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Therapeutic Strategies for Intervertebral Disc Degeneration 2022

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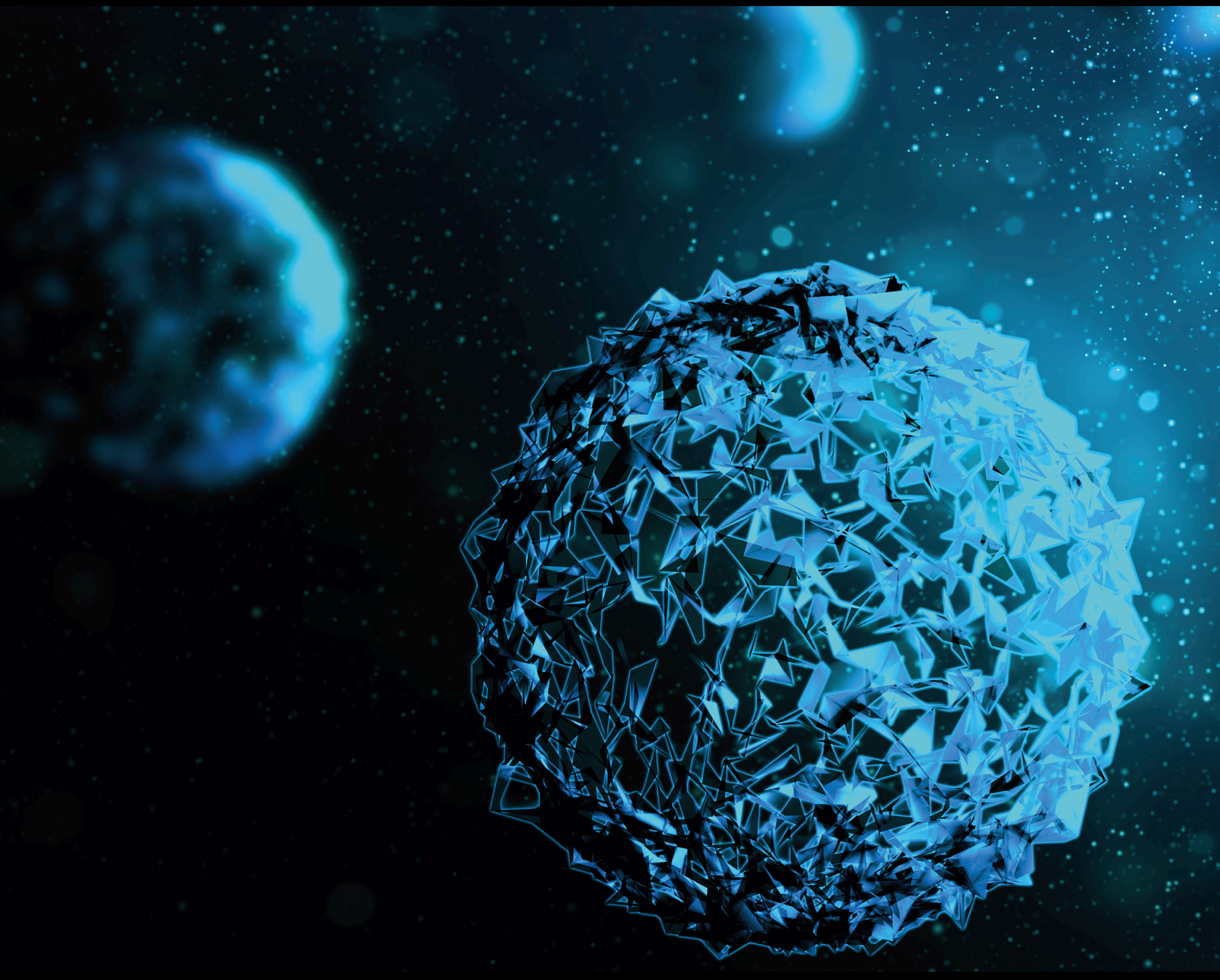

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Research Article

Network Pharmacology-Based Dissection of the Mechanism of Drynariae Rhizoma for Low Back Pain

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Objective. To explain the potential mechanisms of Drynariae Rhizoma (DR) in the treatment of low back pain (LBP). *Design*. Network pharmacology was used to reveal the potential mechanisms including collecting the active ingredients of DR, analyzing the common gene targets of LBP and DR, constructing protein-protein interaction (PPI) network, collecting protein classification, performing Gene Ontology (GO) functional analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, and verifying significant gene targets. *Results*. 234 different gene targets and 18 active compounds altogether were obtained. AKT1, VEGFA, and HIF1A were deemed to be major gene targets based on the degree values. According to GO analysis, steroid metabolic process involved 42 (18.10%) potential therapeutic LBP targets, neuronal cell body involved 24 (10.30%) potential therapeutic LBP targets, and protein serine/threonine kinase activity involved 28 (12.02%) potential therapeutic LBP targets in biological process (BP), cellular component (CC), and molecular function (MF), respectively. According to KEGG and pathway interaction analyses, the PI3K-Akt signaling pathway involved 34 (15.89%) potential therapeutic LBP targets, and PI3K-Akt signaling pathway played a significant role in the treatment of LBP. The mRNA expression levels of AKT1 and HIF1A were upregulated in healthy nucleus pulposus (NP) tissue than in degenerative NP tissue. In contrast, the mRNA expression level of VEGFA was downregulated in healthy NP tissue than in degenerative NP tissue. *Conclusions*. In this study, we identified a potential relationship between LBP and DR in this work, as well as a synergistic mechanism of DR in the treatment of LBP, which serves as a benchmark for further in vivo and in vitro research.

1. Introduction

Low back pain (LBP) is a very common and high-impact health problem all over the world. The lifetime prevalence of LBP is 84%, the prevalence of chronic LBP is approximately 23%, and 11% to 12% of people are disabled due to LBP [1, 2]. The researches have shown that low back pain (LBP) is the second most commonly diagnosed pain condition in the United States, and although most people experience pain resolution in the acute phase, an estimated 40% experience persistent pain [3, 4]. Two-thirds of adults will suffer from low back pain and its associated disorders at some point in their lives [5]. LBP is now clearly recognized as a major public health problem. Symptoms of LBP are the second most common complaint after the common cold. In 70% of cases, LBP has no apparent etiology or well-known pathogenesis [5, 6]. Conventional treatments including drug therapy and surgery have shown some effects. Likewise, these treatments also brought some adverse effects. For example, some surgical treatments experienced failure. Even worse, some people will repeat surgical interventions at a rate of 13.4% to 32% [2]. Under the circumstances, better treatments should be widely applied to clinics.

Traditional Chinese medicine (TCM) is based on the fundamental theory of balance between yin and yang and five basic elements [4]. TCM has been widely used to treat

numerous diseases such as intervertebral disc degenerative diseases [7]. Acupuncture and Chinese herbal medicine are frequently used to successfully treat pain-related disorders such as neck pain and low back pain. Due to its low risk of side effects, safety, and effective results, Drynariae Rhizoma (DR), a type of Chinese herbal medicine (gusuibu), is frequently used in the treatment of osteoporosis and fracture [8, 9]. The clinical outcomes have confirmed that naringin, a main active component of the DR, can alleviate the symptoms of low back pain (LBP). What is more, basic studies have shown that naringin enhanced cell proliferation by inhibiting TNF-α and MMP-3 and raising the expression of collagen II and aggrecan. This substance may also reduce local inflammation, which would slow intervertebral disc degeneration. The research also indicated that naringin may become an alternative therapeutic agent for pain associated with disc degeneration such as NP and LBP [10]. With the development of network pharmacology, we believe that multiple targets of diseases can be regulated by various ingredients contained in an herb [11]. Nonetheless, no research on the mechanisms of DR in the management of LBP has been published.

Network pharmacology has played a significant role in modern TCM research, which has provided powerful theoretical evidence for the discovery of new therapeutic targets of TCM [12]. Our study will research the new therapeutic targets of DR for LBP and provide new theoretical support for DR in the treatment of LBP.

2. Method

2.1. Screening for Active Ingredients of Drynariae Rhizoma. We screened for the active ingredients of Drynariae Rhizoma by searching for the database of traditional Chinese medicine system and analyzing platforms (TCMSP) [13] on the basis of ADME (absorption, distribution, metabolism, and excretion) criterion, which includes chemicals, targets and drug-target networks, associated drug-target-disease networks, etc. According to TCMSP, oral bioavailability (OB) $\geq 30\%$ and druglikeness (DL) ≥ 0.18 are used to assess the potential active ingredients of DR in the treatment of LBP.

2.2. Searching the Chemical Structure and Gene Target of Active Ingredients. We downloaded the chemical structures of the active ingredients of DR from TCMSP or PubChem [14] and stored them in mol2 format. The PubChem database is the largest collection of freely accessible chemical information in the world. The related SMILES of these potential active ingredients obtained from TCMSP and PubChem were imported into the SwissTargetPrediction database [15] to gain gene target.

2.3. Gene Target Prediction between Drynariae Rhizoma and Low Back Pain. There were several databases being used to search for the gene targets associated with LBP, including Genecards database [16], DisGeNET database [17], and OMIM database [18]. Whereafter, we would delete the duplicate and wrong gene targets. Last but not least, we used the Venny tool (http://bioinfogp.cnb.csic.es/tools/venny/index.html) to obtain the common gene targets of LBP and DR.

2.4. Building the Ingredient-Target Network of Drynariae Rhizoma. The Cytoscape software (version 3.7.1) was used to construct the ingredient-target network of DR with the utilization of the obtained common gene targets. The Cytoscape software is an open source software platform for visualizing molecular interaction networks and biological pathways and integrating these networks with annotations, gene expression profiles, and other state data [19].

2.5. Constructing Protein-Protein Interaction (PPI) of Drynariae Rhizoma. We used the STRING database to construct protein-protein interaction of the common gene targets of LBP and DR. The STRING database (http://string-db.org/, version 11.0) is based on completing a comprehensive and objective global network. Many available sources of protein-protein interaction information have been collected and integrated into the STRING database. The latest version (11.0) of the STRING database covers more than 5000 organisms [20]. The specific procedure was followed. Firstly, the common protein targets of LBP and DR were imported into the STRING database. Homo sapiens was selected, and the highest confidence was set 0.9 in the minimum required interaction score. Then, the TSV format of the results was exported. Meanwhile, these results were imported into the Cytoscape software (version 3.7.1) to analyze the protein-protein interaction. Finally, the network results of protein-protein interaction were exported.

2.6. Gene Ontology (GO) Functional Analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis. To analyze the common gene targets of LBP and DR, we made use of Gene Ontology (GO) functional analysis and identified the important signaling pathway through Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The processes above were performed with the help of the Metascape database (http://metascape.org). Metascape is a database providing a comprehensive gene list annotation and analysis resource. The database contains functional enrichment, interactome analysis, and gene annotation [21]. The processes of analysis were followed. First, the common gene targets of NP and DR were imported into the Metascape database. Homo sapiens was chosen, and we clicked on the custom analysis. Second, the P value was set to 0.01, and the min enrichment was set to 5. In particular, we selected GO biological processes (BP), GO cellular components (CC), GO molecular functions (MF), and KEGG pathway. Finally, we clicked the enrichment analysis and downloaded the data of GO and KEGG pathways. The GraphPad Prism 7.0 software was used to process the data for GO analysis, and an online analysis tool (http://www.aipufu.com/index.html) was used to process the data for KEGG pathways into bubble charts.

2.7. Verification of the Effect of DR. We obtained nucleus pulposus (NP) tissues from two patients with low back pain. According to the Pfirrmann classification score of magnetic resonance imaging, relatively healthy NP tissue was grades I~II, and degenerated NP tissue was grades III~V [22, 23].

Table 1: Active ingredients of Drynariae Rhizoma.

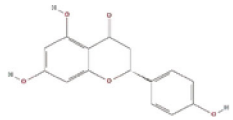
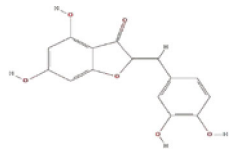
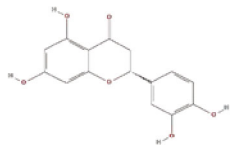
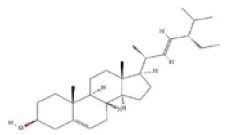
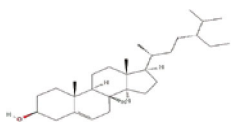
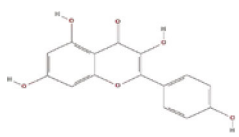
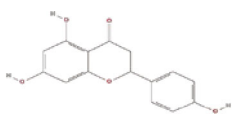
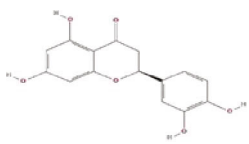
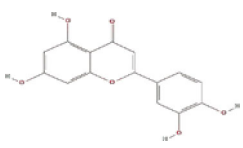
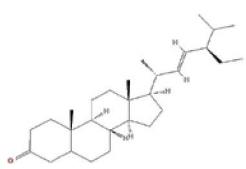
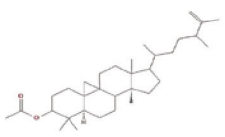
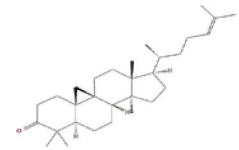
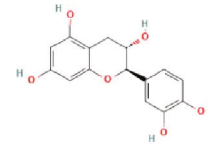
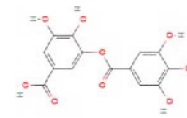
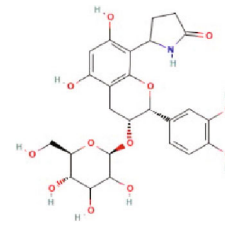
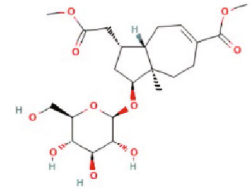
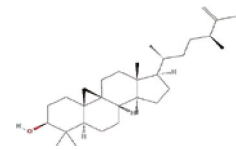
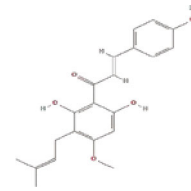
Molecule ID	Molecule name	Structure	OB (%)	DL
MOL001040	(2R)-5,7-Dihydroxy-2-(4-hydroxyphenyl) chroman-4-one		42.36	0.21
MOL001978	Aureusidin		53.42	0.24
MOL002914	Eriodyctiol (flavanone)		41.35	0.24
MOL000449	Stigmasterol		43.83	0.76
MOL000358	Beta-sitosterol		36.91	0.75
MOL000422	Kaempferol		41.88	0.24
MOL004328	Naringenin		59.29	0.21
MOL005190	Eriodictyol		71.79	0.24
MOL000006	Luteolin		36.16	0.25
MOL009061	22-Stigmasten-3-one		39.25	0.76
MOL009063	Cyclolaudenol acetate		41.66	0.79

Table 1: Continued.

Molecule ID	Molecule name	Structure	OB (%)	DL
MOL009075	Cycloartenone		40.57	0.79
MOL000492	(+)-Catechin		54.83	0.24
MOL000569	Digallate		61.85	0.26
MOL009078	Davallioside A_qt		62.65	0.51
MOL009087	marioside_qt		70.79	0.19
MOL009076	Cyclolaudenol		39.05	0.79
MOL009091	Xanthogalenol		41.08	0.32

The Pfirrmann grades for these two NP tissues were grade II and grade IV, respectively. NP tissues were harvested under sterile conditions and immediately sent to the laboratory. Written informed consent was obtained from each patient. The study was approved by the Ethics Committee of Hubei Provincial Hospital of Traditional Chinese Medicine. The ethics number was HBZY2022-C03-02.

2.8. Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) Analysis. We extracted RNA from nucleus pulposus tissue as well as cells using TRIzol reagent (Ambion, Foster City, CA, USA) following the manufacturer's instructions. We apply PrimeScript RT Master Mix (Takara Bio, Shiga, Japan) to obtain first-strand cDNA of whole RNA, and for qPCR detection, we used One-Step SYBR PrimeScript RT-PCR Kit (Takara Bio). The primer sequences were designed as follows: AKT1: forward: 5′-TGGACTACCTG CACTCGGAGAA-3′, reverse: 5′-GTGCCGCAAAAGGT CTTCATGG-3′; VEGFA: forward: 5′-TTGCCTTGCTG CTCTACCTCCA-3′, reverse: 5′-GATGGCAGTAGCTG CGCTGATA-3′; H1F1A: forward: 5′-TATGAGCCAGA AGAACTTTTAGGC-3′, reverse: 5′-CACCTCTTTTGGCA AGCATCCTG-3′; and GAPDH: forward: 5′-TCCACT

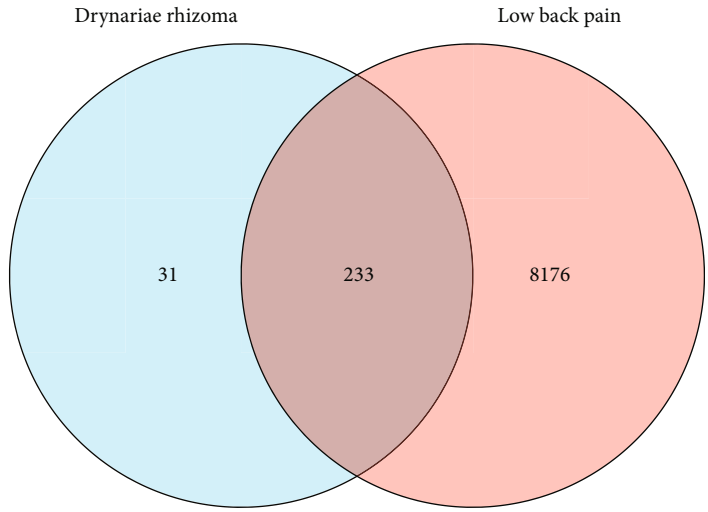


Figure 1: Venn diagram of common gene targets of LBP and DR.

GGCGTCTTCACC-3′, reverse: 5′-GGCAGAGATGATGA CCCTTTT-3′. We used $2^{-\Delta\Delta Ct}$ way to count these relative expression standards.

2.9. Statistical Analysis. Data are presented as mean ± standard deviation (SD). Statistical analysis was performed by the SPSS 26.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 7.0 software. Each experiment was performed at least three times. Multiple group outcomes were tested by one-way analysis of variance (ANOVA) test followed by Tukey's post hoc test. The Student's *t*-test was applied to analyze the two sets of parameters. Statistical significance was $P < 0.05$.

3. Results

3.1. Active Ingredients of Drynariae Rhizoma. We obtained 71 ingredients of DR and 18 active ingredients from TCMSP. After excluding the invalid ingredients including (+)-catechin, (2R)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one,22-stigmasten-3-one, and beta-sitosterol_qt, we finally selected 18 active ingredients of DR including (2R)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one, aureusidin, eriodyctiol (flavanone), stigmasterol, beta-sitosterol, kaempferol, naringenin, (+)-catechin, eriodictyol, digallate, luteolin, 22-stigmasten-3-one, Cyclolaudenol acetate, cycloartenone, cyclolaudenol, davallioside A_qt, marioside_qt, and xanthogalenol. The basic information of 18 active ingredients is shown in Table 1.

3.2. Gene Target Prediction. We obtained 264 gene targets associated with DR and 8409 gene targets associated with LBP after excluding invalid and duplicate gene targets. A total of 233 common gene targets are shown in Figure 1.

3.3. Ingredient-Target Network of Drynariae Rhizoma. The Cytoscape software was used to construct the ingredient-target network as shown in Figure 2. The orange oval nodes are 15 selected active ingredients of DR, and the light blue rectangle nodes are the common gene targets of LBP and DR. The network contains 264 nodes. According to the network, DR has multicomponent and multitarget characteristics due to the presence of multiple relationships between the active ingredient and the gene target.

3.4. Protein-Protein Interaction of Drynariae Rhizoma String. The network of PPI analyzed 231 common protein targets as shown in Figure 3. These nodes represent different proteins, and the size and color of these nodes represent different values of degree. The greater the value of degree, the larger these nodes and brighter the color. According to degree values, the three significant protein targets were AKT1, VEGFA, and HIF1A as shown in Table 2.

3.5. GO Functional Analysis and KEGG Pathway Enrichment Analysis. After GO functional analysis of the common gene targets of DR and LBP through the Metascape database ($P < 0.05$), we obtained a total of 2947 enriched results, including 2478 results of biological processes (BP), 111 results of cellular components (CC), and 221 results of molecular functions (MF). We selected the top several enrichment results as shown in Figure 4. In the enrichment results of BP (Figure 4), we found that steroid metabolic process involved 42 (18.10%) potential therapeutic LBP targets, organic anion transport involved 39 (16.81%) potential therapeutic LBP targets, regulation of small molecule metabolic processes and regulation of lipid metabolic process involved 38 (16.38%) potential therapeutic LBP targets, and so on. In the enrichment results of CC (Figure 5), we found that neuronal cell body involved 24 (10.30%) potential therapeutic LBP targets, nuclear envelope and vesicle lumen involved 17 (7.30%) potential therapeutic LBP targets, cytoplasmic vesicle lumen involved 16 (6.87%) potential therapeutic LBP targets, and so on. In the enrichment results of MF (Figure 6), protein serine/threonine kinase activity involved 28 (12.02%) potential therapeutic LBP targets, protein tyrosine kinase activity involved 21 (9.01%) potential therapeutic LBP targets, steroid hormone receptor activity involved 19 (8.15%) potential therapeutic LBP targets, nuclear receptor activity and transcription factor activity, direct ligand regulated sequence-specific DNA binding and endopeptidase

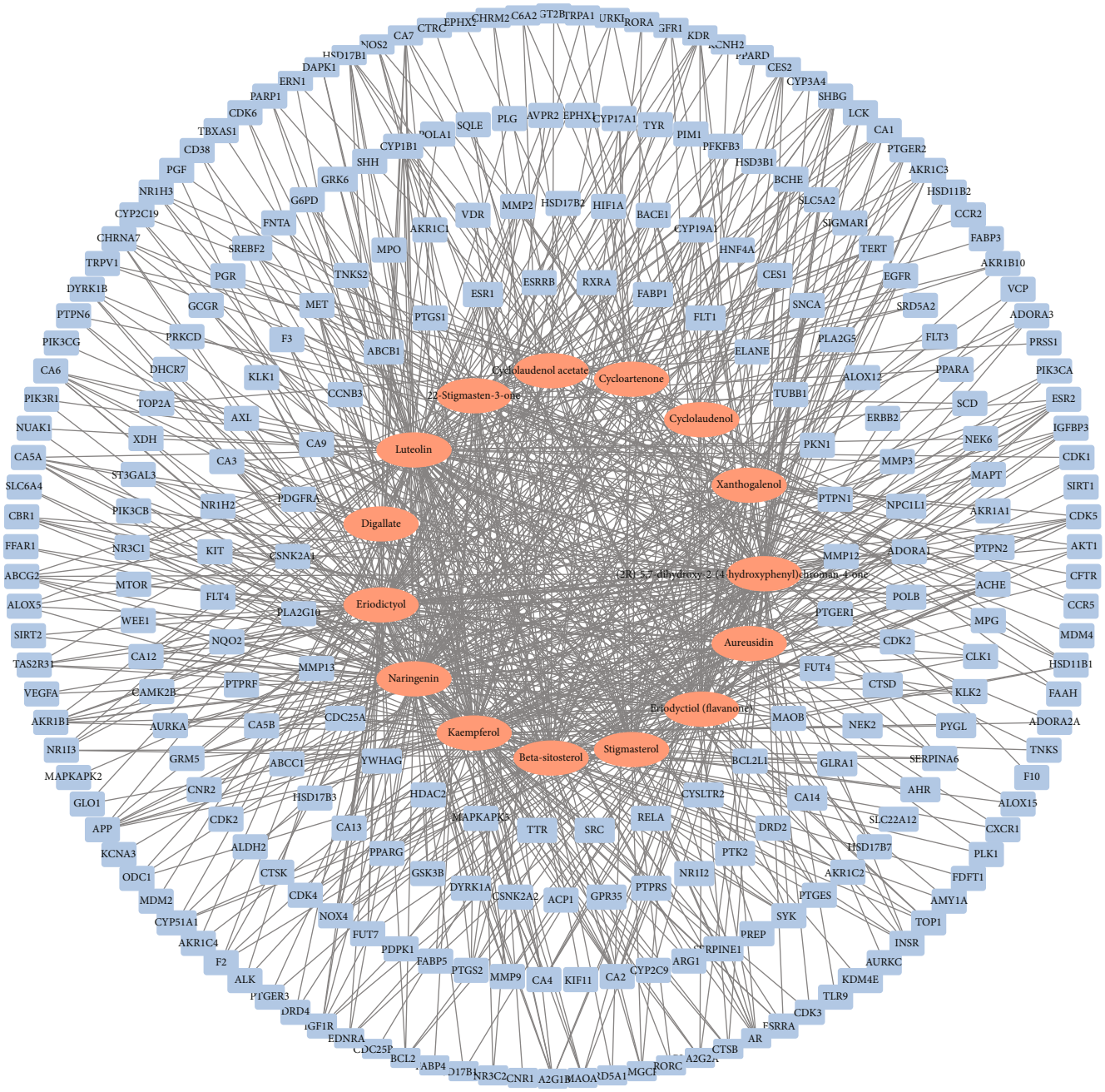


Figure 2: Ingredient-target network of Drynariae Rhizoma. Note: the orange oval nodes represent active ingredients of DR, and the light blue rectangle nodes are the common gene targets of LBP and DR.

activity involved 18 (7.72%) potential therapeutic LBP targets and so on.

