Not applicable</td>
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<tr>
<td>For what types of analyses?</td>
<td>Any purpose.</td>
<td>To achieve aims in the approved proposal.</td>
<td>For individual participant data meta-analysis.</td>
<td>Not applicable</td>
</tr>
<tr>
<td>By what mechanism will data be made available?</td>
<td>Data are available indefinitely at (Link to be included).</td>
<td>Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third party website (Link to be included).</td>
<td>Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University’s data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (Link to be provided).</td>
<td>Not applicable</td>
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* These examples are meant to illustrate a range of, but not all, data sharing options.

As described below. Clinical trials that begin enrolling participants on or after January 1, 2019 must include a data sharing plan in the trial’s registration. The ICMJE’s policy regarding trial registration is explained at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record. All of the authors of research articles that deal with interventional clinical trials must submit data sharing plan of example 1 to 4 in Table 1. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site. For the policies on the research and publication ethics not stated in this instructions, International standards for editors and authors (https://publicationethics.org/resources/resources-and-further-reading/international-standards-editors-and-authors) can be applied.

All correspondences, business communications and manuscripts should be mailed to:

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   If there are conflicts of interest, authors should state their content on the title page of the manuscript.

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   1) Formats and contents of the manuscripts are checked by corresponding author. □ Yes / □ No
   2) All manuscripts should be written in English. Manuscripts may be no longer than 5,000 English words for original articles except for references, tables, and figures. □ Yes / □ No
   3) Manuscripts should be prepared in the following orders.
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   4) "Editing in English is done prior to submission of a manuscript." □ Yes / □ No

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