After KEGG pathway enrichment analysis of the common gene targets of DR and LBP through the Metascape database ($P < 0.05$), we obtained a total of 136 enriched results. We selected the top 10 enrichment results as shown in Figure 7. According to the results of bubble chart, PI3K-Akt signaling pathway involved 34 (15.89%) potential therapeutic LBP targets, microRNAs in cancer and proteoglycans in cancer; Ras signaling pathway involved 23 (10.75%) potential therapeutic LBP targets; neuroactive ligand-receptor interaction involved 22 (10.28%) potential therapeutic LBP targets; prostate cancer, Rap1 signaling pathway, Alzheimer disease, and MAPK signaling pathway involved 20 (9.35%) potential therapeutic LBP targets and so on.

3.6. Validation of the Significant Protein Targets. PCR analysis was used to verify the mRNA expression levels of these 3 significant protein targets. The mRNA expression levels of AKT1 and HIF1A were upregulated in healthy NP tissue than in degenerative NP tissue. On the contrary, the mRNA expression level of VEGFA was downregulated in healthy NP tissue than in degenerative NP tissue. These results are shown in Figure 8.

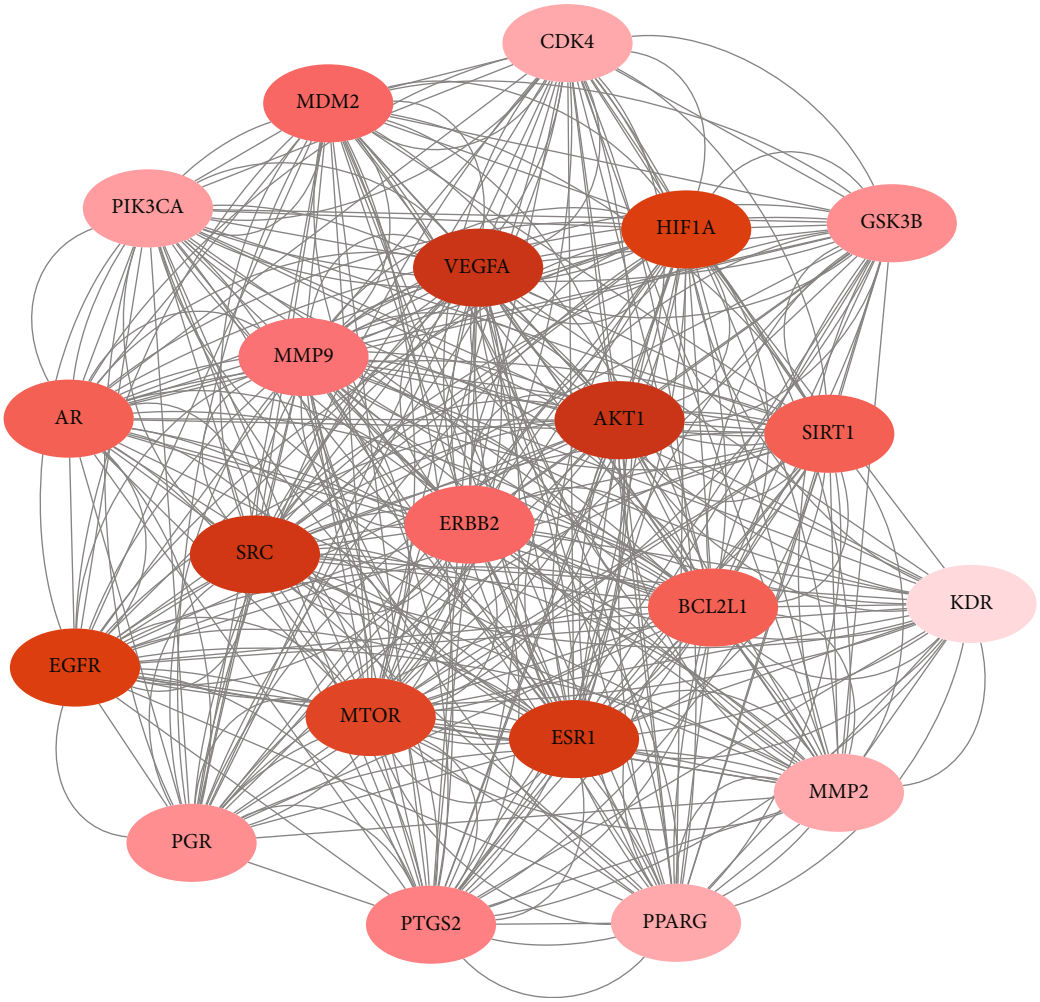


Figure 3: Protein-protein interaction network of Drynariae Rhizoma. Note: the size and color represent different degree values.

Table 2: Basic information of three significant protein targets.

No.	Gene targets	Degree	Betweenness centrality	Closeness centrality
1	AKT1	78	54.833	0.976
2	VEGFA	78	46.911	0.976
3	HIF1A	72	33.905	0.909

4. Discussion

Low back pain has been a public problem, which seriously affecting people's daily life. Low back pain is mainly secondary to the diseases of cervical disc degeneration, cervical spondylosis, trauma, and so on. It is indicated that low back pain is the fourth most common reason for disability in the US, and women are more likely than men to experience low back pain [24]. We constructed a biological network between active ingredients of DR and common gene targets to reveal the mechanism of DR in the treatment of LBP. In the biological network, we selected 18 active ingredients, including (2R)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one, aureusidin, eriodyctiol (flavanone), stigmasterol, beta-sitosterol, kaempferol, naringenin, (+)-catechin, eriodictyol, digallate, luteolin, 22-stigmasten-3-one, cyclolaudenol acetate, cycloartenone, cyclolaudenol, davallioside A_qt, marioside_qt, and xanthogalenol, most of which are flavonoid compounds. As a main active ingredient, it has been reported that naringenin plays an important role in treating degenerative human nucleus pulposus cells through inhibiting the expression of inflammatory factors such as TNF-α [10]. Clinical evidence has revealed that non-steroidal anti-inflammatory drugs are effective for low back pain [23, 24]. Similarly, the extraction method with 70% ethanol of DR results in higher antioxidant activity [25]. Based on the strong relationship between these

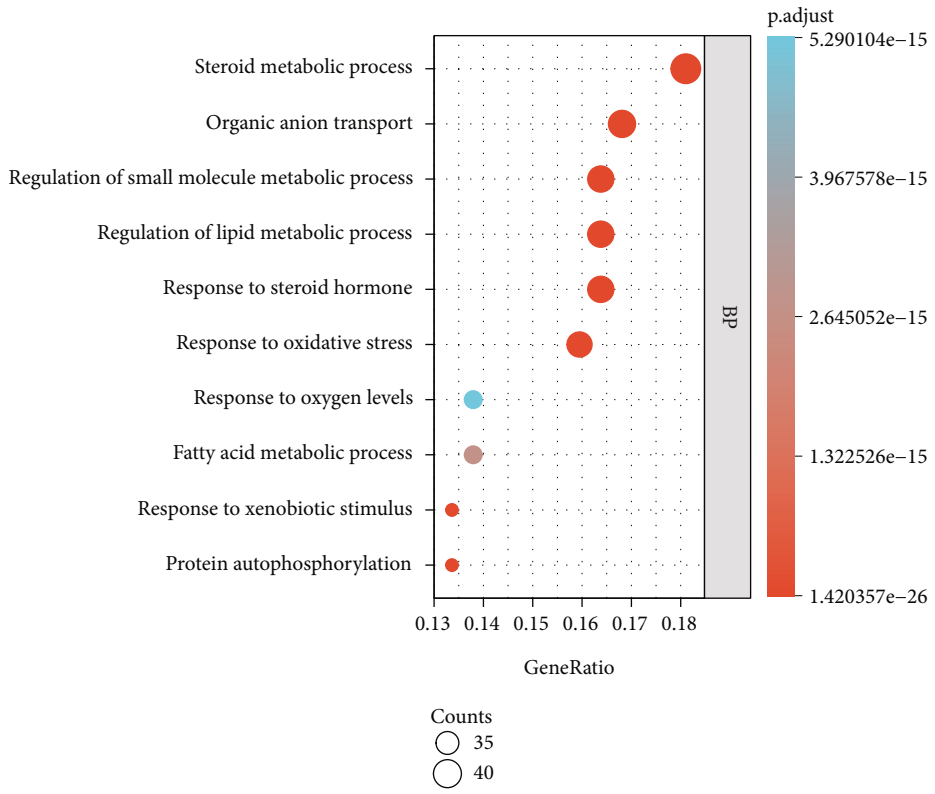


Figure 4: The Gene Ontology functional analysis of common gene targets.

active ingredients and common gene targets in the network, we predict that DR will have an effect in the treatment of LBP via anti-inflammatory and antioxidant functions.

A total of 8176 gene targets of LBP were found, and a total of 264 common gene targets were selected in the network, some of which have played a significant role in the progress or cure of LBP secondary to cervical disc herniation and so on. These common gene targets have effects of anti-inflammatory, angiogenesis, proliferation, and inhibition of disc herniation, which has the similar modern drug theory of "multi-ingredients, multitarget" [26].

We constructed a PPI network to analyze the interactions of these common proteins. In this network, a total of 234 protein targets were selected. These protein targets have different effects, such as anti-inflammatory, antiapoptosis, and proliferation, some of which have been confirmed by some cell experiments. AKT1, VEGFA, and HIF1A were identified as three significant protein targets according to the degree values. Studies have shown that VEGFA plays an important role in spare nerve injury- (SNI-) induced neuropathic pain, which is mediated by enhancing the expression and colocalization of VEGFA, p-AKT, and TRPV1 in a SNI-induced neuropathic pain model, which also improves expression of VEGFA, VEGFR2, p-AKT and TRPV1 in the spinal cord [27–29]. Pasku et al and Chen et al. indicated that AKT1 was associated with disc herniation and pain. The study found that when AKT1 transcription was activated, disc herniation was deteriorated and AKT1 mRNA was related to AKT3 only in herniated discs. They also confirmed that neovascularization was associated with disc degeneration and herniation, and AKT1 was associated with angiogenesis [30, 31]. According to much evidence shown above, we predict that the 18 active ingredients of DR have the potential ability to combine with the protein targets of LBP. As a major nuclear transcription factor regulated by hypoxia, HIF-1a has a broad target gene spectrum and can regulate about 1% of all genes in human, including the following: genes related to angiogenesis, including the coding genes of VEGF and its vascular endothelial growth factor receptor (VEGFR); genes related to cell proliferation and apoptosis, including insulin-like growth factor-2 (IGF-2) and transforming growth factor-A (TGF-a) p42/p44 mitogen activated protein kinase, P13K, p53, MDM2, and other coding genes; glucose metabolism, including glucose transporters GLUT 1 and GLUT 3 and transmembrane hydrogenase; and genes related to iron metabolism, including transfer receptor and ceruloplasmin.

We performed GO functional analysis to analyze the common genes of LBP and DR. According to analysis results, we found that these common genes have multiple functions in BP, CC, and MF. In the BP, the steroid metabolic process involved 42 (18.10%) gene targets, while organic anion transport involved 39 (16.81%) gene targets, promoting cell proliferation in the treatment of LBP. A study has proposed that epidural steroid injections are one of the most common nonsurgical treatments for low back pain. In general, corticosteroid treatment often results in bone loss and osteoporosis. Neuronal cell body involved 24 (10.30%) gene targets, nuclear envelope and vesicle lumen involved 17 (7.30%) gene targets, and cytoplasmic vesicle lumen involved 16 (6.87%) gene targets in the CC, which reveals that these gene targets may make

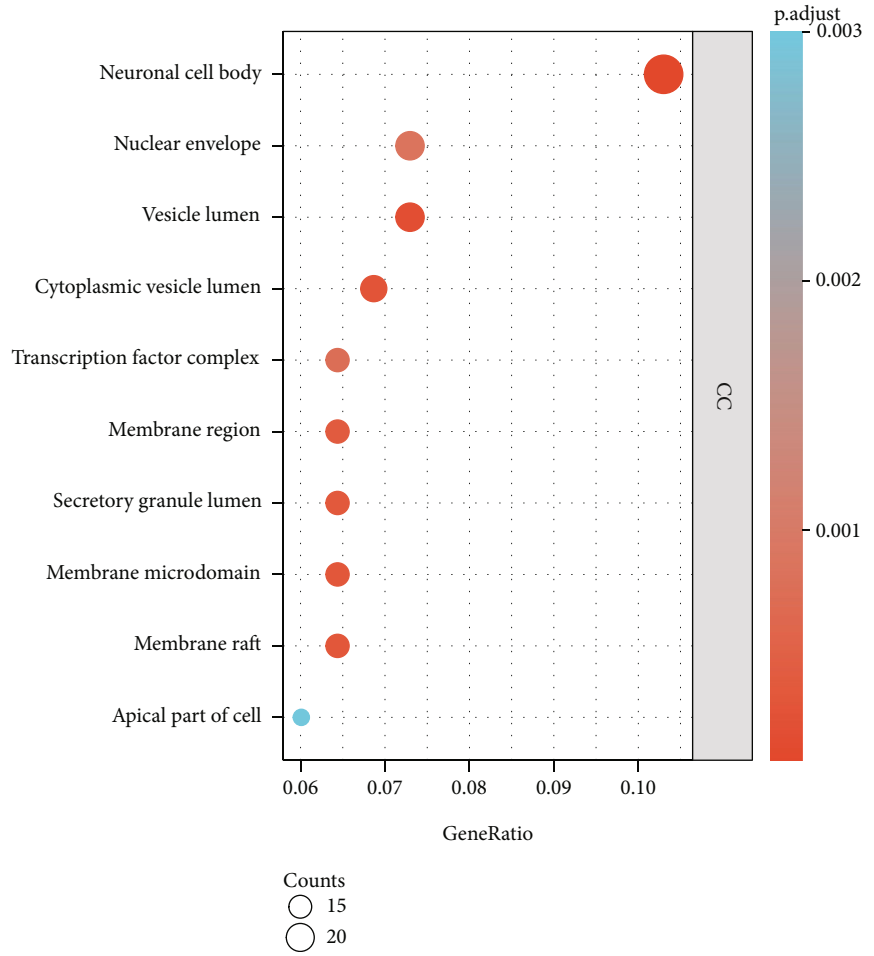


Figure 5: The Gene Ontology functional analysis of common gene targets.

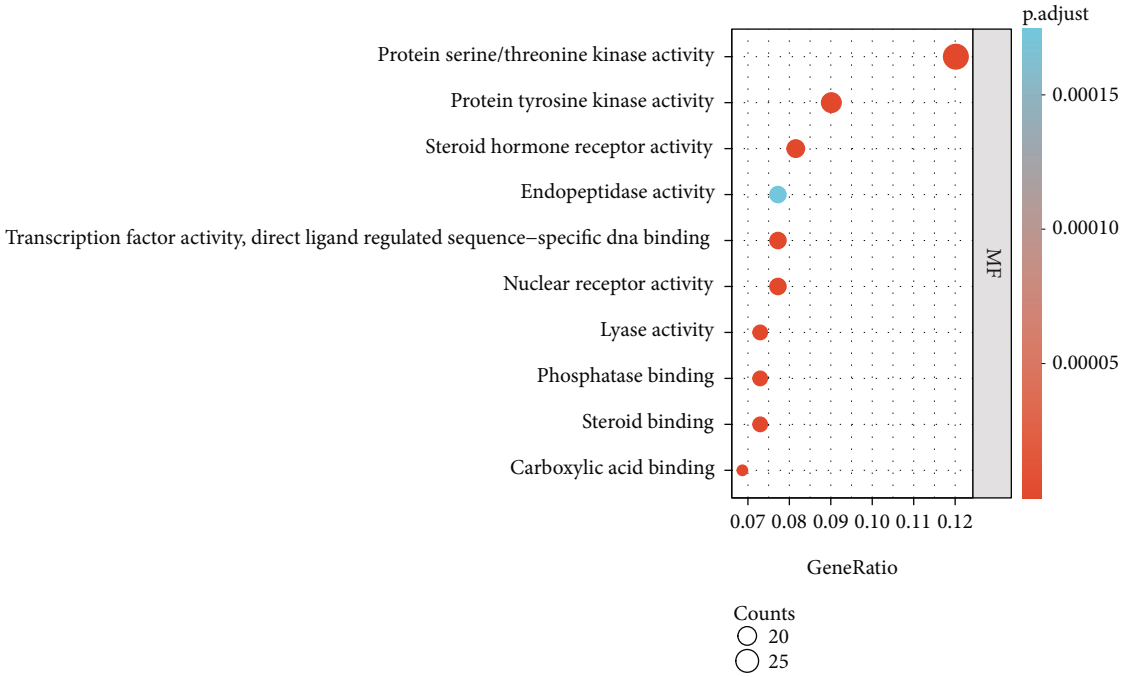


Figure 6: The Gene Ontology functional analysis of common gene targets.

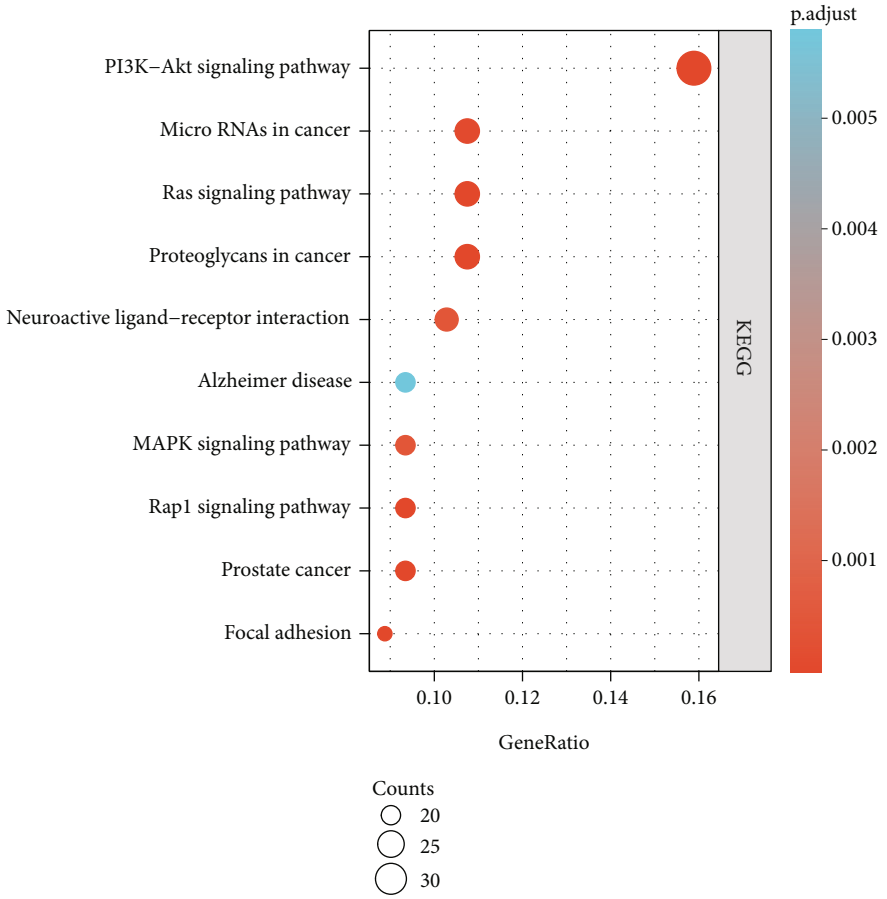


Figure 7: The KEGG pathway enrichment analysis of common gene targets.

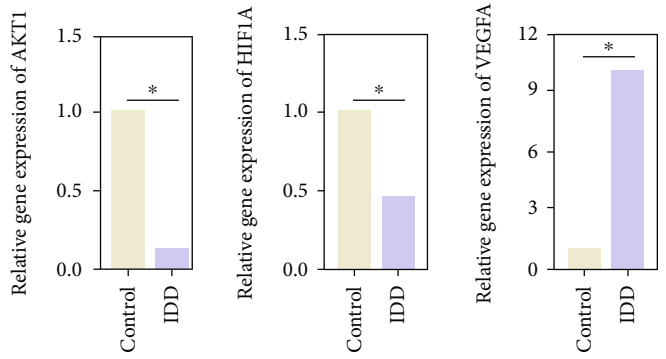


Figure 8: The mRNA expression levels of three significant targets.

effects through plasma membrane. Protein serine/threonine kinase activity involved 28 (12.02%) gene targets, protein tyrosine kinase activity involved 21 (9.01%) gene targets, and steroid hormone receptor activity involved 19 (8.15%) gene targets in the MF, which reveals that ribonucleotide binding may play a significant role in the regulation of gene targets for DR.

We summarized the pathway enrichment analysis through the KEGG database to clarify the mechanism between DR and LBP. PI3K-Akt signaling pathway involved 34 (15.89%) gene targets, microRNAs in cancer and proteoglycans in cancer; Ras signaling pathway involved 23 (10.75%) gene targets; neuroactive ligand-receptor interaction involved 22 (10.28%) gene targets; prostate cancer, Rap1 signaling pathway, Alzheimer disease, and MAPK signaling pathway involved 20 (9.35%) gene targets and so on. In these pathways, PI3K-Akt signaling pathway and Ras signaling pathway play a significant part in the development of LBP. Xu et al. found that the activation of PI3K-Akt signaling pathway is associated with high expression of inflammatory-related factors in intervertebral disc herniation [32]. Radicular pain was contributed via the activation of p38 MAPK signaling pathway [33]. According to the network pharmacology, we provide PI3K-Akt and Ras signaling

pathways as references to reveal the mechanism of DR in the treatment of LBP.

In conclusion, we used network pharmacology to indicate the potential association between DR and LBP and synergistic mechanism of DR in the treatment of LBP through prediction of gene and protein targets, which provides a reference for future study in vivo and in vitro.

Data Availability

Our data can be found in the TCMSP database.

Conflicts of Interest

All authors declare no conflicts of interest.

Authors' Contributions

Yan Cheng designed the study. Feng Wen and Jun Yu collected data and wrote the manuscript. Feng Wen and Jun Yu have contributed equally to this work.

Acknowledgments

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Research Article

Motion of Lumbar Endplate in Degenerative Lumbar Scoliosis Patients with Different Cobb Angle In Vivo: Reflecting the Biomechanics of the Lumbar Disc

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Study Design. Controlled laboratory study. *Objective*. To evaluate the influence of degenerative lumbar scoliosis (DLS) with different Cobb angles and degenerative discs on the range of motion (ROM) of the lumbar endplates during functional weight-bearing activities in vivo. *Summary of Background*. DLS data might influence spinal stability and range of motion of the spine. Altered lumbar segment motion is thought to be related to disc degeneration. However, to date, no data have been reported on the motion patterns of the lumbar endplates in patients with DLS in vivo. *Methods*. We recorded 42 DLS patients with the apical disc at L2-L3 and L3-L4. Patients were divided into A group with a coronal Cobb angle >20° (number: 13; 62.00 ± 8.57 years old) and group B with a coronal Cobb angle <20° (number: 28; 65.79 ± 6.66 years old). Patients' discs were divided into a degenerated disc group (III-V) and a nondegenerated disc group (I-II) according to the Pfirrmann classification. Computed tomography (CT) was performed on every subject to build 3-dimensional (3D) models of the lumbar vertebrae (L1–S1), and then the vertebras were matched according to the dual fluoroscopic imaging system. The kinematics of the endplate was compared between the different Cobb angle groups and the healthy group reported in a previous study and between the degenerative disc group and nondegenerative disc group by multiway analysis of variance. *Results*. Coupled translation at L5-S1 was higher than other levels during the three movements. During the flexion-extension of the trunk, around the anteroposterior axis, rotation in group A was higher than that in the control group at L2-L3 and L3-L4 (6.62 ± 3.61 mm vs 4.36 ± 2.55 mm, 5.01 ± 3.19 mm; $P < 0.05$, $P < 0.05$). During the left-right bending of the trunk, around the mediolateral axis, rotations in groups A and B were higher than those in the control group at L5-S1 (17.52 ± 11.43°, 17.25 ± 9.22° vs 10.08 ± 5.42°; $P < 0.05$, $P < 0.05$). During the left-right torsion, around the anteroposterior axis, rotation in group A was higher than that in group B and the control group at L2-3 (9.69 ± 5.94° vs 5.77 ± 4.02°, 4.47 ± 2.00°; $P < 0.05$, $P < 0.05$). In patients with Cobb angle <20°, coupled translation was higher in the degenerated disc group than in the nondegenerated disc group, especially along the anteroposterior axis. *Conclusion*. An increase in the coupled rotation of the endplate at the scoliotic apical level in patients with DLS was related to a larger Cobb angle. Moreover, segments with degenerative discs had higher coupled translations in the anteroposterior direction than segments with nondegenerative discs in DLS patients with Cobb angle <20°. These data might provide clues regarding the etiology of DLS and the basis for operative planning.

1. Introduction

Degenerative lumbar scoliosis (DLS) was defined as a coronal Cobb angle greater than 10°. DLS is a de novo scoliosis with no previous history and is mainly related to age [1–3], with an incidence of up to 60% [4]. DLS can cause severe symptoms, such as low back pain, radiculopathy, and neurogenic claudication. The pathogenesis of DLS is

both complex and controversial. Intervertebral disc degeneration (DD) has also been implicated in the development of DLS [5]. Aebi and Phillips et al. [1, 6] hypothesized that asymmetric loading and degeneration of discs contribute to the development of deformities. Kobayashi et al. [7] reported that asymmetric disc degeneration could predict the incidence of DLS. Murata et al. suggested that DLS could be caused by disc degeneration at any level [8]. In a previous study, asymmetry of the endplates in the midsagittal plane was a risk factor for lumbar disc degeneration [9]. Therefore, the kinematics of the lumbar endplate in DLS patients in vivo should be helpful for the etiology of DLS.

To the best of our knowledge, data on the range of motion (ROM) of the endplate in DLS patients in vivo was scarce. Wang et al. [10] developed a finite element (FE) model to simulate DLS scattering and showed asymmetric loading in the increased asymmetry of the lumbar spine. Zheng et al. [11] also developed an FE model of DLS based on only one patient. There have also been some studies of the human cadaveric spine indicating a relationship between the degenerative disc and ROM of the spine [12–14]. However, they could not reflect the actual status of the lumbar disc and ROM. This study explored the ROM of the lumbar vertebral endplate in vivo to reflect disc deformation using a dual fluoroscopic imaging system. It was reported that the repeatability of the method in reproducing in vivo human spine 6 degree of freedom (DOF) kinematics was <0.3 mm in translation and <0.7° in orientation [15].

This study is aimed at exploring the motion of lumbar endplates in DLS patients with different Cobb angles. Intervertebral DD is believed to have a detrimental effect on the ROM of the spinal segments in degenerative scoliosis [16]. Therefore, we also aimed to investigate the relationship between DD and the ROM of the lumbar vertebral endplates in patients with DLS. We hypothesized that the ROM of the lumbar endplate would be different in DLS patients with different Cobb angles. DD can increase the ROM of the lumbar vertebral endplate in patients with DLS.

2. Methods

2.1. Subjects and Grouping. In this study, we recruited 42 DLS patients with apical discs at L2-L3 and L3-L4 who were undergoing lumbar surgery, with ages ranging from 41 to 77 years old. We divided the patients into A group with coronal Cobb angle >20° (number:13; 62.00 ± 8.57 years old) and B group with coronal Cobb angle <20° (number:28; 65.79 ± 6.66 years old). We also involved 12 healthy participants reported in the previous study with 52.08 ± 3.18 years old, ranging from 40 to 56 years old, as the control group. L2-L3 and L3-L4 were considered segments around the scoliotic apex, whereas L1-L2, L4-L5, and L5-S1 were considered adjacent apical segments. The institutional review board (IRB) approved this study before initiation. Written consent was obtained prior to any testing. The inclusion criteria were as follows: (1) diagnosed with degenerative adult lumbar scoliosis and the main curve located in the lumbar segments; (2) coronal Cobb angle >10°; and (3) age >40 years. The exclusion criteria were as follows: (1) history of adolescent scoliosis, (2) history of major vertebral trauma, (3) severe joint pain in the lower limbs, (4) leg length discrepancy, (5) history of metabolic disorder, and (6) history of lumbar surgery. In this study, every segment of the lumbar spine (L1-L2, L2-L3, L3-L4, L4-L5, and L5-S1) in all subjects was studied. The magnitude of intervertebral disc degeneration at each segment was determined based on the Pfirrmann classification system [17] (Table 1). Five grades were collected on sagittal T2-weighted images, representing progression from normal disc to severe disc degeneration, in which Pfirrmann grades I and II represented the nondegenerated disc group, whereas Pfirrmann grades III–V represented the degenerated disc group [9]. Disc degeneration was graded by two experienced spine surgeons with more than 5-year experience in degenerative spinal disease. The two surgeons independently and blindly performed the measurements. We selected the mean values of the two surgeons.

2.2. Three-Dimensional Models Based on Computed Tomography (CT). First, we obtained CT images of the lumbar spine of each participant using a CT scanner (Sensation; Siemens, Erlangen, Germany). Images were obtained at a thickness of 0.625 mm. The CT images of the L1-S1 spinal segments were then imported into software (MIMICS 21.0; Materialize, Leuven, Belgium) to build a model of the lumbar spine (Figures 1(a), 1(b), and 1(c)).

2.3. Dual Fluoroscopic Imaging System. The position of the lumbar spine was imaged using a dual-fluoroscopic system. Two fluoroscopes (BV Pulsera; Phillips, Bothell, WA, USA) were placed perpendicular to each other. In this way, images of the lumbar spine were simultaneously obtained from two directions. The volunteers were asked to stand between the two perpendicular image intensifiers and make movements, including trunk flexion at 45°, maximal extension, maximal left-right bending, and maximal left-right rotation (Figure 2). A minimum stillness span of 2 s was required for each posture while the two fluoroscopes captured the images. 3D CT-based models of the vertebrae at various body postures were reproduced using the modeling software Rhinoceros (Robert McNeel & Associates, Seattle, WA, USA). Thereafter, the vertebral models were independently translational and rotational in 6DOF until their outlines matched the outlines on the two fluoroscopic images (Figure 2). Using this technique, vertebral endplate positions in vivo were reproduced in different postures.

2.4. Coordinate Systems of Vertebral Endplates. Right-hand Cartesian coordinate systems were placed at the center of each vertebral endplate (Figure 1(d)). The center was defined as the volumetric center of the endplate. Based on the geometry of the endplate, the x-axis was set parallel to the coronal axis to represent the mediolateral direction and pointed to the left direction. The y-axis was set in the horizontal plane and pointed posteriorly to indicate the anteroposterior direction. The z-axis was set perpendicular to the transverse plane, representing the cephalad-caudad direction, and pointed in the cranial direction. After moving the vertebrae to different virtual positions, the motion of the inferior endplate of the cranial vertebra was determined relative to that

Table 1: Pfirrmann classification of disc degeneration in DLS Patients (Cobb > 20 ∘ and Cobb < 20 ∘).

	L1-L2	L2-L3	L3-L4	L4-L5	L5-S1
A group	2.92 ± 0.86	3.08 ± 0.64	3.38 ± 0.96	3.69 ± 0.63	3.69 ± 0.95
Range of grade	1-5	2-4	2-5	3-5	2-5
B group	2.72 ± 0.96	2.79 ± 0.68	3.31 ± 0.81	3.66 ± 0.86	3.66 ± 0.94
Range of grade	2-4	2-4	2-5	3-5	2-5

The values were presented as mean ± SD. DLS: degenerative lumbar scoliosis; A group: coronal Cobb > 20 ∘ ; B group: coronal Cobb < 20 ∘ .

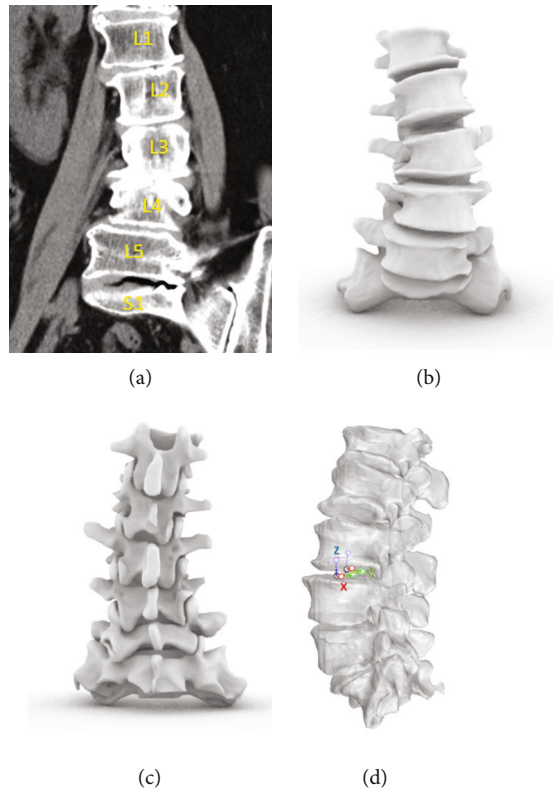

Figure 1: (a) Digitized contours of lumbar vertebrae in coronal plane. (b, c) Three-dimensional anatomic vertebral model constructed from the computed tomography. (d) Anatomic coordinate system to measure kinematics of the endplates.

of the superior endplate of the caudal vertebra. Flexion-extension, left-right bending, and left-right torsion of the trunk were compared to the natural upright posture.

2.5. Statistical Analysis. A two-way repeated measures ANOVA was used to compare the ROM of the endplates at the L1-L2, L2-L3, L3-L4, L4-L5, and L5-S1 levels. Kinematics was the dependent variable, and vertebral level and activity were the independent variables. The level of statistical significance was set at $P < 0.05$. Another multiway analysis of variance was used to compare the kinematics between patients with different coronal Cobb angles. The participant group was the categorical factor, and the levels and activities were independent variables. When a statistically significant difference was detected, a Newman-Keuls post hoc test was performed, and the level of significance was again set at $P < 0.05$. This was similar in the nondegenerated and degenerated disc groups. Statistical analysis was performed using SPSS version 23 (IBM Corp.) and Prism 7 software (Version 5.01; GraphPad Software Inc., CA, USA).

3. Results

3.1. Primary Rotations and Translations of Endplates in DLS Patients. During the flexion-extension of the trunk, the mean flexion and extension ranges were 9.42 ± 3.83°, 10.05 ± 5.37°, 11.78 ± 6.46°, 12.59 ± 8.00°, and 12.08 ± 6.73° for the L1-L2, L2-L3, L3-L4, L4-L5, and L5-S1 levels, respectively. During left-right bending of the trunk, the mean left-right bending ranges were 9.44 ± 4.03°, 8.18 ± 4.19°, 9.23 ± 5.39°, 7.97 ± 5.33°, and 8.75 ± 4.95° for the L1-L2, L2-L3, L3-L4, L4-L5, and L5-S1 levels, respectively. During left-right torsion of the trunk, the mean left-to-right twisting ranges were 7.82 ± 4.23°, 7.71 ± 4.73°, 8.86 ± 3.82°, 8.91 ± 6.00°, and 7.92 ± 4.77° for the L1-L2, L2-L3, L3-L4, L4-L5, and L5-S1 levels, respectively. There was no significant

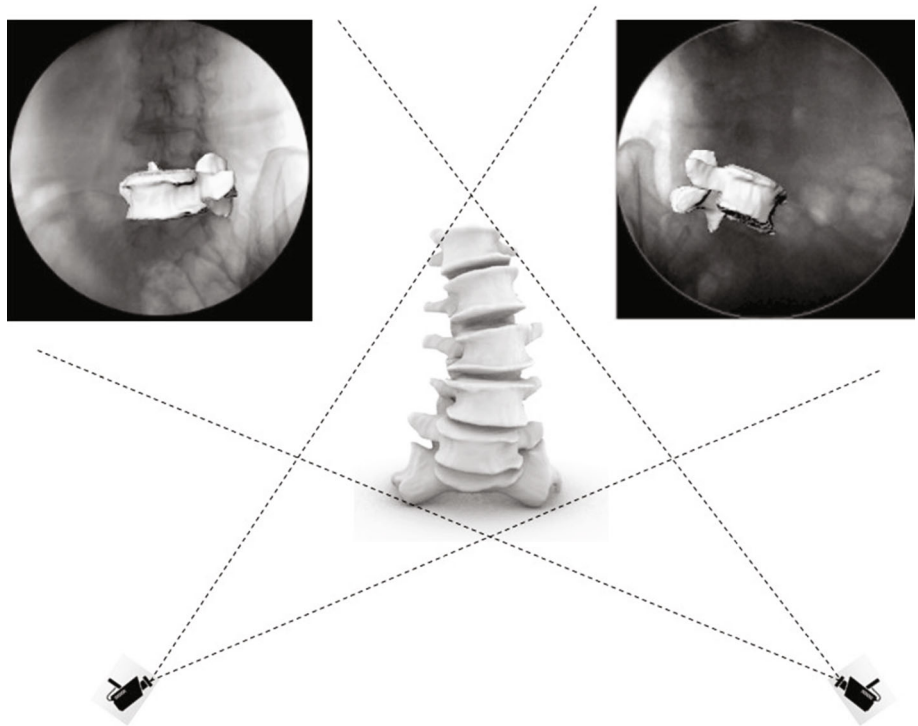

Figure 2: Each 3D vertebral model was separately translated and rotated until their contours matched the corresponding vertebral bony outline captured on the 2 fluoroscopic images.

difference in the rotational ROM at different levels around the primary axis during the three movements (Figure 3(a)).

3.2. Coupled Rotations and Translations of Endplates in DLS Patients. During the flexion-extension of the trunk, along the *z*-axis, translational ROM at L5-S1 was higher than that at L2-L3 and L3-L4 (6.62 ± 3.61 mm vs 4.36 ± 2.55 mm, 5.01 ± 3.19 mm; $P < 0.05$, $P < 0.05$) (Figure 3(d)). Along the *y*-axis, translational ROM at L5-S1 was higher than that at L1-L2 and L2-L3 (8.53 ± 4.76 mm vs 6.04 ± 2.99 mm, 5.45 ± 2.96 mm; $P < 0.05$, $P < 0.05$) (Figure 3(d)). During the left-right bending of the trunk, around the *x*-axis, rotational ROM at L5-S1 was higher than that at L1-L2, L2-L3, L3-L4, and L4-L5 ($17.33 \pm 9.82^\circ$ vs $9.68 \pm 6.12^\circ$, $9.04 \pm 5.68^\circ$, $8.82 \pm 5.28^\circ$, $11.41 \pm 6.79^\circ$; $P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.05$) (Figure 3(b)). Along the *y*-axis, translational ROM at L5-S1 was higher than that at L1-L2, L2-L3, and L3-L4 (9.28 ± 6.55 mm vs 4.70 ± 3.07 mm, 6.03 ± 4.35 mm, 5.88 ± 4.31 mm; $P < 0.05$, $P < 0.05$, $P < 0.05$). In addition, along the *z*-axis, translational ROM at L5-S1 was higher than that at L3-L4 (6.65 ± 3.51 mm vs 4.22 ± 2.53 mm; $P < 0.05$) (Figure 3(e)). During left-right torsion of the trunk, around the *x*-axis rotation at L5-S1 was higher than that at L1-L2 ($9.12 \pm 5.21^\circ$ vs $7.44 \pm 4.26^\circ$, $P < 0.05$). Along *x*-axis, translational ROM at L5-S1 was higher than that at L1-L2 and L3-L4 (8.73 ± 4.88 mm vs 5.73 ± 3.75 mm, 5.93 ± 3.22 mm; $P < 0.05$, $P < 0.05$). Along *y*-axis, translational ROM at L5-S1 was higher than other levels (10.73 ± 5.85 mm vs 4.67 ± 2.58 mm, 5.96 ± 4.03 mm, 5.69 ± 3.94 mm, 6.87 ± 3.93 mm; $P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.05$). Along *z*-axis, translational ROM at L5-S1 was higher than that at L1-L2, L2-L3, and L3-L4 (6.60 ± 3.98 mm vs 4.06 ± 2.42 mm, 4.59 ± 3.17 mm, 4.27 ± 2.58 mm; $P < 0.05$, $P < 0.05$, $P < 0.05$) (Figure 3(f)).

3.3. Comparison of ROMs between Different Cobb Angles and Healthy Subjects (Tables 2 and 3). During the flexion-extension of the trunk around the *y*-axis, rotation in group A (>20°) was higher than that in the control group at L2-L3 and L3-L4 ($10.73 \pm 5.11^\circ$ vs $4.54 \pm 2.97^\circ$, $8.68 \pm 5.21^\circ$ vs $3.91 \pm 2.39^\circ$; $P < 0.05$, $P < 0.05$). During the left-right bending of the trunk around the *x*-axis, rotations in groups A and B were higher than those in the control group at L5-S1 ($17.52 \pm 11.43^\circ$, $17.25 \pm 9.22^\circ$ vs $10.08 \pm 5.42^\circ$; $P < 0.05$, $P < 0.05$). During the left-right torsion of the trunk around the *z*-axis, rotation in the control group was higher than that in groups A and B at L1-L2 ($16.48 \pm 6.37^\circ$ vs $8.69 \pm 5.56^\circ$, $7.43 \pm 3.54^\circ$; $P < 0.05$, $P < 0.05$) and L5-S1 ($17.05 \circ \pm 6.68^\circ$ vs. $7.69 \circ \pm 5.31^\circ$, $8.03 \circ \pm 4.59^\circ$; $P < 0.05$, $P < 0.05$). Around the *y*-axis, rotation in group A was higher than that in group B and the control group at L2-L3 ($9.69 \pm 5.94^\circ$ vs $5.77 \pm 4.02^\circ$, $4.47 \pm 2.00^\circ$; $P < 0.05$, $P < 0.05$).

3.4. The Effect of Lumbar Disc Degeneration on ROM of Endplate (Table 4). During the flexion-extension of the trunk, along the *y*-axis, translation was higher in the degenerated disc group than that in the nondegenerated disc group (6.94 ± 4.09 mm vs 5.37 ± 3.20 mm, $P < 0.05$). In patients with Cobb < 20°, it was significantly different between the degenerated disc group and the nondegenerated disc group along *y*-axis (7.08 ± 4.26 mm vs 5.21 ± 2.91 mm, $P < 0.05$). During left-right bending of the trunk around the *x*-axis, rotation was higher in the degenerated disc group

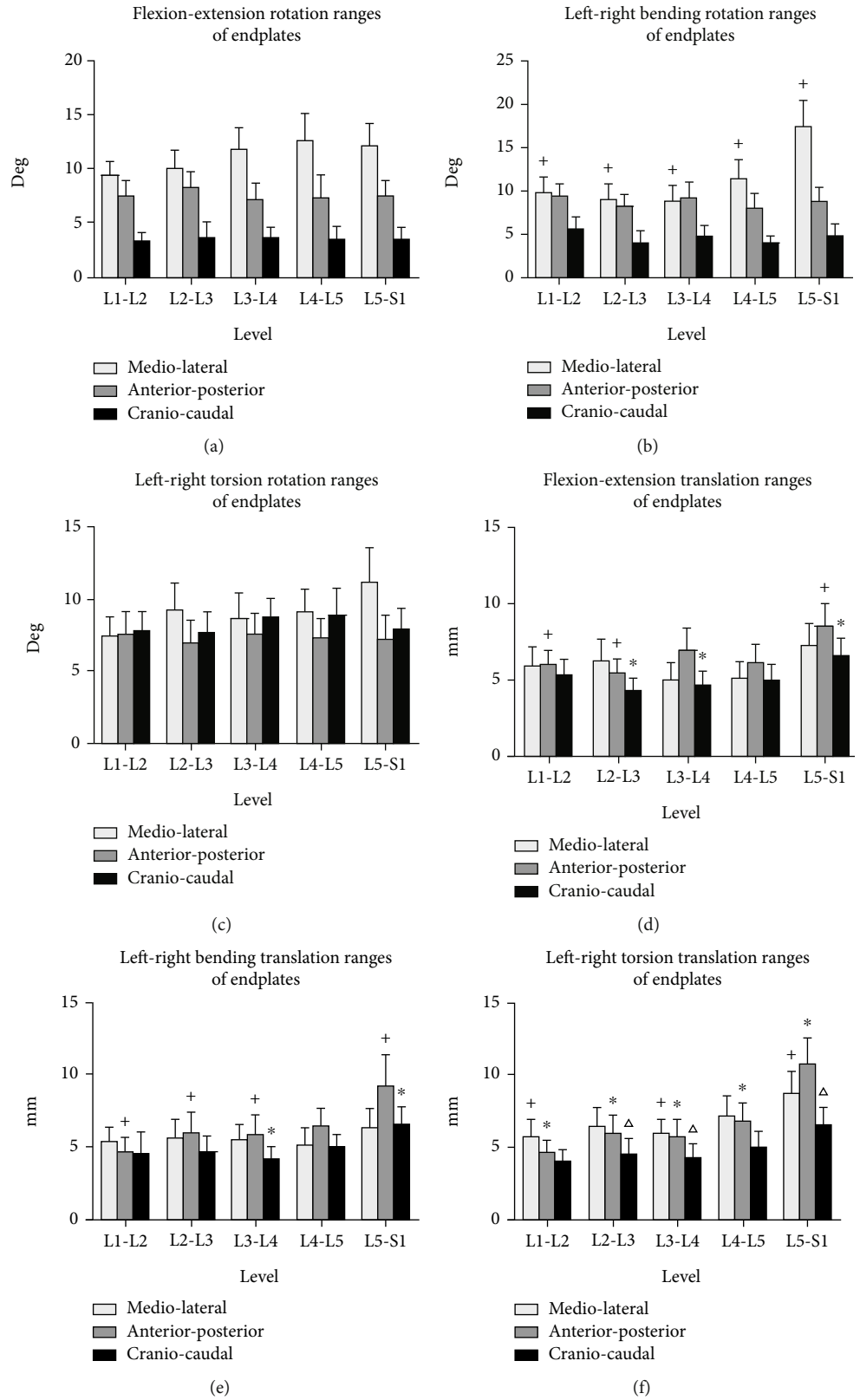

Figure 3: Range of motion of endplates in DLS patients during standing up and along three principal axes under (a, d) flexion-extension, (b, e) bending, and (c, f) torsion of the trunk. The symbols (*, +, △) represent statistical significance on comparison of different level ($P < 0.05$).

Table 2: Comparison of rotation ranges (°) between normal participants and DLS patients (Cobb > 20 ∘ and Cobb < 20 ∘).

Level	L1-L2			L2-L3			L3-L4			L4-L5			L5-S1		
Axis	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*
Flexion-extension															
A group	10.09 ± 4.56	8.82 ± 4.88	3.75 ± 3.92	9.26 ± 4.43	10.73 ± 5.11	4.64 ± .3.92	11.20 ± 5.94	8.68 ± 5.21	4.14 ± 2.73	13.75 ± 8.48	6.90 ± 3.77	4.63 ± 4.56	12.21 ± 7.20	9.07 ± 5.55	3.56 ± 4.81
B group	9.12 ± 3.51	7.01 ± 4.22	3.06 ± 2.12	10.40 ± 5.78	7.24 ± 4.13	3.20 ± 4.59	12.04 ± 6.76	6.42 ± 4.52	3.52 ± 3.15	12.07 ± 7.89	7.53 ± 7.55	3.06 ± 2.95	12.02 ± 6.63	6.78 ± 3.72	3.52 ± 2.44
Normal	9.40 ± 3.84	7.05 ± 4.22	3.43 ± 2.73	9.40 ± 5.08	7.48 ± 4.62	3.52 ± 4.15	11.37 ± 5.94	6.41 ± 4.56	3.73 ± 3.01	11.83 ± 7.46	7.06 ± 6.02	3.56 ± 3.91	12.46 ± 6.32	7.01 ± 4.16	4.58 ± 3.96
Left-right bending															
A group	12.72 ± 7.92	9.01 ± 3.75	5.77 ± 4.57	9.51 ± 5.96	10.52 ± 4.94	6.20 ± 5.57	9.32 ± 4.84	8.51 ± 5.43	3.91 ± 2.93	11.75 ± 7.13	6.19 ± 4.38	4.23 ± 2.86	17.52 ± 11.43	8.65 ± 4.87	6.99 ± 6.78
B group	8.32 ± 4.67	9.63 ± 4.19	5.39 ± 4.84	8.82 ± 5.65	7.13 ± 3.40	2.99 ± 3.34	8.59 ± 5.53	9.55 ± 5.43	5.05 ± 4.82	11.25 ± 6.75	8.77 ± 5.59	3.79 ± 2.78	17.25 ± 9.22	8.79 ± 5.07	3.81 ± 2.37
Normal	7.53 ± 3.76	9.11 ± 4.28	4.60 ± 4.70	8.25 ± 4.36	5.96 ± 2.54	4.05 ± 3.23	9.78 ± 5.07	8.50 ± 4.14	4.68 ± 4.93	8.34 ± 4.50	5.24 ± 3.44	3.47 ± 2.79	10.08 ± 5.42	10.06 ± 4.31	7.85 ± 4.38
Left-right torsion															
A group	9.55 ± 3.04	9.39 ± 5.94	8.69 ± 5.56	10.53 ± 6.24	9.69 ± 5.67	9.95 ± 6.74	6.21 ± 4.44	8.22 ± 5.63	10.48 ± 4.10	8.36 ± 4.74	7.33 ± 2.19	11.17 ± 7.91	10.66 ± 7.66	6.01 ± 5.93	7.69 ± 5.31
B group	6.49 ± 4.42	6.76 ± 4.33	6.71 ± 3.15	8.72 ± 5.89	5.77 ± 4.02	6.71 ± 3.15	9.79 ± 5.93	7.25 ± 4.43	8.13 ± 3.52	9.47 ± 5.45	7.37 ± 4.80	7.89 ± 4.74	11.45 ± 8.03	7.87 ± 4.73	8.03 ± 4.59
Normal	8.74 ± 7.66	5.71 ± 3.30	16.48 ± 6.37	7.62 ± 3.89	4.47 ± 2.00	11.29 ± 4.91	10.74 ± 5.10	5.93 ± 3.87	15.64 ± 6.29	8.18 ± 7.34	4.76 ± 2.93	11.79 ± 7.27	10.18 ± 5.27	5.49 ± 3.67	17.05 ± 6.68

Mean values were presented as ± standard deviation. Rotation around axis: *x*, *y*, and *z*. DLS: degenerative lumbar scoliosis; *x*: mediolateral.axis; *y*: anteroposterior axis; *z*: craniocaudal axis; A group: coronal Cobb > 20 ∘ ; B group: coronal Cobb < 20 ∘ .

Table 3: Comparison of translation ranges (mm) between normal participants and DLS patients (Cobb > 20° and Cobb < 20°).

Level	L1-L2			L2-L3			L3-L4			L4-L5			L5-S1		
Axis	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z
Flexion-extension															
A group	5.37 ± 3.71	5.75 ± 3.68	5.47 ± 2.74	7.31 ± 3.78	5.18 ± 2.34	5.31 ± 2.96	5.14 ± 2.81	6.29 ± 3.39	5.63 ± 3.47	5.57 ± 3.13	6.03 ± 3.47	4.52 ± 3.02	6.66 ± 2.84	9.47 ± 4.61	6.78 ± 2.99
B group	6.15 ± 4.33	6.17 ± 2.69	5.25 ± 3.77	5.83 ± 4.59	5.57 ± 3.23	3.93 ± 2.27	5.01 ± 3.72	7.24 ± 5.02	4.25 ± 2.29	4.96 ± 3.47	6.25 ± 3.79	5.22 ± 3.29	7.58 ± 4.98	8.11 ± 4.84	6.54 ± 3.89
Normal	3.97 ± 1.69	4.58 ± 3.16	4.05 ± 1.90	4.28 ± 2.03	4.76 ± 3.31	3.58 ± 2.44	4.61 ± 2.78	6.12 ± 4.45	4.59 ± 2.40	4.26 ± 1.39	6.15 ± 4.75	5.63 ± 2.69	5.99 ± 4.77	9.68 ± 7.18	5.58 ± 2.55
Left-right bending															
A group	5.22 ± 4.15	4.28 ± 2.40	3.53 ± 1.91	6.01 ± 3.76	6.95 ± 5.32	5.85 ± 3.84	5.87 ± 3.64	7.22 ± 5.86	3.90 ± 2.06	6.45 ± 4.38	6.61 ± 3.68	4.84 ± 2.53	7.28 ± 4.20	9.94 ± 6.05	6.90 ± 4.18
B group	5.47 ± 2.63	4.89 ± 3.35	4.98 ± 5.57	5.46 ± 4.19	5.61 ± 3.87	4.14 ± 3.22	5.29 ± 3.30	5.28 ± 3.35	4.36 ± 2.73	4.53 ± 3.46	6.43 ± 3.74	5.19 ± 2.48	5.98 ± 3.97	8.98 ± 6.84	6.53 ± 3.25
Normal	5.35 ± 2.95	5.22 ± 2.51	4.71 ± 2.22	5.77 ± 3.25	7.58 ± 2.82	3.53 ± 2.12	5.59 ± 2.04	4.79 ± 2.87	5.04 ± 2.41	4.93 ± 2.15	7.55 ± 4.83	6.20 ± 4.79	8.76 ± 6.56	7.19 ± 5.94	4.93 ± 3.08
Left-right torsion															
A group	5.28 ± 2.13	5.38 ± 2.79	4.35 ± 2.30	7.98 ± 5.05	5.18 ± 4.24	5.46 ± 4.45	5.60 ± 2.78	5.42 ± 4.55	3.82 ± 1.96	7.02 ± 3.71	6.43 ± 3.12	5.49 ± 4.51	8.96 ± 4.84	12.98 ± 5.40	6.50 ± 3.30
B group	5.93 ± 4.31	4.36 ± 2.47	3.93 ± 2.49	5.84 ± 3.49	6.31 ± 3.96	4.20 ± 2.39	6.08 ± 3.43	5.81 ± 3.71	4.48 ± 2.82	7.27 ± 4.70	7.07 ± 4.28	4.81 ± 2.99	8.61 ± 4.98	9.73 ± 5.86	6.65 ± 4.30
Normal	6.37 ± 3.32	4.78 ± 3.21	5.12 ± 4.01	4.64 ± 3.54	5.85 ± 2.69	5.11 ± 2.57	6.37 ± 3.47	4.68 ± 2.72	2.96 ± 2.17	5.26 ± 2.63	6.52 ± 4.05	5.42 ± 4.17	7.68 ± 4.96	9.25 ± 6.79	3.45 ± 2.40

Mean values were presented as ± standard deviation. Rotation around axis: x, y, and z. DLS: degenerative lumbar scoliosis; x: mediolateral axis; y: anteroposterior axis; z: craniocaudal axis; A group: coronal Cobb > 20°; B group: coronal Cobb < 20°.

Table 4: Comparison of translation ranges between normal participants and DLS patients (Cobb > 20 ∘ and Cobb < 20 ∘).

Number		A group Nondegenerative disc 10	A group Degenerative disc 55	A group P value	B group Nondegenerative disc 32	B group Degenerative disc 113	B group P value
Rotations (°)							
Flexion-extension	x	10.93 ± 4.68	11.37 ± 6.61	0.840	9.60 ± 4.88	11.56 ± 6.61	0.121
	y	8.24 ± 4.67	8.95 ± 5.02	0.676	6.82 ± 3.94	7.05 ± 5.24	0.813
	z	4.48 ± 3.17	4.08 ± 4.09	0.737	3.16 ± 3.77	3.31 ± 2.94	0.831
Left-right bending	x	9.31 ± 5.21	12.68 ± 8.47	0.192	8.66 ± 5.31	11.47 ± 7.67	0.063
	y	9.25 ± 5.10	8.45 ± 4.75	0.629	7.69 ± 3.69	9.08 ± 5.07	0.149
	z	6.39 ± 4.02	5.25 ± 4.92	0.421	4.48 ± 3.97	4.13 ± 3.80	0.672
Left-right torsion	x	8.15 ± 3.17	9.23 ± 5.88	0.602	8.70 ± 5.55	9.32 ± 6.38	0.608
	y	10.03 ± 8.05	7.78 ± 4.64	0.168	6.64 ± 3.67	7.10 ± 4.68	0.625
	z	8.90 ± 5.34	9.72 ± 6.16	0.610	7.17 ± 3.02	7.77 ± 4.17	0.528
Translations (mm)							
Flexion-extension	x	5.85 ± 3.95	6.04 ± 3.20	0.893	5.56 ± 4.66	6.01 ± 4.21	0.579
	y	5.89 ± 4.15	6.66 ± 3.74	0.569	5.21 ± 2.91	7.08 ± 4.26	0.019*
	z	4.88 ± 3.02	5.67 ± 3.06	0.476	5.17 ± 3.56	5.00 ± 3.20	0.797
Left-right bending	x	4.16 ± 4.90	6.53 ± 3.71	0.061	4.80 ± 2.88	5.50 ± 3.70	0.338
	y	5.66 ± 4.12	7.25 ± 5.20	0.327	4.68 ± 3.08	6.68 ± 4.88	0.035*
	z	3.75 ± 3.10	5.23 ± 3.20	0.220	3.92 ± 2.44	5.36 ± 3.90	0.041*
Left-right torsion	x	5.30 ± 2.52	7.27 ± 4.16	0.168	5.18 ± 2.75	7.19 ± 4.56	0.016*
	y	5.61 ± 5.24	7.35 ± 4.96	0.272	4.59 ± 3.49	7.24 ± 4.60	0.004*
	z	4.90 ± 2.27	5.17 ± 3.68	0.813	4.19 ± 2.51	4.99 ± 3.34	0.228

Mean values were presented as ± standard deviation. Rotation around axis: x, y, and z. *, P value < 0.05. DLS: degenerative lumbar scoliosis; x: mediolateral.axis; y: anteroposterior axis; z: craniocaudal axis; A group: coronal Cobb > 20 ∘ ; B group: coronal Cobb < 20 ∘ .

than in the nondegenerated disc group (11.87 ± 7.94° vs 8.82 ± 5.23°, $P < 0.05$). For the patients with Cobb < 20°, along the y- and z-axis, translations were higher in the degenerated disc group than those in the nondegenerated disc group (6.68 ± 4.88 mm vs 4.68 ± 3.08 mm, 5.36 ± 3.90 mm vs 3.92 ± 2.44 mm; $P < 0.05$, $P < 0.05$). During the left-right torsion of the trunk, along the x- and y-axis, translations were higher in the degenerated disc group than those in the nondegenerated disc group (x: 7.22 ± 4.23 mm vs 5.20 ± 2.67 mm, y: 7.28 ± 4.71 mm vs 4.83 ± 3.93 mm; $P < 0.05$, $P < 0.05$). In patients with Cobb < 20°, it is similar along the x- and y-axis (x: 7.19 ± 4.56 mm vs 5.18 ± 2.75 mm, y: 7.24 ± 4.60 mm vs 4.59 ± 3.49 mm; $P < 0.05$, $P < 0.05$). However, in patients with Cobb angle >20°, there was no significant difference between the degenerated and the nondegenerated disc groups in the three movements.

4. Discussion

The degeneration of the lumbar disc was closely correlated with spinal flexibility in DLS [18]. In this study, we measured the ROM of the vertebral endplates in DLS patients to reflect the biomechanics of the lumbar disc when performing unrestricted weight-bearing activities. The ROM at the lumbosacral junction had a larger ROM of the endplates in coupled rotations and translations than other levels in DLS patients during the three movements. Patients with a Cobb angle >20° had higher coupled rotations at scoliotic apical levels than patients with a Cobb angle <20° and healthy subjects. In DLS patients with Cobb angle <20°, the degenerated disc group had higher coupled translation and rotation than those in the nondegenerated disc group.

In the literature, kinematic measurements of vertebrates in healthy subjects have been investigated in vivo. Shin et al. [19] found that dynamic lumbar axial rotation coupled with lateral binding was segment–dependent. Wu et al. [20] demonstrated that L4–5 and L5–S1 showed larger anteroposterior and proximal–distal translations in healthy participants, respectively. Li et al. [21] found that each vertebral level responded differently to flexion-extension and left-right bending but similarly to left-right twisting in healthy subjects. Some in vivo studies have reported the kinematics of the lumbar spine in patients with low back pain [22], degenerative disc disease [23], and degenerative spondylolisthesis [24]. There have also been some studies of the human cadaveric spine indicating a relationship between the degenerative disc and ROM of the spine [12–14]. Fujiwara et al. [13] noted that segmental motion initially increases with degeneration, similar to our study. However, kinematics of the lumbar spine in DLS patients has only been conducted using the FE model. Wang et al. [10] built FE models with three different Cobb angles modified from a normal lumbar spine

and found that asymmetric loading on facet joint contact forces accelerates asymmetry in the lumbar spine. However, in vivo studies on DLS kinematics were scarce.

In our study, the difference in vertebral endplate ROM between patients with DLS and healthy participants was mainly in rotational ROM. In patients with DLS, the ROM of the endplates around the apical disc was larger in coupled motions. At the adjacent levels, particularly in the lumbosacral joint, the ROMs of the coupled motion were high. Moreover, patients with a larger coronal Cobb angle had larger coupled motions at the scoliotic apical level, which might induce more changes in adjacent biomechanics after fusion to the scoliotic apical level. Rustenburg et al. [16] also found a positive correlation between the Cobb angle and coupled motions, suggesting that the magnitude of coupled motions increased as the disease progressed in the cadaveric spines. This implied that the coupled motions increased as the asymmetry of the spine increased at all levels, which might be due to less alignment in the local axes [25]. In addition, Rustenburg et al. [16] reported that spines with DLS tend to be stiffer and less flexible. This might be related to the larger coupled motion around the apical level. In Schlösser et al.'s study [26], the degree of torsion also correlated significantly with the Cobb angle, and they thought that morphological modifications of vertebrates were rather a consequence of the deformity. In addition, the anatomical deformation trend of vertebral endplates in Schlösser et al.'s article [26] might be caused by the increased coupled motion of DLS. Generally, a greater increase in coupled motion in patients was related to a larger Cobb angle. These data may help explore the etiology of DLS.

Kobayashi et al. [7] found that asymmetric disc degeneration could be a predictive factor for the incidence of DLS using logistic regression analysis in a community-based cohort. Primary degeneration of the disc is considered an initiating event of secondary deterioration of the facets and ligaments [27]. In our study, degenerative discs had higher coupled motions than nondegenerative discs in patients with DLS, particularly in patients with a small Cobb angle. This might be related to the degenerative disc located around the coronal scoliotic apex. However, increased coupled motion might also increase disc degeneration. Murata et al. [8] studied human cadaveric spinal motion segments and suggested that all lumbar interval spaces from L1–L2 to L5–S1 could trigger degenerative lumbar scoliosis. In our study, we found that the coupled motion of the degenerative disc at any level was larger, which might be related to Murata et al.'s results. Ellingson et al. [12] found positive correlations between Pfirrmann grade and axial rotation ROM. Schmidt et al. [14] reported increased ROM for axial rotation, flexion-extension, and lateral bending with increased disc degeneration. Fujiwara et al. [13] found that degeneration increased the ROMs in all rotational modes in discs with moderate degeneration, similar to our study. Murata et al. [8] suggested that disc degeneration might cause wedging progression. When the angle of the consequential wedging, which was bent to the side opposite the initial wedging to preserve balance, became larger than that of the initial wedging, the lumbar spine might attempt to maintain balance by making the initial wedging progress [8]. The increased coupled motion of the degenerative disc might be associated with sequential wedging to maintain balance. In Bao et al.'s study [28], the regional lumbar disc Pfirrmann score was also strongly correlated with the Cobb angle on the coronal plane. In our study, we found that degenerative discs in DLS patients with a coronal Cobb angle of $<20^{\circ}$ had larger coupled motions. A possible reason might be that patients with mild DLS had a more flexible ability to compensate for balance than patients with severe DLS, which also contributed to the development of DLS. Therefore, it should be considered cautiously about the fixed levels when there is already severe disc degeneration at the adjacent segment, even in DLS patients with a small Cobb angle, to avoid future failure at adjacent levels.

Our study had some limitations. First, the sample size of the patients with severe DLS was relatively small. Furthermore, the patients involved in the study were specifically selected with apical discs at the L2-L3 and L3-L4 levels, which represented only a portion of all patients with DLS. Finally, although we attempted to make the same movements for everyone, DLS patients might move more or less differently because of back pain.

5. Conclusions

In general, this study used an in vivo technique to quantify the abnormal motion of the vertebral endplates in DLS patients during various postures. An increase in the coupled motion of the endplate in DLS patients at the scoliotic apical level was related to a larger Cobb angle. Moreover, the segment with degenerative disc had higher coupled translations in the anteroposterior direction than the nondegenerative disc in DLS patients with Cobb angle $<20^{\circ}$. These data might provide clues regarding the etiology of DLS and the basis for operative planning.

Data Availability

The datasets used and/or analysed during the current study were available from the corresponding author on reasonable request.

Conflicts of Interest

There was no conflict of interest.

Authors' Contributions

Fei Xu, Shuai Jiang, and Longjie Wang contributed equally to this work.

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Research Article

Percutaneous Endoscopic Lumbar Discectomy for the Treatment of Recurrent Lumbar Disc Herniation: A Meta-analysis

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Objective. To evaluate the incidence and safety of clinical complications associated with percutaneous endoscopic lumbar discectomy (PELD) for the treatment of recurrent lumbar disc herniation (RLDH) by meta-analysis. *Methods*. PubMed, Embase, The Cochrane Library, and Web of Science electronic databases were searched for clinical studies on complications related to the treatment of RLDH with PELD. The search time extended from the databases' inception until May 2021. RevMan5.4 software was used for meta-analysis after two researchers independently scanned the literature, gathered data, and assessed the bias risk of the included studies. *Results*. A total of 8 clinical studies, including 1 randomized controlled trial and 7 cohort studies including 906 individuals, were included. According to the results of the meta-analysis, the overall complications (OR = 0.18, 95% CI: 0.04-0.83, $p = 0.03$) and dural tear rates (OR = 0.11, 95% CI: 0.01-0.92, $p = 0.04$) of PELD were lower than those of traditional fenestration nucleus pulposus removal. Moreover, the PELD group had a greater recurrence rate compared to the MIS-TLIF group (OR = 19.71, 95% CI: 3.68-105.62, $p = 0.0005$), and the difference was statistically significant. However, compared with MED and MIS-TLIF, there were no significant differences in the incidence of overall complications, dural tear, nerve root injury, and incomplete nucleus pulposus removal ($P > 0.05$). *Conclusion*. PELD is an effective and safe method for the treatment of recurrent lumbar disc herniation, with a lower incidence of complications and higher safety profile than traditional fenestration nucleus pulposus removal.

1. Introduction

Recurrent lumbar disc herniation (RLDH) is a disorder in which the nucleus pulposus of the lumbar disc herniates ipsilateral or contralateral to the original segment after previous surgical treatment for LDH, resulting in back and leg pain [1, 2]. As the number of surgical interventions increases, similarly, the incidence of postoperative recurrence of LDH increases; the incidence of postoperative recurrence varies, with an overall range of 3% to 18% [3]. RLDH is typically defined as a "painless period" of more than 6 months following the first lumbar discectomy, during which the intervertebral disc tissue of the original operative segment protrudes again on the operative side or contralateral side [4]. Surgical intervention is indicated for patients with a definite diagnosis of RLDH if the pain is not relieved after a period of conservative treatment. However, the scar tissue in the surgical area following the first operation increases the difficulty of repeated discectomy and increases the risk of permanent nerve root injury, dural tear with cerebrospinal fluid leakage, and sunburn complications [5]. Meanwhile, further resection of the posterior structure may increase the likelihood of lumbar segmental instability [6]. The ongoing advancements and maturation in percutaneous endoscopic lumbar discectomy (PELD) offer a novel approach for the therapy of RLDH. Compared with other operations, its advantages such as less trauma, faster recovery, less bleeding, and favorable curative effect have been recognized by spinal surgeons. However, some studies have recently

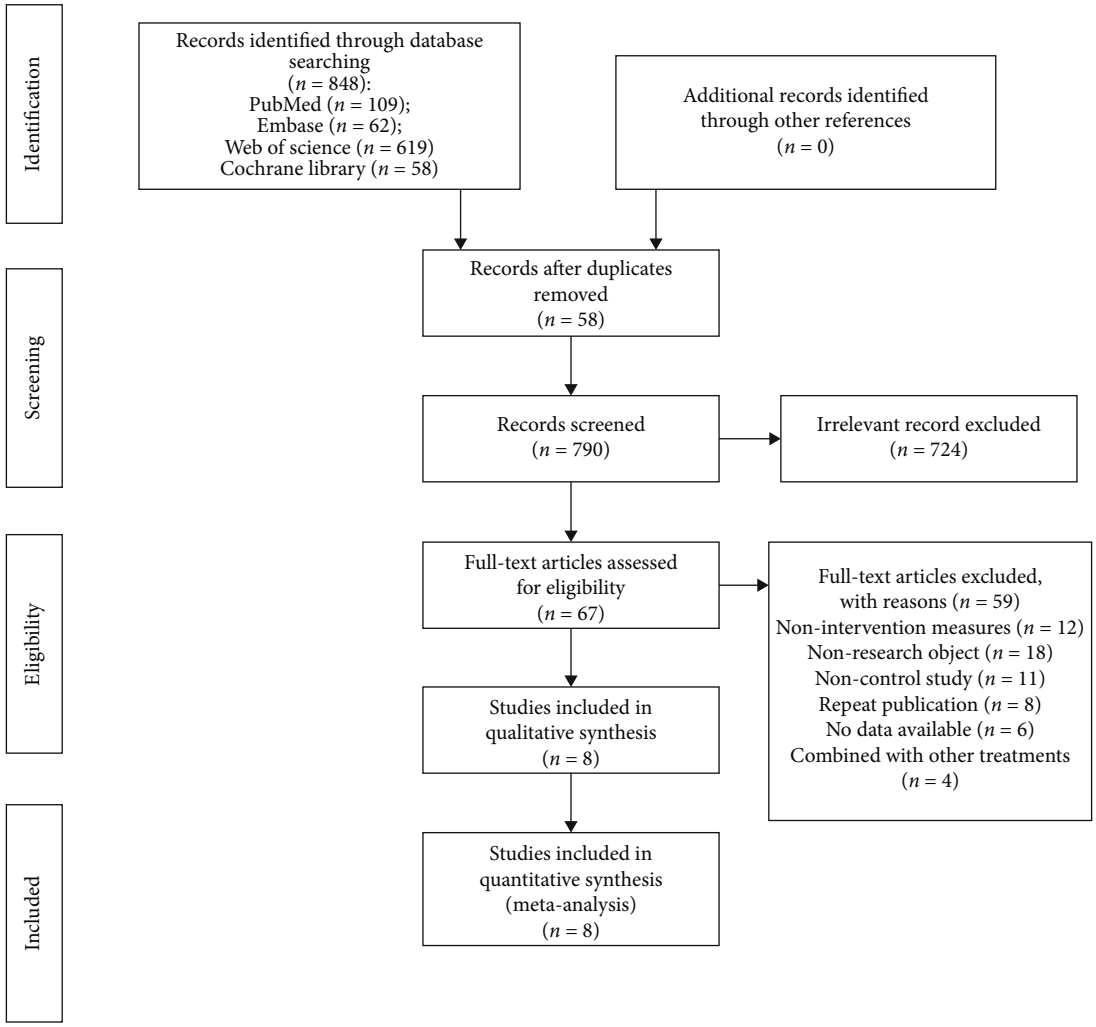

Figure 1: Flow chart of the literature search.

reported the occurrence of clinical complications of PELD for the treatment of RLDH; therefore, it is imperative to conduct a thorough meta-analysis to assess the safety of PELD in the treatment of RLDH, so as to further provide an evidence-based foundation for clinical application.

2. Materials and Methods

2.1. Literature Search Strategy. The PubMed, Embase, The Cochrane Library, and Web of Science databases were electronically searched, and clinical studies related to the complications of PELD for the therapy for RLDH were collected until May 2021. In addition, the references included in the research were manually searched for supplementary and pertinent literature. The keyword researched including "recurrent," "intervertebral disc displacement," "disc herniation," "microdiscectomy," "percutaneous lumbar discectomy," "endoscopy discectomy," "transforaminal lumbar discectomy," "endoscopic transforaminal diskectomy," "endoscopic interlaminar discectomy," and "minimally invasive discectomy."

2.2. Study Inclusion Criteria and Exclusion Criteria. The following are the inclusion criteria: (1) Study design includes randomized controlled trials (RCT), nonrandomized controlled trials, cohort studies, and case-control studies; (2) patients in the study experienced recurrent symptoms more than 6 months following the first lumbar discectomy, with reoccurrence of low back pain with lower limb nerve root pain and numbness. Moreover, lumbar intervertebral disc herniation of the same segment was confirmed by imaging techniques. (3) In the observation group, patients with RLDH were treated with PELD. The surgical methods included percutaneous endoscopic discectomy via the foraminal or interlaminar approach. In the control group, patients received traditional lamina fenestration discectomy, posterior lumbar interbody fusion (PLIF), posterior transforaminal lumbar interbody fusion (TLIF), MIS-TLIF, or posterior microendoscopic discectomy (MED). (4) The primary outcomes included the incidence of total complications, dural tear, intervertebral space infection, nerve root injury, recurrence, and incomplete removal of nucleus pulposus. The following factors determined exclusion: (1) the study included patients with spinal

Table 1: The basic characteristics of the included literature.

Author, year	Design	Operation type		Sample size (male/female)		Mean age (years)		Follow-up (months)	
		Observe group	Control group	Observe group	Control group	Observe group	Control group	Observe group	Control group
Chen (2015)[1]	RCS	PELD	NPLW	18 (12/6)	25 (14/11)	57.40 ± 12.40	54.90 ± 16.60	NR	NR
Lee (2009)[6]	RCS	PELD	NPLW	25 (16/9)	29 (22/7)	42.0 ± 11.4	47.7 ± 12.2	34.0 ± 4.4	34.3 ± 4.6
Lee (2018)[12]	RCS	PELD	NPLW	35 (25/10)	48 (30/18)	52.20 ± 12.87	50.13 ± 11.56	24.17 ± 11.83	23.65 ± 7.94
Liu (2017)[13]	RCS	PELD	MIS-TLIF	209 (110/99)	192 (92/100)	57.2	55.9	43.7	45.3
Ruetten (2009)[9]	RCT	PELD	MED	50	50	39	39	24	24
Wang (2020)[16]	RCS	PELD	MIS-TLIF	24 (14/10)	22 (14/8)	49.25 ± 13.95	56.00 ± 7.76	12	12
Yao (2017)[14]	RCS	PELD	MED/ MIS-TLIF	28 (18/10)	20 (11/9)/26 (13/13)	53.68 ± 17.70	51.05 ± 16.38 /51.62 ± 10.04	12	12
Yao (2017)[14]	RCS	PELD	MIS-TLIF	47 (72.34%)	58 (72.41%)	47.91 ± 14.77	46.76 ± 12.37	12	12

Note: RCT: randomized controlled trial; PCS: prospective cohort study; RCS: retrospective cohort study; PELD: Percutaneous endoscopic lumbar discectomy; NPLW: nucleus pulpotomy by lamina window; MED: microendoscopic discectomy; MIS-TLIF: minimally invasive transforaminal lumbar interbody fusion; NR: not reported.

deformity, apparent lumbar instability, lumbar spinal stenosis, spinal infection, tumor or tuberculosis, blood coagulation dysfunction, severe cardiopulmonary dysfunction, and other diseases; (2) non-English literature; (3) duplicated publications from the same hospital or research center; (4) incomplete or missing data, the author of the original study cannot be contacted.

2.3. Data Extraction. Two authors extracted pertinent data separately from eligible studies and cross-checked them. In the event of disagreements, they were resolved through dialogue or collaboration with an outside party. The contents of data extraction included (1) first author, publication time, study design, baseline characteristics of subjects, type of operation, and follow-up time. (2) Clinical outcome indices included overall incidence of complications, including postoperative sensory abnormality, dural tear rate, postoperative infection, and so on.

2.4. Methodological Quality. The two authors analyzed the risk of bias in the research independently and cross-checked their findings. For case-control and cohort studies, the Newcastle-Ottawa scale (NOS) [7] was used; for randomized controlled trials, the Cochrane manual-recommended RCT bias risk assessment tool [8] was used to evaluate the bias risk.

2.5. Statistical Analysis. The meta-analysis was performed using the Review Manager (RevMan version 5.4) software. The mean difference or standard deviation of the mean difference was used as the effect index for continuous variables, while the odds ratio (OR) was utilized for dichotomous variables. The estimated value and 95% CI of each effect quantity were calculated. Chi-square was utilized to examine statistical heterogeneity among the research results and was combined with the I^2 test to quantitatively estimate the magnitude of heterogeneity. If $p > 0.1$ and $I^2 < 50\%$, the fixed effect model was used for the meta-analysis; if $p \leq 0.1$ or $I^2 \geq 50\%$, the random effect model was used for meta-analysis after excluding the studies with high heterogeneity. $\alpha = 0.05$ was considered statistically significant.

Table 2: Results of risk assessment of bias in cohort studies.

Study	Selection	Comparability	Outcome	Total
Chen (2015)[10]	★★★★	★	★	6
Lee (2009)[6]	★★★★	★★	★★★	9
Lee (2018)[12]	★★★★	★★	★★★	9
Liu (2017)[13]	★★★★	★★	★★★	9
Wang (2020)[16]	★★★★	★★	★★★	9
Yao (2017)[14]	★★★★	★	★★★	8
Yao (2017)[14]	★★★★	★	★★★	8

3. Result

3.1. Identification of Eligible Studies. A total of 848 studies were obtained through an electronic database search. Figure 1 illustrates the literature screening procedure. After preliminary examination, rescreening, and finally including 8 articles comprising 1 RCT study and 7 cohort studies [9–16], there were a total of 906 participants in this study.

3.2. Characteristics of Included Studies. There was no statistically significant difference between gender, age, and other

Table 3: RCT bias risk assessment results.

Included study	Random method	Distribution and hidden	Participant blind method	Blind method of outcome evaluation	Integrity of outcome data	Publish research results selectively	Other sources of bias
Ruetten (2009)[9]	Random number table	Dimness	Single blind	Dimness	No lost of follow-up	No	Dimness

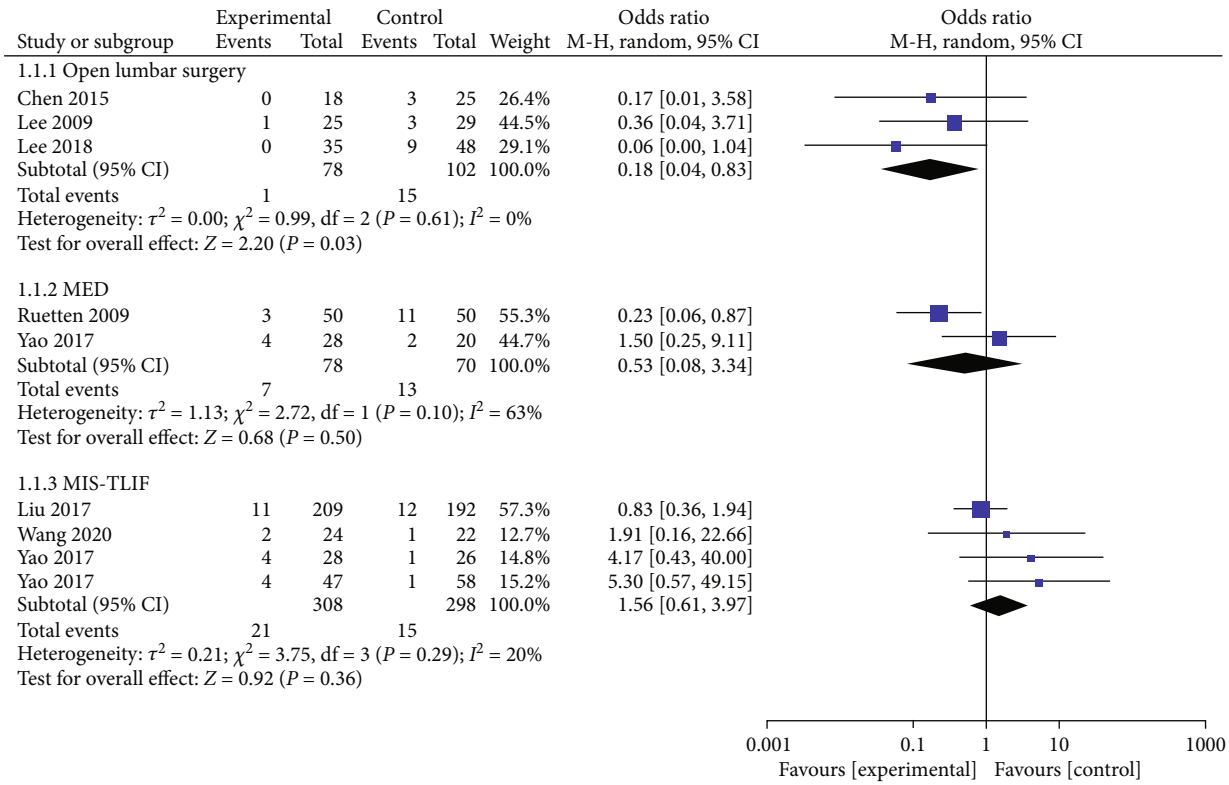

Figure 2: Forest chart of the overall incidence of complications.

baseline characteristics of patients included in the literature (Table 1).

3.3. Quality of Included Studies. For the 7 included cohort studies, the NOS bias risk score was 6~9 (Table 2). For the included RCT study, the bias risk was assessed according to the Cochrane manual (Table 3).

3.4. Meta-analysis Outcomes

3.4.1. Overall Incidence of Complications. A total of 8 studies reported complications. Of the 436 patients in the PELD group, 25 had complications, representing an incidence of 5.73%. The outcomes of the random effect model meta-analysis revealed that the overall incidence of complications in the PELD group was significantly lower than that in the open lumbar surgery group (OR = 0.18, 95% CI: 0.04-0.83, $p = 0.03$). Compared with the MED and MIS-TLIF groups, PELD group incidence was lower than MED group incidence, However, the disparity was not statistically significant (Figure 2).

3.4.2. Dural Tear. There were 6 studies that reported the incidence of intraoperative dural tears. Among the 394 patients in the PELD group, 3 suffered from dural tears (0.76%). The results of the meta-analysis of the fixed effect model exposed that the incidence of dural tears in the PELD group was lower than that in the open lumbar surgery group (OR = 0.11, 95% CI: 0.01-0.92, $p = 0.04$). The incidence of dural tear was quantitatively reduced in the PELD group compared to the MIS-TLIF group, but the meta-analysis revealed no significant difference between the two groups (Figure 3).

3.4.3. Nerve Root Injury. Five studies reported the occurrence of nerve root injury. Of the 362 patients who underwent PELD, 7 experienced complications (1.93%). The meta-analysis with a fixed effect model revealed that the incidence of nerve root injury was lower in the PELD group than in the MED group, but the difference was not statistically significant. Compared with the MIS-TLIF group, the incidence of nerve root injury in the PELD group was higher, but the difference was not statistically significant (Figure 4).

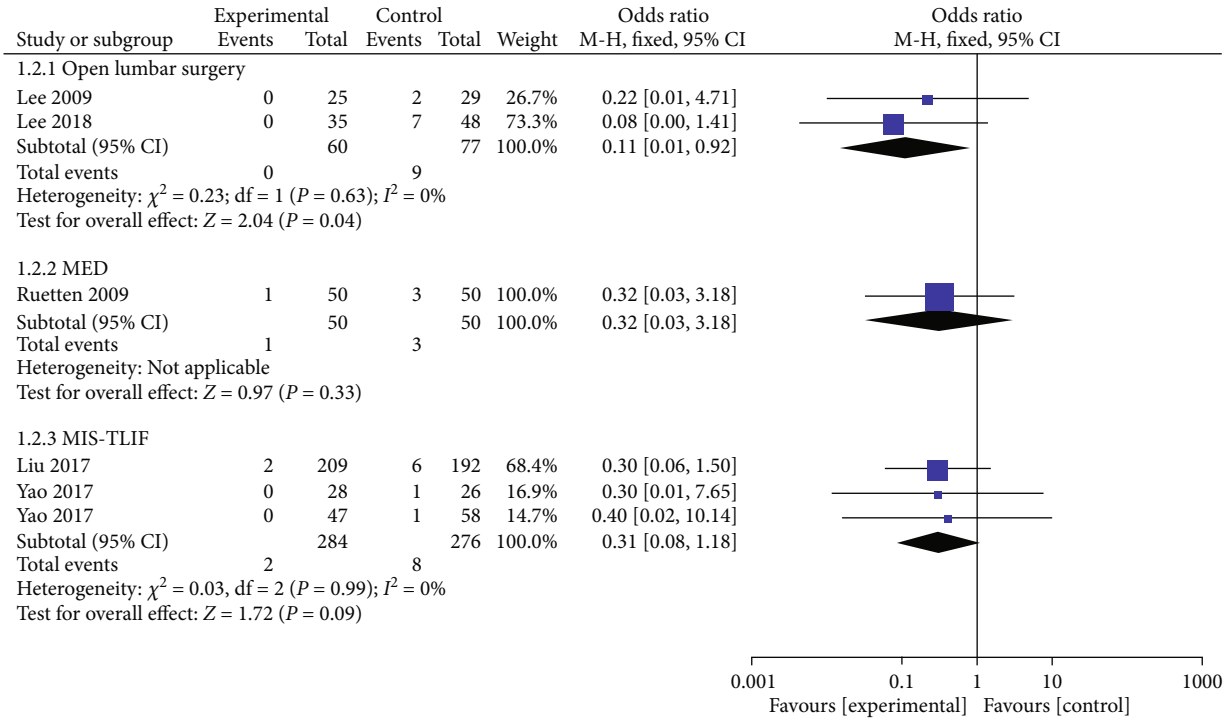

Figure 3: Forest chart of the incidence of dural tears.

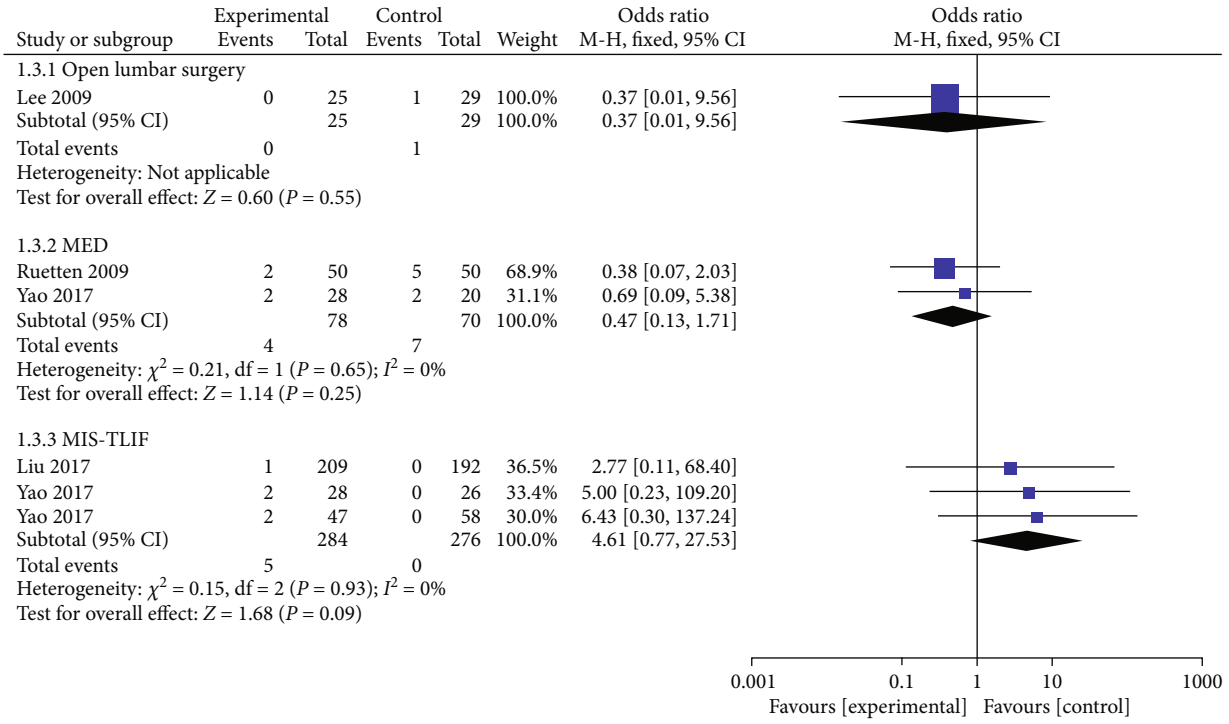

Figure 4: Forest chart of the incidence of nerve root injury.

3.4.4. Recurrence Rate. A total of 6 studies investigated the incidence of postoperative recurrence; of the 394 patients who underwent PELD, 37 cases recurred, with an incidence of 9.39%. The meta-analysis using a fixed effect model demonstrated that the recurrence rate in the PELD group was lower than that in the open lumbar surgery group, but the difference was not statistically significant. Likewise, compared with the MED group, the incidence of recurrence in the PELD group was higher. However, no statistical difference existed between the two groups. More importantly,

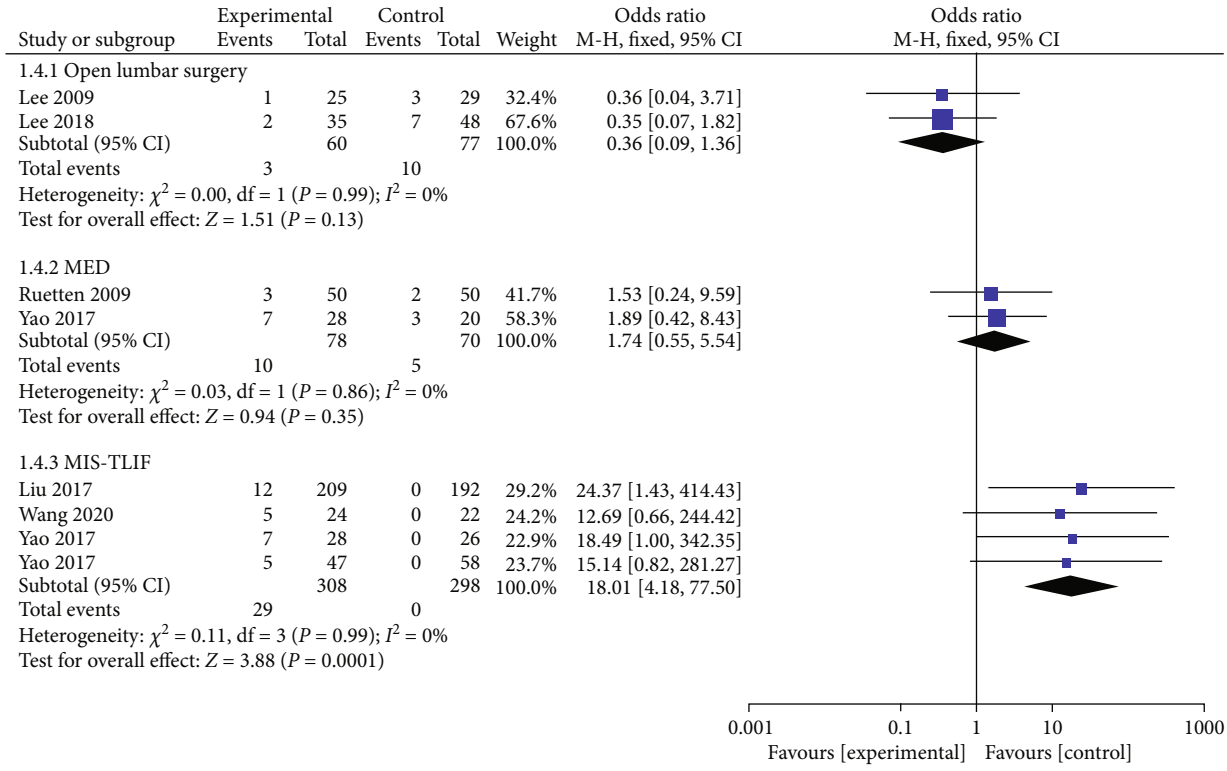

Figure 5: Forest chart of postoperative recurrence rate.

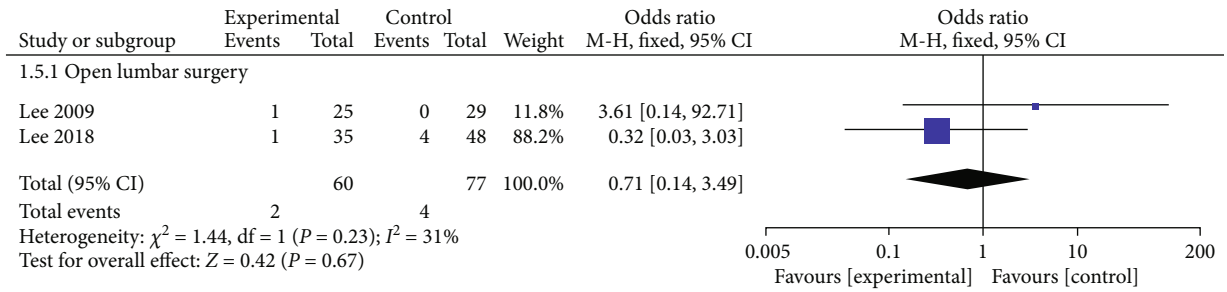

Figure 6: Forest chart of the incidence of incomplete nucleus pulposus excision.

the results revealed that the PELD group had a greater recurrence rate than the MIS-TLIF group, and the difference was statistically significant (OR = 19.71, 95% CI: 3.68-105.62, $p = 0.0005$) (Figure 5).

3.4.5. Incomplete Nucleus Pulposus Extirpation. Only 2 articles reported the incidence of incomplete removal of nucleus pulposus in the PELD and open lumbar surgery groups. Complications occurred in 2 cases (1.9%) in the PELD group and 4 cases (5.7%) in the open lumbar surgery group. The fixed effect model meta-analysis revealed that the PELD group had a lower rate of incomplete nucleus pulposus removal than the open lumbar surgery group, but the difference was not statistically significant (OR = 0.71, 95% CI: 0.14-3.49, $p = 0.67$) (Figure 6).

3.4.6. Postoperative Infection. Two articles documented the incidence of postoperative infection in the PELD and open lumbar surgery groups. There were no cases of postoperative infection in the PELD group. The results of the fixed effect model meta-analysis revealed no statistically significant difference between the PELD and open lumbar surgery groups (Figure 7).

3.5. Sensitivity Analysis. The sensitivity of the main index of overall complications was analyzed by excluding individual studies from the meta-analysis, and the results of the meta-analysis were not significantly altered, suggesting a low heterogeneity in the meta-analysis.

3.6. Publication Bias. From the funnel chart employed to test the publication bias in the outcome index of overall complications, it can be deduced that the distribution of each study is symmetrical, demonstrating a low likelihood of publication bias (Figure 8).

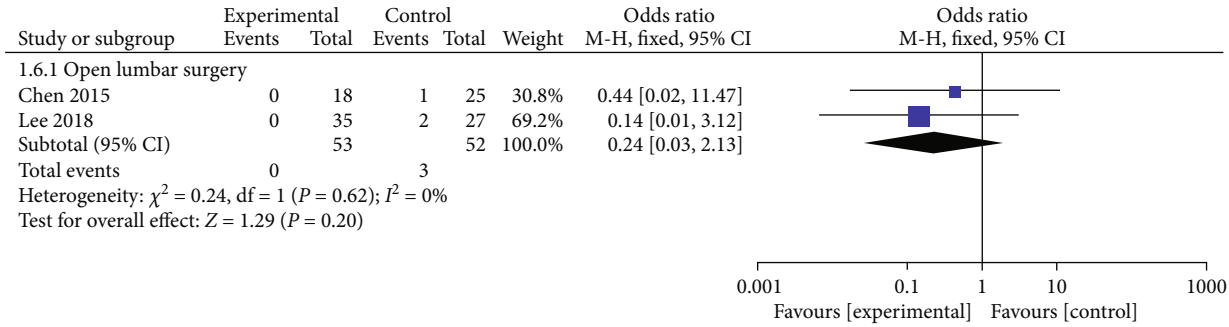

Figure 7: Forest chart of the incidence of postoperative infection.

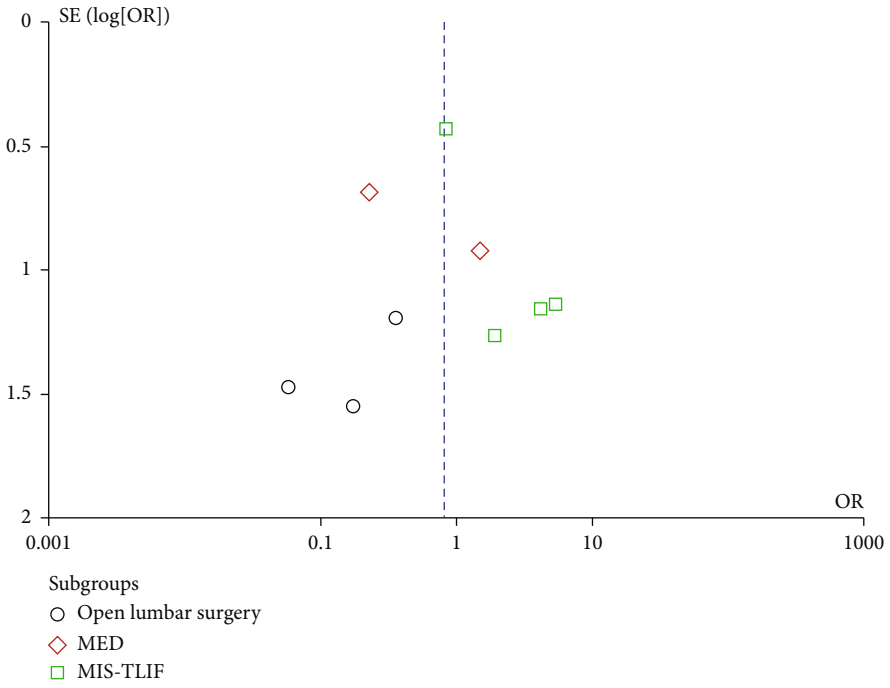

Figure 8: Funnel plot of the overall complication rate.

4. Discussion

Laminectomy was long regarded as the treatment of choice for LDH, but several studies have reported that the recurrence rate following LDH ranged from 5% to 18% [17], while the reoperation rate was 13.9% [18]. Repeated fenestration of the nucleus pulposus is regarded as the therapy of choice for recurrent lumbar disc herniation following the initial surgical procedure [19, 20]. However, after RLDH revision surgery, the incidence of complications including nerve root injury, dural tear, and postoperative sensory abnormalities increased, as well as the degeneration of spinal motor units such as facet joints [21]. During the past decade, numerous minimally invasive operations have been developed for the treatment of RLDH, including microscopic disc removal, discoscopic nucleus pulposus extraction (MED), collagenase injection combined with targeted radiofrequency, minimally invasive (Quadrant channel expansion system), and spinal endoscopic techniques, and the clinical outcomes are comparable to that of traditional open surgery [10]. PELD is an established minimally invasive surgical treatment. With advancements in PELD for the treatment of LDH, more and more spinal surgeons have recognized that complications related to scar tissue and posterior structure trauma can be solved by PELD. Yeung and Tsou [22] introduced PELD for the treatment of RLDH first time and accomplished satisfactory results with "intradiscal-extradiscal" clearance of herniated nucleus pulposus tissues from the intervertebral space under direct vision. Since then, increasingly more studies have discovered that the application of PELD for RLDH provides a minimally invasive and effective treatment alternative for RLDH patients [23].

Earlier researches have validated that the clinical efficacy of PELD for the treatment of RLDH is similar to that of other revision surgeries, and some studies have described that its clinical efficacy is actually superior to that of other revision surgeries [24–26]. As per studies, epidural and perineural scar tissue heightens the danger of nerve root injury as well as intraoperative dural rupture [25]. According to previous studies, the incidence of dural tear in lumbar

discectomy is 6.9%-20%, which has an adverse impact on the clinical outcomes of the operation [27]. Herein, 11.69% of patients undergoing conventional windowed nucleus pulposectomy suffered from dural tears, compared to no dural tears in patients of the PELD group. In PELD surgery, scar tissue can be selectively excised from nerve tissue under a microscope, and residual scar tissue can be employed as a protective layer of nerve tissue, which may be the reason behind the low incidence of dural injury in patients undergoing PELD.

Reviewing the related literature [28] corroborated that the incidence of nerve root adhesion following transforaminal PELD is low, and patients with uncalcified disc herniation, nonsevere neurological defect, confirmed diagnosis of sciatica, and symptom duration less than 3 months after recurrence should be prioritized. Nevertheless, the interlaminar approach remains the optimal treatment for patients with large intraspinal prolapse, high prolapse, calcified disc herniation, L5/S1 disc herniation with the high iliac spine, and severe lumbar intervertebral foramen osseous stenosis. The transforaminal approach or interlaminar approach for PELD can effectively avoid scar tissue resulting from the first posterior operation, thus limiting the degradation of the spine's posterior structure without compromising its stability and minimizing the incidence of severe complications such as nerve injury and dural tear caused by traditional reoperation to separate the posterior scar tissue.

Prior studies have reported that the recurrence rate of patients who had undergone MED, PELD, or open discectomy and required revision PELD surgery was 4.62%~7.69% [26]. In this study, the recurrence rate of PELD for the treatment of RLDH was 8.37%. The results demonstrated that MIS-TLIF had a much lower recurrence rate than PELD, which is consistent with the findings of prior research [24]. A few studies have also pointed out that the effect of surgery after the recurrence of intervertebral disc herniation relates to the type of the initial operation [29]. Moreover, given the steep learning curve of PELD, many surgeons lack the experience to estimate the number of intervertebral disc materials to be removed during surgery, leaving the possibility of residual nucleus pulposus. However, this study found that the rate of residual nucleus pulposus following PELD (3.33%) was lower than that of traditional windowing surgery (5.19%).

Eight studies were examined for this study, and the bias risk assessment results of the various design types indicated that the studies were of excellent quality. Sensitivity analysis was utilized to exclude studies one by one from the meta-analysis. Lastly, the funnel chart displayed that the possibility of publication bias was small, showing the reliability of the results of this meta-analysis.

The following are the limitations of this meta-analysis: (1) sample sizes in individual research were modest, which impacted the extrapolation of the results; (2) only a single randomized controlled trial was included in the analysis, and the allocation of hidden and blind methods was not mentioned; hence, the likelihood of implementation and measurement bias is higher; (3) the duration of follow-up considerably varied, and the number of cases developing postoperative complications in the PELD and MED groups was relatively low. Therefore, the long-term complication rate and recurrence rate of PELD for the treatment of RLDH require additional study.

To sum up, compared with traditional lamina fenestration, PELD has a lower incidence of complications and a higher safety profile for the treatment of RLDH. Nevertheless, PELD has a similar incidence of complications for the treatment of RLDH compared to MED and MIS-TLIF. Therefore, we postulate that PELD is an efficient and safe surgical technique for treating individuals with RLDH without imaging lumbar instability. As a result of the restricted number of included studies, the aforementioned conclusions require additional validation by high-quality, large sample size studies.

Data Availability

The data that support the findings of this study are openly available in PubMed, Embase, The Cochrane Library, and Web of Science electronic databases.

Conflicts of Interest

There were no conflicts of interest concerning this article. Each author certifies that he has no commercial associations that might pose conflicts of interest in connection with the submitted article.

Authors' Contributions

Ke Zhao contributed to the conceptualization, methodology, formal analysis, investigation, and writing—original draft. Lin-Da Li contributed to the formal analysis, investigation, and writing—original draft. Tong-Tong Li contributed to the writing—review and editing and supervision. Yong Xiong contributed to the validation and supervision. Ke Zhao and Lin-Da Li have contributed equally to this work.

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Research Article

Biomechanical Characterization of Unilateral and Bilateral Posterior Lumbar Interbody Fusion Constructs

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Study Design. Cadaveric biomechanical study. *Objectives*. To compare the biomechanical stability of two-level PLIF constructs with unilateral and bilateral pedicle screw fixations. *Methods*. Six cadaveric lumbar segments were evaluated to assess biomechanical stability in response to pure moment loads applied in flexion-extension (FE), lateral bending (LB), and axial rotation (AR). Each specimen was tested in six sequential configurations: (1) intact baseline; (2) facetectomy; (3) unilateral pedicle screws (UPS); (4) bilateral pedicle screws (BPS); (5) unilateral pedicle screws and cage (UPSC); and (6) bilateral pedicle screws and cage (BPSC). *Results*. Significant reductions in motion were observed when comparing all instrumented conditions to the intact and facetectomy stages of testing. No significant differences in motion between UPS, BPS, UPSC, or BPSC were observed in response to FE range of motion (ROM) or neutral zone (NZ). ROM was significantly higher in the UPS stage compared to BPS in response to LB and AT loading. ROM was significantly higher in UPSC compared to BPSC in response to LB loading only. Similarly, NZ was significantly higher in UPSC compared to BPSC in response to only LB loading. In response to AT loading, ROM was significantly higher during UPS than BPS or BPSC; however, no significant differences were noted between UPSC and BPSC with respect to AT ROM or NZ. *Conclusion*. BPS fixation is biomechanically superior to UPS fixation in multilevel PLIF constructs. This was most pronounced during both LB loading. Interbody support did contribute significantly to immediate stability.

1. Introduction

Thoroughly understanding the biomechanical characteristics of the lumbar spine is critical to furthering the treatment of spinal pathologies. One such treatment includes the use of pedicle screws and rods for spinal stabilization. This approach is widely popular for single and multilevel spinal fusions for various lumbar disorders. Several posterior fixation techniques are currently available to promote spinal fusion with bilateral fixation being considered the "gold standard" [1]. This is a result of its ability to improve arthrodesis rates, increase fusion, and prevent nonunion. Posterior lumbar interbody fusion (PLIF) also has the ability to decompress the dural sac and nerve roots while maintaining disc height and increases the rate of recovery from spinal fusion procedures [2].

While considered the gold standard in treatment, there are some drawbacks associated with the use of rigid fixation during spinal procedures. Lumbar spinal fusion has been shown to increase the rate of degeneration of lumbar segments adjacent to the instrumentation and has the potential for issues involving the device (i.e., subsidence and migration) and osteoporosis [3]. This may be due to changes in the distribution of forces with the use of stiff bilateral constructs, which have the potential to offload the disc space and thus reduce bony formation according to Wolf's Law. Numerous techniques have been studied in order to combat these deleterious effects. For example, minimally invasive

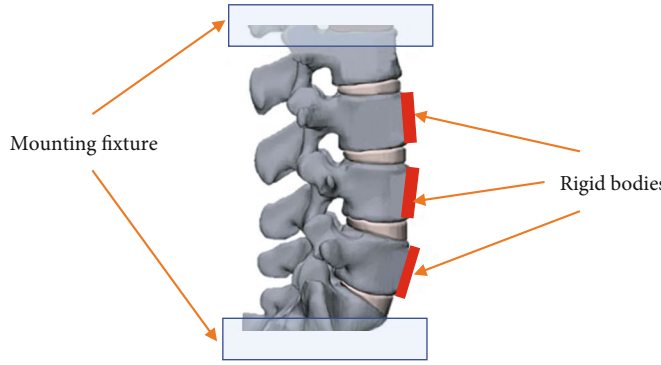

Figure 1: Illustration of specimen preparation showing placement of mounting fixtures at L2 and S1 as well as rigid tracking bodies attached to the anterior aspect of L3, L4, and L5.

approaches—such as the use of unilateral pedicle screw fixation—have the potential to increase graft loading while decreasing operating time, intraoperative blood loss, recovery time, and the risk of adjacent segment disease [4, 5]. One of the major advantages of unilateral fixation is the decrease in patient morbidity. Due to less instrumentation, there is a decrease in OR time, blood loss, and hospital stay associated with unilateral constructs [6]. The two major differences between the surgical approaches for unilateral and bilateral pedicle screws are in the amount of instrumentation used and the size of the operative field. Bilateral fixation requires dissection of both paravertebral muscles and insertion points. This is opposed to the single dissection required for unilateral fixation which allows for less tissue damage and potentially earlier functional recovery [7]. However, there is limited data comparing UPS to standard of care procedures. In addition, the data available is contradictory insofar that some studies state that unilateral fixation is as effective as bilateral fixation when used with interbody devices, while other studies have demonstrated better fixation results associated with bilateral fixation [8–11]. While it is unclear whether unilateral and bilateral fixations with interbody fusion are equitable and both sufficient for spinal fusion, limited studies have been able to accurately compare the procedures using pure moments.

Our objective was to determine if unilateral pedicle screw fixation can provide stability comparable to that of bilateral pedicle screw fixation. More specifically, the goal of this study was to investigate the stability of multilevel PLIF constructs with both UPS and BPS in response to pure moment loading.

2. Methods

Six cadaveric lumbar segments were obtained. Specimens were then cleaned and dissected down to osteoligamentous structures and disarticulated at the L1-L2 index level to produce L2-S1 vertebral segments for testing. Once thoroughly cleaned, an intact vertebral column was potted into custom aluminum potting rings using a thermosetting polymer, polyester resin, and hardener (Bondo, 3M, Atlanta, GA) as seen in Figure 1. After the polymer was allowed to cure, each segment was loaded into a Bose six-degrees-of-freedom spine testing apparatus and subjected to a series of pure moment flexibility tests in flexion-extension (FE), lateral bending (LB), and axial torsion (AT) modes of loadings as described by Cook et al. [12]. Figure 2 shows how this works.

The initial testing condition is referred to as Intact and is used to characterize the functional spinal unit's (FSU) baseline biomechanical characteristics before surgical intervention and instrumentation. Treatments were randomized to either the left or the right side of the segment according to Table 1. The second stage of testing, hereby referred to as Facetectomy for the remainder of this paper, involved a unilateral facetectomy followed by flexibility testing and was intended to represent the destabilized condition. The L3-L5 index levels were then instrumented in a series of procedures in both the unilateral and bilateral states. Flexibility tests were performed for each level in order to determine the efficacy of the pedicle screw constructs with and without intervertebral cages. The constructs were then tested in order from least destructive to most destructive states. Unilateral pedicle screw instrumentation (UPS) was completed immediately following the completion of unilateral Facetectomy testing, followed by bilateral pedicle screws (BPS), unilateral pedicle screws with a PLIF cage (UPSC), and finally bilateral pedicles screws with a cage (BPSC). The 6 specimens were sequentially measured on intact, unilateral facetectomy, UPS, BPS, UPSC, and BPSC. The sets of data of flexion-extension, lateral bending, and axial rotation were measured at each stage. All tested constructs were imaged via an O-arm (Medtronic) to confirm pedicle screw and cage placement.

The posterior vertebral fixation construct utilized over the course of this study was the CD Horizon Legacy Spinal System (Medtronic, Minneapolis, MN). Each construct was composed of six pedicle screws, ranging from size 5.5×40 mm to 6.5×50 mm as designated in Table 1. 5.5×70 mm CD Horizon Legacy titanium rods were implemented into each construct with the exception of one larger specimen, for which a 55×100 mm Zodiac titanium rod (Alphatec, Carlsbad, Ca) was used. All of the interbody devices used came from the Capstone Spinal System (Medtronic, Minneapolis, MN). The intervertebral cage size information for each specimen can also be found in Table 1. All screws, rods, and interbody devices were placed by a trained spinal surgeon according to the manufacturer's protocol recommendations.

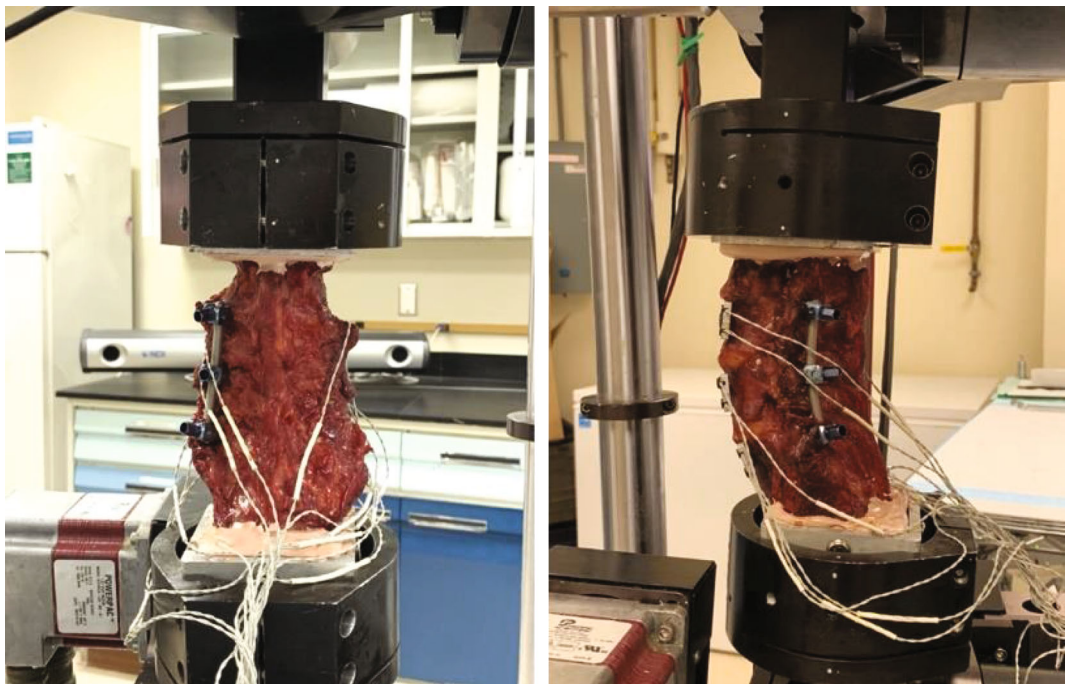

Figure 2: Illustration of specimen with L3-L5 unilateral pedicle screw fixation which was tested in Bose six-degrees-of-freedom spine testing apparatus.

Table 1: Specimen and device information.

Specimen	Facetectomy	Level	Cage
1	Left	L3/L4	12 × 26 mm
		L4/L5	10 × 22 mm
2	Right	L3/L4	10 × 22 mm
		L4/L5	12 × 26 mm
3	Left	L3/L4	12 × 22 mm
		L4/L5	10 × 22 mm
4	Right	L3/L4	10 × 22 mm
		L4/L5	8 × 26 mm
5	Left	L3/L4	8 × 26 mm
		L4/L5	10 × 22 mm
6	Right	L3/L4	12 × 22 mm
		L4/L5	12 × 26 mm

All biomechanical testing was conducted using a six-degrees-of-freedom spine tester (Bose, Smart Test Series, Eden Prairie, MN) under a standard flexibility protocol with independent motors driven in load control. This characterizes the FSU's baseline flexibility and allows each specimen to serve as its own control. The flexion-extension and lateral bending protocols apply a uniform pure moment across the specimen through counteracting superior and inferior mounted stepper motors [13]. The magnitude for the pure moment protocol has been referenced in numerous peer-reviewed articles dealing with in vitro cadaveric studies [13, 14] as well as finite element analysis [15]. Each specimen was subjected to 7.5 Nm pure moment loads in flexion-extension, lateral bending, and axial torsional with no compressive preload. All samples were not damaged by the pure moment load of 7.5 Nm during the test.

During flexibility testing, the loads for FE, LB, and AT were applied for three cycles with the last cycle being use for data analysis. The range of motion (ROM) of each segment was measured using an optoelectric tracking system (Opotrak Certues, Northern Digital, Waterloo, ON) with rigid bodies fixed to the anterior aspect of the L3, L4, and L5 vertebral bodies. The rigid component, known as a Tracking Body, houses four light emitting diodes (LEDs) and was attached to the anterior surface of each vertebral body prior to each test. Four points defining the orientation of the test apparatus motor axes were digitized relative to the L3 and L5 Tracking Bodies to form an anatomically relevant coordinate system. Positional data from each rigid body were used to calculate the relative angular motion (ROM) and neutral zones (NZ) between the L3-L4 and L4-L5 disc spaces.

For statistical analysis, the ROM and NZ for each level at each stage were normalized to the intact condition. Changes in ROM or NZ from stage to stage are therefore presented as percent changes relative to the intact condition. A repeated measure ANOVA with Bonferroni post hoc analysis was performed to elucidate statistically significant differences between cohorts.

3. Results

All present data can be seen in Figure 3. The data shows significant reduction in motion for all instrumented cadaveric

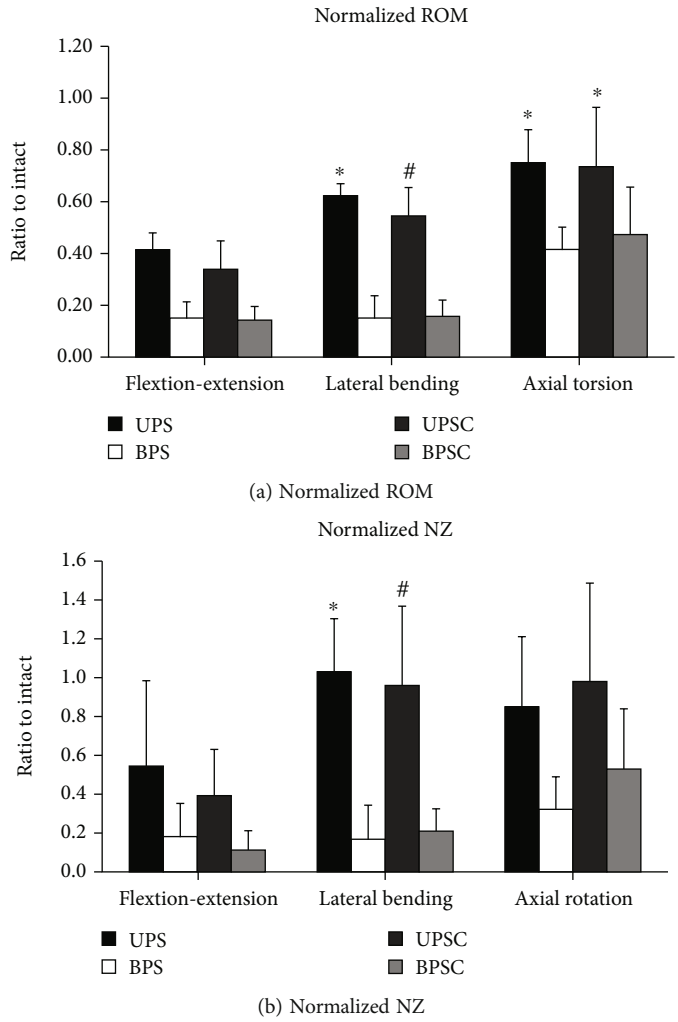

Figure 3: Results of flexibility testing normalized to the intact condition: (a) range of motion results for each stage of testing; (b) neutral zone results for each stage of testing. *Denotes significant difference compared to BPS; #denotes significant difference compared to BPSC.

spines with respect to the intact and facetectomy stages of testing, indicating solid fixation for all treatments. O-arm images were reviewed for confirmation of proper pedicle screw and cage placement. There were no signs of breach in any of the instrumented spines.

Descriptive statistics for flexion-extension loading can be seen in Table 2. Sphericity was violated, $\chi^2(14) = 51.354$, and degrees of freedom were therefore corrected using the Greenhouse-Giesser method ($\varepsilon = 0.314$). This revealed a significant difference between the cohorts with respect to normalized FE ROM, $F(1.57, 17.29) = 36.709$, $p = 0.000$. Post hoc analysis showed significant decreases in motion from the Facetectomy stage of testing to all instrumented conditions; however, there were no significant differences in motion between unilateral and bilateral constructs with or without the implanted cage. Mauchly's test of sphericity indicated that sphericity was violated for the FE neutral zone data as well as $\chi^2(14) = 53.03$, and degrees of freedom were corrected using the Greenhouse-Giesser method ($\varepsilon = 0.296$). The repeated measure ANOVA according to the Greenhouse-Giesser correction showed no significant difference between the cohorts with respect to normalized FE NZ, $F(1.48, 16.304) = 2.37$, $p = 0.135$.

Descriptive statistics for lateral bending loading can be seen in Table 3. Mauchly's test of sphericity indicated that sphericity was violated for both ROM and NZ, $\chi^2(14) = 47.1$, $p = 0.000$ ($\varepsilon = 0.45$) and $\chi^2(14) = 45.43$, $p = 0.000$ ($\varepsilon = 0.467$), respectively. The repeated measure ANOVA revealed a significant difference between the cohorts with respect to normalized LB ROM, $F(2.338, 25.717) = 17.41$, $p = 0.000$. Angular motion during the UPS stage of testing was significantly larger than during the bilateral stage of testing, $p = 0.000$, or the BPSC stage, $p = 0.000$. Similarly, ROM during the UPSC stage was significantly higher than the BPS, $p = 0.000$, or BPSC, $p = 0.000$, stages of testing. The repeated measure ANOVA revealed a significant difference between the cohorts with respect to normalized LB NZ, $F(1.761, 14.087) = 45.394$, $p = 0.000$. Review of post hoc analysis showed a significantly higher NZ during the UPS stage compared to the BPS stage ($p = 0.000$) or BPSC ($p = 0.000$). UPSC also demonstrated significantly larger NZ than both BPS ($p = 0.0004$) and BPSC ($p = 0.0001$).

Table 2: FE-loading descriptive statistics.

Stage	Flexibility parameters	Raw				Normalized			
		Mean	Std. deviation	95% LCL	95% UCL	Mean	Std. deviation	95% LCL	95% UCL
Intact	ROM	6.87	0.92	4.85	8.89	1.00	—	—	—
	NZ	1.47	0.28	0.86	2.08	1.00	—	—	—
Facetectomy	ROM	7.22	0.88	5.28	9.15	1.14	0.07	0.98	1.29
	NZ	1.41	0.26	0.84	1.99	0.91	0.10	0.68	1.13
Unilateral	ROM	2.89	0.46	1.88	3.90	0.44	0.03	0.37	0.51
	NZ	0.71	0.18	0.30	1.11	0.67	0.16	0.31	1.02
Bilateral	ROM	1.22	0.16	0.87	1.57	0.32	0.12	0.04	0.59
	NZ	0.27	0.07	0.11	0.43	0.52	0.33	-0.21	1.24
Unilateral+cage	ROM	2.51	0.44	1.54	3.48	0.42	0.06	0.28	0.56
	NZ	0.64	0.18	0.24	1.03	0.67	0.25	0.12	1.22
Bilateral+cage	ROM	1.20	0.14	0.89	1.52	0.34	0.13	0.05	0.63
	NZ	0.21	0.06	0.07	0.34	0.31	0.14	0.00	0.63

FE: results of flexion-extension testing. Raw values indicate motion measured in degrees while normalized values represent the amount of motion as a percentage of intact values.

Table 3: LB-loading descriptive statistics.

Stage	Flexibility parameters	Raw				Normalized			
		Mean	Std. deviation	95% LCL	95% UCL	Mean	Std. deviation	95% LCL	95% UCL
Intact	ROM	8.13	0.68	6.64	9.63	1.00	—	—	—
	NZ	1.35	0.18	0.96	1.75	1.00	—	—	—
Facetectomy	ROM	8.55	0.71	7.00	10.10	1.05	0.02	1.00	1.11
	NZ	1.62	0.21	1.15	2.09	1.24	0.14	0.94	1.54
Unilateral	ROM	5.23	0.48	4.17	6.28	0.65	0.05	0.54	0.77
	NZ	1.42	0.18	1.03	1.81	1.12	0.15	0.79	1.45
Bilateral	ROM	1.74	0.35	0.98	2.50	0.24	0.06	0.11	0.37
	NZ	0.43	0.15	0.09	0.76	0.41	0.17	0.02	0.79
Unilateral+cage	ROM	4.83	0.56	3.59	6.07	0.59	0.05	0.48	0.70
	NZ	1.34	0.23	0.83	1.84	0.98	0.11	0.74	1.23
Bilateral+cage	ROM	1.78	0.38	0.94	2.62	0.24	0.06	0.1	0.38
	NZ	0.41	0.11	0.16	0.66	0.36	0.12	0.09	0.63

LB: results of lateral bending testing. Raw values indicate motion measured in degrees while normalized values represent the amount of motion as a percentage of intact values.

Descriptive statistics for Axial Torsion loading can be seen in Table 4. Using the Greenhouse-Gieser correction due to violation of sphericity, the repeated measure ANOVA revealed a significant difference between the cohorts with respect to normalized AT ROM, $F(1.843, 20.283) = 23.079$, $p = 0.000$. Angular motion during the UPS stage of testing was significantly larger than during the bilateral stage of testing ($p = 0.000$) or the BPSC stage ($p = 0.036$). Similarly, ROM during the UPSC stage was significantly higher than the ROM measured during the BPS stage ($p = 0.005$); however there was no significant difference between the UPSC and BPSC stages. The repeated measure ANOVA revealed a significant difference between the cohorts with respect to normalized AT NZ, $F(1.638, 18.02) = 10.298$, $p = 0.0017$. Nonetheless, these significant differences were between the Facetectomy stage and all instrumented conditions, and there were no significant differences between instrumented cohorts. In addition, the BPS stage of testing showed significantly lower NZ than the intact condition. Figure 3 below illustrates these results.

4. Discussion

Posterior fusion procedures of the lumbar spine attempt to stabilize vertebral segments in order to create optimal conditions for arthrodesis to occur. These procedures are often performed with the utilization of rods and screws to immobilize the intervertebral space and allow fusion. In some instances, a surgeon may place an interbody cage within the intervertebral disc space to further promote immobilization of the spinal segment and encourage bone growth. There are a wide variety of approaches that can be utilized in order to place the interbody cage, and each has their own set of advantages and disadvantages [16]. One of the

Table 4: AT-loading descriptive statistics.

Stage	Flexibility parameters	Raw				Normalized			
		Mean	Std. deviation	95% LCL	95% UCL	Mean	Std. deviation	95% LCL	95% UCL
Intact	ROM	3.63	0.42	2.70	4.55	1.00		—	—
	NZ	0.86	0.17	0.48	1.23	1.00			
Facetectomy	ROM	4.53	0.51	3.40	5.66	1.26	0.14	0.95	1.58
	NZ	1.05	0.20	0.61	1.49	1.49	0.28	0.86	2.11
Unilateral	ROM	2.67	0.36	1.86	3.47	0.74	0.10	0.52	0.97
	NZ	0.63	0.14	0.32	0.93	0.89	0.20	0.46	1.33
Bilateral	ROM	1.48	0.16	1.12	1.83	0.41	0.04	0.31	0.51
	NZ	0.26	0.05	0.15	0.36	0.36	0.07	0.21	0.52
Unilateral+cage	ROM	2.46	0.27	1.86	3.07	0.69	0.08	0.52	0.85
	NZ	0.66	0.09	0.45	0.86	0.69	0.08	0.52	0.85
Bilateral+cage	ROM	1.64	0.19	1.22	2.07	0.46	0.05	0.34	0.58
	NZ	0.38	0.06	0.25	0.51	0.55	0.08	0.36	0.73

AT: results of axial-torsion testing. Raw values indicate motion measured in degrees while normalized values represent the amount of motion as a percentage of intact values.

most common procedures performed during spinal fusion surgeries is the PLIF. During a PLIF, a surgeon must introduce unilateral or bilateral facet injury in order to allow the placement of the interbody device. Because of the destructive nature of this procedure, it is generally recommended that surgeons combine the use of a posterior interbody cage with pedicle screw fixation [17]. As this is the case, we aimed to explore whether or not unilateral pedicle screw fixation was equivalent to bilateral fixation when performing multilevel posterior lumbar fusion procedures.

The results of this study showed variations in construct stability based on the direction of applied load. The most pronounced differences between the UPSC and BPSC cohorts were observed during LB loading, with significantly higher ROM (59% vs. 24% of intact) and NZ (98% vs. 36% of intact) in the UPSC group compared to the BPSC cohort. Unsurprisingly, ROM and NZ measured in response to lateral bending loading were significantly higher when comparing unilateral and bilateral pedicle screw fixations without the inclusion of an interbody cage. Significant differences were also observed in axial loading conditions, with significantly higher angular motion measured during UPS testing compared to BPS constructs; however, differences between the UPSC and BPSC cohorts were insignificant. There were no significant differences observed with respect to both ROM and NZ measured during FE loading. Furthermore, the addition of a unilateral standard PLIF cage did not have a significant effect on stability in any of the tested conditions.

While in vitro cadaveric studies comparing the stability of unilateral and bilateral PLIF constructs are limited, these results correlate well with those reported in the literature. A 2008 study conducted by Yucesoy et al. showed significant reductions in the stability of two-level unilateral constructs in comparison to bilateral constructs, with lateral bending as the clear weakness of unilateral constructs [11]. Finite element models aimed at comparing the stability of unilateral and bilateral PLIF constructs have also yielded similar conclusions [6, 8]. Perhaps the most valid comparison to the present work is the finite element model presented by Kim et al. comparing the stability of unilateral and bilateral constructs with a hemilaminectomy. In this study, the authors report the ranges of motion for unilateral constructs in response to FE, LB, and AT loads of 32%, 31.7%, and 61.7% of the intact motion compared to reductions to 8%, 26.8%, and 50% of the intact motion for bilateral constructs. Another finite element study conducted by Ambati et al. produced similar results; showing reductions in angular motion to 50% of intact left bending motion and 63% of axial rotation for unilateral constructs compared to values reported for bilateral constructs of 10% of intact motion for left bending and 10% of motion for axial rotation. Furthermore, Ambati et al. found that the shape and position of the interbody device did not have a significant influence on the reported ROM [8]. This is similar to our results, which show that the addition of an interbody cage did not significantly influence the ROM or NZ at the index level. These results indicate that the stability of PLIF constructs is primarily driven by posterior instrumentation. In contrast, studies focused on comparing unilateral and bilateral fixation in conjunction with larger interbody devices such as lateral cages have shown comparable stability regardless of posterior fixation [10].

Numerous clinical studies have been published in the last decade comparing the efficacy of unilateral and bilateral PLIF and TLIF constructs, underscoring the importance of a sound biomechanical understanding of each treatment modality [5, 9, 18–21]. Results of these studies are not as clear as those biomechanics studies previously discussed in terms of establishing the superiority of unilateral or bilateral pedicle screw fixation. Many studies report similar fusion rates, complication rates, and patient reported outcomes with improvements in perioperative measures such as blood loss, OR time, and length of stay [18, 19, 21]. Those studies which included cost analysis of the two fixation strategies demonstrated significant reductions in medical expenses, with an average expense of $3,500 USD for unilateral pedicle

screw fixation compared to $4,800 for bilateral pedicle screw fixation [21]. However, a 2012 study conducted by Duncan et al. contradicts these results, concluding that unilateral TLIF constructs have a higher propensity for cage migration compared to bilateral constructs (23% vs. 11%, respectively) [9]. Finally, a series of in vivo dynamic motion measurements conducted on 13 patients with unilateral pedicle screw fixation and 15 patients with bilateral pedicle screw fixation conducted by Nie et al. provides a bridge between clinical and biomechanics studies. This study showed that the increase in axial rotation observed in biomechanics studies does translate to the clinical scenario, with an average left-right twist ROM of 2.11 ± 0.52 degrees for unilateral constructs compared to 0.73 ± 0.32 degrees for bilateral constructs. The authors also reported a reduced effect on adjacent segments with unilateral constructs, as indicated by a reduction in adjacent segment motion [5]. Unfortunately, no outcome data was included in this report making it difficult to determine the clinical implications of these differences in motion characteristics.

There are several limitations to this study. First is the fact that only a single cage was used as opposed to a bilateral intervertebral device, as the use of bilateral cages may have changed the results and would require additional testing. The second limitation of this study is in the implementation of an in vitro cadaveric model. Cadaveric models only allow us to assess immediate stability provided by a construct after surgery but before arthrodesis has occurred. This model will never allow us to directly compare the arthrodesis capability between a unilateral and a bilateral spinal construct. For this reason, it is difficult to extrapolate the results from biomechanical testing to direct clinical outcomes. Due to the inherent condition of a cadaveric model, the lack of biologics can also directly affect spinal fusion competence. Although the sample size for this study is statistically in line with other impactful studies, cadaveric variations may have played a role in various motions seen during each testing stage and thus affect the reproducibility of the study. Lastly, posterior spinal instrumentation can have a major impact on observed segment motion due to the size of screws, rod, and interbody devices implanted during surgery. Variables among the instrumentation could be one potential explanation for the diversity of conclusions seen with regard to the comparison of unilateral and bilateral constructs seen in the literature. Additional biomechanical studies are needed to clarify our understanding of this comparison. Extensive clinical research is required before these biomechanical results can be translated into clinical practice, but it is our hope that this study will serve to demonstrate the idea that there are severe biomechanical differences between unilateral and bilateral PLIF constructs that should be considered when deciding upon the appropriate treatment modality.

5. Conclusion

Surgeons must consider a multitude of factors when selecting the appropriate treatment strategy for each patient, including biomechanical, perioperative, and postoperative factors in order to reduce the physical and financial burdens of spinal surgery. Unilateral pedicle screw fixation offers a number of benefits with respect to reducing the morbidity of spinal fusion procedures. However, from a biomechanical perspective, PLIF constructs with bilateral pedicle screw fixation provide superior stability compared to unilateral constructs. This trend was observed during both lateral bending and axial torsion loading conditions. Unilateral spinal fixation may be a viable option in some patients during single-level fusion procedures, but caution should be taken when applying the same doctrine to a multilevel scenario. Further research is needed to garner substantiating conclusions regarding the use of unilateral fixation during multilevel spinal fusion procedures.

Data Availability

All present data can be seen in Figure 3.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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Research Article

Risk Factors of Total Blood Loss and Hidden Blood Loss in Patients with Adolescent Idiopathic Scoliosis: A Retrospective Study

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Objectives. To investigate the risk factors of total blood loss (TBL) and hidden blood loss (HBL) in adolescent idiopathic scoliosis (AIS) patients undergoing posterior orthopedic surgery. *Methods*. The AIS patients who visited department of spine surgery between January 2015 and December 2020 were retrospectively reviewed. Those with a history of posterior orthopedic surgery for AIS were identified, and their clinical data were collected. Gross formula was used to calculate the TBL and HBL. SPSS 20.0 was used for statistical analysis. The potential risk factors of TBL and HBL were assessed by independent *t*-test or univariate analysis. The risk factors of TBL and HBL were determined by multiple linear regression. *Results*. A total of 114 patients were included in this study. Operative time ($P < 0.001$), postoperative platelets (PLT) ($P = 0.001$), the number of surgical fixation segments ($P < 0.001$), implanted screws ($P < 0.001$), hospital stay ($P = 0.006$), type of scoliosis ($P < 0.001$), and correction angle of scoliosis ($P = 0.063$) were the potential risk factors of TBL. Operative time ($P < 0.000$), postoperative PLT ($P = 0.095$), the number of surgical fixation segments ($P < 0.001$), implanted screws ($P < 0.001$), type of scoliosis ($P < 0.001$), correction angle of scoliosis ($P = 0.073$), and total blood volume ($P = 0.098$) were the potential risk factors of HBL. Multiple linear regression analysis showed that operative time ($P = 0.003$) and the number of surgical fixation segments ($P = 0.014$) were risk factors of TBL, while the number of surgical fixation segments ($P = 0.004$) was a risk factor of HBL. *Conclusions*. In AIS patients undergoing posterior internal fixation surgery, the operative time and the number of surgical fixation segments are risk factors of TBL, and the number of surgical fixation segments is a risk factor of HBL. Surgeons need to consider these factors when making surgical strategies for AIS patients.

1. Introduction

Posterior pedicle screw internal fixation is the main surgical technique for adolescent idiopathic scoliosis (AIS). This surgical technique can greatly improve spine curvature and clinical outcomes, but it usually requires a long surgical incision and multilevel fixation and thus may result in a large amount of blood loss [1, 2]. Massive blood loss may prolong the period of incision healing and recovery, increase the risk of infection, and even cause organ failure [3]. Although intraoperative blood loss and postoperative drainage blood loss can be directly estimated, blood can still be lost in invisible ways, such as surgical interval and hemolysis. This part of blood loss is called hidden blood loss (HBL) [4, 5]. However, HBL is often overlooked by doctors in clinical scenarios. This would result in delayed recovery, anemia, and other adverse symptoms in patients. Therefore, assessment and accurate calculation of blood loss are very important for guiding clinical treatment.

Previous studies have shown that the HBL can account for 26%-60% of the total blood loss (TBL) in various orthopedic surgeries, and minimally invasive surgery can significantly reduce HBL [6–8]. Other studies have found that the average TBL of patients undergoing posterior spinal

fusion surgery can reach 1450 mL, and HBL can also reach 600 mL, with HBL accounting for 42% of TBL [9, 10]. However, studies on HBL in AIS patients undergoing surgical treatment are rare.

In this study, we retrospectively analyzed the clinical data of patients with idiopathic scoliosis who received posterior orthopedic fixation and calculated the TBL and HBL by the formula of Nadler et al. and Gross [4, 5]. By evaluating risk factors of TBL and HBL, this study could provide a theoretical basis for reducing blood loss in AIS surgery.

2. Materials and Methods

2.1. Patients. The AIS patients who visited the department of spine surgery of the Third Hospital of Hebei Medical University between July 2015 and December 2020 were retrospectively reviewed. The study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University. Informed consent was obtained from each patient or guardian before the study, and all data remained anonymous.

Inclusion criteria:

(1) Adolescent patients (10-19 years old) with idiopathic scoliosis were treated with simple posterior internal fixation orthopedic surgery, with only varying degrees of posterior column osteotomy and bone grafting without interbody fusion

(2) The patient has complete clinical data

Exclusion criteria:

(1) The patients suffered from congenital scoliosis, and the presence of spinal dysplasia such as failure of segmentation, hemivertebra, blocked vertebra, and fused vertebra can be observed by X-ray or CT [11]

(2) The patients suffered from scoliosis caused by trauma, inflammation, infection, and tumor

(3) The patients underwent anterior and middle column osteotomy and intervertebral fusion

(4) The patients had hematological diseases, including congenital or acquired diseases such as hemophilia and thrombocytopenic purpura. Coagulation abnormalities due to other organ diseases, drugs, or malnutrition were also excluded

(5) The patients had infection, massive bleeding, and other complications during perioperative period

2.2. Surgical Procedure and Follow-Up Treatment. All surgeries were performed by the same chief surgeon. During a surgery, the patient was placed in prone position and intubated under general anesthesia. After disinfection, the skin, subcutaneous tissue, and fascia were cut successively to expose the spinous process, lamina, and intervertebral space of the corresponding segment, and pedicle screws were implanted. Small bleeding spots were stopped by electrocoagulation and suture ligation. Part of the posterior column of the spine were removed, including the spinous process, lamina, and articular process. Then, the connecting rods were installed and rotated to correct the scoliosis, pressurize, or expand properly as required. Finally, the nuts were tightened to fix the connecting rod. X-ray fluoroscopy confirmed the correct position of pedicle screws and rods. The drainage tube was placed, and each layer of tissue and skin was sutured successively. The incision was covered with sterile dressings. The anesthesiologists ensured the stability of the patients' respiratory and circulatory system during the surgeries. In particular, we ensured that the patients' blood pressure was within a reasonable range, and there was no large fluctuation. The appropriate use of muscle relaxants facilitated the smooth progress of a surgery.

After surgery, patients were properly rehydrated to maintain body fluid balance. All patients were treated with heparin anticoagulation until discharge. The drainage tube was removed 2-3 days after the operation according to the drainage condition (drainage volume less than 50 mL per day) of the drainage tube.

2.3. Data Collection. Basic information (gender, age, weight, height, hospital stay, operative time, intraoperative blood loss, drainage volume, blood transfusion volume, the number of surgical fixation segments and pedicle screws, correction angle of scoliosis, type of scoliosis, and Risser sign) and laboratory test results (hematocrit (HCT) and platelets (PLT) before and after surgery) were collected. The hospital stay was from the day of surgery to the day of discharge. Body mass index (BMI) is calculated according to the World Health Organization (WHO) standards. $\mathrm{BMI} = \mathrm{Weight\,(kg)/Height\,(m)^2}$. Drainage volume was the volume of the drainage tube three days after surgery. The type of scoliosis (Lenke classification) and Rissier sign were determined by X-ray and CT. The correction angle of scoliosis was the change of Cobb angle before and after surgery. If double scoliosis or more existed, the change of Cobb angle of maximum scoliosis was taken.

2.4. Calculation of TBL and HBL. Nadler formula was used to calculate the total blood volume (TBV) of the patients, and HCT was put into Gross formula to calculate the TBL and HBL of the patients [4, 5].

$$\begin{aligned}\mathrm{TBV}: {} & \mathrm{K1} * \mathrm{height(m)}^3 + \mathrm{K2} * \mathrm{weight(kg)} \\ & + \mathrm{K3(male}: \mathrm{K1} = 0.3669, \mathrm{K2} = 0.03219, \mathrm{K3} \\ & = 0.6041\,; \mathrm{Female}: \mathrm{K1} = 0.3561, \mathrm{K2} = 0.03308, \mathrm{K3} = 0.1833).\end{aligned} \tag{1}$$

$\mathrm{TBL} = \mathrm{TBV} * (\mathrm{HCT_{pre}} - \mathrm{HCT_{post}})/\mathrm{HCT_{ave}}$. $\mathrm{HCT_{pre}}$ is the preoperative HCT, and $\mathrm{HCT_{post}}$ is the postoperative HCT. The $\mathrm{HCT_{ave}}$ is the average of $\mathrm{HCT_{pre}}$ and $\mathrm{HCT_{post}}$.

Measurable blood loss (MBL) is the sum of intraoperative blood loss (the volume of liquid in the suction bottles volume of lavage fluid used) and drainage blood loss.

$$\mathrm{HBL}: \mathrm{TBL} + \text{blood transfusion volume} - \mathrm{MBL}. \tag{2}$$

Since the patient had no significant perioperative

bleeding or electrolyte disturbance, we assumed that the TBV of the patient was constant throughout the hospital stay to facilitate the calculation of blood loss.

If the patient is transfused with allogeneic blood, 1 U of red blood cells equals 200 mL of whole blood volume. Drainage blood loss: 20% of the drainage fluid on the first day, 15% of the drainage fluid on the second day, and 5% of the drainage fluid on the third day were calculated as the blood loss in the drainage fluid [10, 12].

2.5. Statistical Analysis. Statistical analysis was performed using SPSS 20 (SPSS Inc., Chicago, IL, USA). The measurement data were expressed as mean ± SD. The potential risk factors were assessed by independent sample t-test and univariate analysis, $P < 0.1$ indicated potential risk factors. Potential risk factors were included and used in multiple linear regression analysis to investigate risk factors of TBL and HBL; $P < 0.05$ was considered statistically significant.

3. Results

A total number of 114 patients with AIS who underwent simple posterior internal fixation orthopedic surgery were enrolled in this study. The clinical data was shown in Table 1. Potential risk factors of TBL and HBL were assessed by univariate analysis. The potential risk factors were included and used in multiple linear regression analysis to investigate the risk factors of TBL and HBL.

As displayed in Table 2, potential risk factors of TBL included operative time ($P < 0.001$), postoperative PLT ($P = 0.001$), the number of surgical fixation segments ($P < 0.001$), implanted screws ($P < 0.001$), hospital stay ($P = 0.006$), type of scoliosis ($P < 0.001$), and correction angle of scoliosis ($P = 0.063$). Potential risk factors of HBL included operative time ($P < 0.001$), postoperative PLT ($P = 0.095$), the number of surgical fixation segments ($P < 0.001$), implanted screws ($P < 0.001$), type of scoliosis ($P < 0.001$), correction angle of scoliosis ($P = 0.073$), and TBV ($P = 0.098$).

Multiple linear regression analysis showed that the operative time ($P = 0.003$) and the number of surgical fixation segments ($P = 0.014$) were risk factors of TBL, as shown in Table 3. The number of surgical fixation segments ($P = 0.004$) was a risk factor of HBL, as shown in Table 4.

Table 1: The clinical data of 114 patients who underwent posterior orthopedic surgery for AIS.

Parameters	Mean	SD
Gender (male/female)	38/76	
Age (year)	14.86	4.84
BMI (kg/m^2)	18.73	3.45
The number of surgical fixation segments	9.62	2.56
The number of pedicle screws	17.14	4.39
Operative time (min)	311.23	117.63
PLT_{pre} (10^9/L)	235.06	55.28
PLT_{post} (10^9/L)	190.59	73.92
TBV (mL)	3429.19	720.19
Blood transfusion volume (mL)	822.46	523.59
TBL (mL)	1655.51	564.10
TBL (mL/level)	173.51	40.13
HBL (mL)	475.09	197.59
HBL (mL/level)	48.64	13.10
HBL/TBL	0.29	0.08
Hospital stay (day)	12.26	1.95
Type of scoliosis (1/5/others)	68/37/9	
Risser sign	3.46	1.06
Correction angle (°)	29.39	12.84

AIS: adolescent idiopathic scoliosis; BMI: body mass index; TBL: total blood loss; HBL: hidden blood loss; TBV: total blood volume; PLT_{pre}: preoperative platelets; PLT_{post}: postoperative platelets.

4. Discussion

Posterior spinal internal fixation is the most common surgical procedure for adolescent idiopathic scoliosis, which can improve the physiological curvature of the spine and relieve pain, improve patients' cardiopulmonary function, and correct patients' attitude towards life [13]. However, multisegment spinal fixation surgery has put forward higher requirements for surgeons, anesthesiologists, and patients' body functions. Massive blood loss from surgery can not only cause hypotension and hypoxia and even affect organ function. Meanwhile, blood transfusion can also increase the risk of complications, such as the spread of infectious diseases [14, 15]. How to reduce perioperative blood loss and promote faster recovery of patients is a hot research topic in the field. Although many reports have pointed out that the use of procoagulant drugs (such as tranexamic acid) can effectively reduce intraoperative blood loss [16]. However, there are few reports on the risk of surgical blood loss and hidden blood loss in adolescents with AIS [1], especially the HBL, which cannot be measured directly with the naked eye. In this study, the clinical data of 114 adolescent scoliosis patients were analyzed to predict the risk factors of TBL and HBL, providing a theoretical basis for guiding doctors to make blood transfusion plans, reduce the risk of related complications, and shorten the recovery period of patients.

In this study, we assessed patients' TBL and HBL. At the same time, TBL (173.51 ± 40.13 mL) and HBL (48.64 ± 13.10 mL) were calculated for each fixation segment, both lower than in previous studies of posterior spinal fusion in adults [9, 17, 18]. This may be related to the younger age and health status of AIS patients [9, 17, 18]. We also calculated the ratio of HBL to TBL (0.29 ± 0.08), which is similar to previous studies, indicating that HBL is a nonnegligible part of TBL [9, 18].

Similar to previous studies, operative time is a risk factor of blood loss [19]. Prolonged operative time leads to prolonged exposure of muscle, bone, and other tissues and increased blood loss during surgery [19]. However, operative time did not significantly increase the patients' HBL, which means the HBL was not caused directly by surgical procedure. And other studies have shown that more than 4 hours of surgery was

Table 2: The potential risk factors of TBL and HBL.

Parameters	Patients	MBL		P	HBL		P
		Mean	SD		Mean	SD	
Gender							
Male	38	1724.75	542.07	0.356	504.78	200.43	0.258
Female	76	1620.88	575.18		460.24	195.80	
Age (year)							
≥14	62	1600.31	537.45	0.256	465.81	210.45	0.586
<14	52	1721.33	592.82		486.16	182.50	
BMI (kg/m^2)							
≥17.88	57	1733.87	628.72	0.139	478.37	194.67	0.860
<17.88	57	1577.15	484.06		471.80	202.15	
Operative time (min)							
≥300	62	1939.87	549.54	<0.001*	586.50	182.39	<0.001*
<300	52	1316.46	358.23		342.26	116.78	
The number of surgical fixation segments							
≥10	58	2007.51	517.46	<0.001*	614.93	162.55	<0.001*
<10	56	1290.93	332.09		330.24	104.14	
The number of pedicle screws							
≥16.5	57	1972.28	539.72	<0.001*	603.93	176.08	<0.001*
<16.5	57	1338.73	382.78		346.25	118.27	
PLT_{pre} (10^9/L)							
≥234.65	57	1611.10	535.24	0.403	448.19	177.17	0.147
<234.65	57	1699.92	592.96		501.99	214.29	
PLT_{post} (10^9/L)							
≥177.15	57	1482.81	486.91	0.001*	444.15	181.11	0.095*
<177.15	57	1828.21	586.78		506.03	209.84	
TBV (mL)							
≥3318	57	1568.05	544.20	0.417	459.99	210.36	0.098*
<3318	57	1742.97	574.78		490.19	184.57	
Hospital stay (day)							
≥12	77	1755.56	591.98	0.006*	493.30	195.22	0.157
<12	37	1447.30	439.36		437.19	199.77	
Risser sign							
≥4	69	1654.46	619.98	0.980	482.15	216.48	0.639
<4	45	1657.12	472.423		464.26	166.26	
Type of scoliosis							
1	68	1669.90	566.87		469.08	183.24	
5	37	1472.22	438.07	<0.001*	421.81	186.84	<0.001*
Others	9	2300.27	561.28		739.52	149.25	
Correction angle (°)							
≥28	59	1750.31	555.71	0.063*	507.12	183.29	0.073*
<28	55	1553.80	560.21		440.73	208.07	

* indicates a potential risk factor ($P < 0.1$). BMI: body mass index; TBL: total blood loss; HBL: hidden blood loss; TBV: total blood volume; PLT_{pre}: preoperative platelets; PLT_{post}: postoperative platelets.

associated with an increased the risk of bleeding badly in AIS surgery [1]. Therefore, reducing the operative time is an important measure to reduce the amount of operative bleeding on the premise of ensuring the surgical effect and safety.

The increase of fixed segments means longer surgical incision and more muscle dissection [20]. It has been reported that the risk of massive blood loss increased 4.044 times when the number of surgical fixation segments ≥ 10 [21]. Chiu et al. also pointed out that the speed of blood loss during screw placement was the fastest in spinal orthopedic surgery [22]. Wen et al. proved that the number of fixed segments significantly increased HBL in posterior spinal surgery, and

Table 3: Multiple linear regression analysis of risk factors of TBL.

Parameters	Unstandardized B	Unstandardized SE	Standardized beta	t	P	95% CI	
Operative time (min)	1.644	0.543	0.343	3.026	0.003*	0.567	2.721
PLT_{post} (10^9/L)	-0.363	0.493	-0.048	-0.736	0.463	-1.341	0.615
The number of surgical fixation segments	89.647	35.733	0.407	2.509	0.014*	18.802	160.491
The number of pedicle screws	6.437	18.661	0.050	0.345	0.731	-30.559	43.434
Hospital stay	8.231	18.543	0.028	0.444	0.658	-28.531	44.994
Type of scoliosis	17.76	19.889	0.059	0.893	0.374	-21.671	57.191
Correction angle (°)	0.529	2.977	0.012	0.178	0.859	-5.374	6.432

* indicates a risk factor of TBL ($P < 0.05$). PLT_{post}: postoperative platelets.

Table 4: Multiple linear regression analysis of risk factors of HBL.

Parameters	Unstandardized B	Unstandardized SE	Standardized beta	t	P	95% CI	
Operative time (min)	0.241	0.186	0.143	1.296	0.198	-0.128	0.609
PLT_{post} (10^9/L)	0.245	0.169	0.092	1.448	0.150	-0.090	0.581
The number of surgical fixation segments	36.577	12.246	0.474	2.987	0.004*	12.299	60.856
The number of pedicle screws	10.938	6.415	0.243	1.705	0.091	-1.780	23.655
Type of scoliosis	8.579	6.843	0.081	1.254	0.213	-4.989	22.147
Correction angle (°)	-0.721	1.022	-0.047	-0.706	0.482	-2.747	1.304
TBV (mL)	0.018	0.017	0.067	1.061	0.291	-0.016	0.053

* indicates a risk factor of HBL ($P < 0.05$). PLT_{post}: postoperative platelets.

significant HBL may be related to postoperative mortality [19]. Our study was consistent with the results of previous studies. Univariate analysis showed that the number of surgical fixation segments and screw implants increased TBL and HBL. However, multiple linear regression analysis showed that only the number of surgical fixation segments was a risk factor of TBL and HBL. Some studies have shown that there was no significant difference in the orthopedic effect of unilateral, bilateral, or bilateral cross screw placement in three dimensions in the case of reducing the number of screws to ensure the surgical effect [23]. Therefore, surgeons need to balance the effect of surgery with the number of fixed segments and reducing blood loss.

Yu et al. found that large preoperative Cobb angle was related to massive intraoperative blood loss [24]. Large preoperative Cobb angle and correction angle require different degrees of orthopedic osteotomy and more internal fixation segments, correspondingly increasing the operative difficulty and time [24]. In this study, although Cobb correction angle was a potential risk factor of TBL and HBL, multiple linear regression analysis showed that the correction angle was not a risk factor. Feeley et al. found that the preoperative Cobb angle, operative time, and intraoperative blood loss of patients with the scoliosis subtype Lenke A/B were lower than those with the scoliosis subtype Lenke C [25]. We also introduced the scoliosis type of Lenke classification into the study to explore the influence of scoliosis type on TBL and HBL. Univariate analysis showed that TBL and HBL of patients with scoliosis subtype 1 was higher than those with scoliosis subtype 5, but scoliosis type was not a risk factor in multivariate linear regression analysis.

This study has some limitations. First, this is a retrospective study, and the sample size is not large because the incidence of AIS is much lower than the other spine diseases. Moreover, some potential risk factors might have been lost due to the limitation of data collection in a retrospective study. Thus, a prospective study with a larger sample size and more risk factors is warranted in the future. Second, for the calculation of intraoperative blood loss, we only included the volume of blood in the suction bottles. We ignored the volume of blood lost through other ways, such as the blood absorbed by gauze. This led to an underestimation of intraoperative blood loss. Finally, blood loss could persist for a long time, especially HBL [26]. In this study, we only investigated blood loss 2-3 days after surgery and did not follow up for a longer period. Therefore, longer follow-up studies are needed to identify the risk factors of blood loss in AIS patients.

5. Conclusions

In AIS patients undergoing posterior internal fixation surgery, the operative time and the number of surgical fixation segments are risk factors of TBL, and the number of surgical fixation segments is a risk factor of HBL. Surgeons need to consider decreasing the operative time and the number of

surgical fixation segments when making surgical strategies for AIS patients.

Abbreviations

AIS: Adolescent idiopathic scoliosis
BMI: Body mass index
TBL: Total blood loss
HBL: Hidden blood loss
MBL: Measurable blood loss
TBV: Total blood volume
HCT: Hematocrit
PLT: Platelets.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University, in accordance with the provisions of the declaration of Helsinki.

Conflicts of Interest

All the authors declare no conflicts of interest regarding this study.

Authors' Contributions

SY and WD conceived the study. XL and RZ performed data collection and statistical analysis. XL drafted the manuscript. XL, SY, and WD revised the manuscript. All authors read and approved the final manuscript.

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Review Article

Clinical Efficacy of Epidural Injections of Local Anesthetic Alone or Combined with Steroid for Neck Pain: A Systematic Review and Meta-Analysis

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Aims. To compare the effectiveness of cervical epidural injections of local anesthetic with vs. without a steroid. *Methods*. Three databases (PubMed, Embase, and Cochrane library) were used to search and assess all clinical randomized controlled trials regarding the clinical efficacy of epidural injections from January 01, 2009, to October 31, 2020. Cochrane review criteria and the Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment instrument were used to evaluate the methodologic quality of the included studies. Qualitative and quantitative analyses were performed according to best evidence synthesis principles and by single-arm meta-analysis, respectively. *Results*. Based on the search criteria, 4 RCTs were qualitatively and quantitatively analyzed in the single-arm meta-analysis. Treatment with lidocaine alone or with the steroid resulted in decreases of 4.46 and 4.29 points, respectively, in pain scores and of 15.8 and 14.46 points, respectively, in functional scores at 6 months. Similar trends were observed at the 1-year follow-up: pain scores decreased by 4.27 and 4.14 points, while functional scores decreased by 15.94 and 14.44 points in patients with neck pain who received lidocaine without or with the steroid, respectively. In the 3 studies that reported 2-year follow-up data, patients with neck pain treated with lidocaine or lidocaine + steroid showed 4.2- and 4.14-point decreases, in pain score and 15.92- and 14.89-point decreases, respectively, in functional scores. *Conclusions*. The studies showed level I (strong) evidence for short- and long-term improvements in pain relief and functionality with cervical epidural injections of local anesthetic alone or with a steroid in the management of neck pain.

1. Introduction

Degenerative cervical spine lesions and cervical postoperative syndrome are the leading causes of neck pain, including cervical disc herniation and cervical stenosis, which bring higher economic burdens and disability rates to society [1–5]. Chronic cervical pain not only increases the burden of life on patients but also increases the psychological burden of patients and now ranks third among conditions that contribute to disability [6]. Current clinical treatment options for neck pain include conservative and surgical treatment. Conservative treatment is mainly oral drugs and physical therapy. However, conservative treatment is generally ineffective in the treatment of refractory neck pain, oral medication will increase the burden on the gastrointestinal tract, and adverse reactions such as gastric ulcers and bleeding may occur. However, the rate of reoperation due to the failure of surgical interventions is 32% [7–17]. Cervical

epidural injections have been widely used to manage neck pain [18], especially in patients who are poor candidates for surgery [19, 20]. Although a number of randomized trials have investigated the efficacy of cervical epidural injections of local anesthetics alone or in conjunction with steroids, the long-term effectiveness of these treatments in managing chronic neck pain is controversial [8, 10, 12, 21–28].

Steroids are used in cervical epidural injections to control inflammation and suppress edema of the nerve root. In a preliminary report of a systematic review and meta-analysis of the efficacy of fluoroscopically guided cervical epidural steroid injection for the treatment of radicular pain, improvements in vital functions were reported in 58% of patients at 2 months [29]. The mechanisms of action of steroids include suppression of ectopic discharges from inflamed nerves as well as proinflammatory cytokines, improvement of blood flow, and lysing of iatrogenic and inflammatory adhesions [30]. Besides neck pain, steroids are widely used to manage painful diseases including osteoarthritis and gout and are typically combined with local anesthetics to achieve greater efficacy. However, local anesthetics alone can have a comparable effect in terms of pain relief, and there is no evidence that this is enhanced by the addition of steroids. Some studies have reported similar degrees of pain relief and functional improvement in patients with neck pain secondary to disc herniation or postsurgery syndrome who were treated by cervical epidural injections of local anesthetics without or with steroids [31–35].

In order to address this controversy, we carried out a systematic review and meta-analysis evaluating the long-term efficacy of cervical epidural injections with a local anesthetic alone or combined with a steroid in the management of neck pain.

2. Methods

2.1. Study Identification and Search Strategy. The PubMed (http://www.ncbi.nlm, http://nih.gov/pubmed), Embase (http://www.embase.com), and Cochrane library (http://www.thecochranelibrary.com) databases were searched for studies published between January 2009 to October 2020. The following search terms were used: (((((“injections, epidural” OR ((((((((((Extradural Injections OR Peridural Injections OR AND Peridural OR ((“injections” OR “injections” OR “injection” [All Fields]) AND (“Neck Pain” OR ((Neck Pains OR Pain, Neck OR ((“pain” OR “pain” OR “pains”) AND Neck)) OR Neck Ache AND Cervical OR Posterior Cervical Pain AND Anterior Cervical) OR Anterior Neck Pain OR (Anterior [All Fields] AND Neck Pains)) OR ((“neck pain” [MeSH Terms] OR (“neck” AND “pain”) OR “neck pain”) AND Anterior) OR ((“neck pain” OR (“neck” [All Fields] AND “pain”) OR “neck pain” OR (“neck” AND “pains”) OR “neck pains”) AND (“2009/01/01” [PDAT]: “2020/10/20” [PDAT]))))) AND (((((randomized controlled trial [Title/Abstract]) OR randomized [Title/Abstract]) OR placebo [Title/Abstract])) OR (((((((((Health Care Category [Title/Abstract]) OR (Environment [Title/Abstract] AND Public Health [Title/Abstract])) OR Public Health [Title/Abstract]) OR Epidemiologic Methods [Title/Abstract]) OR Epidemiologic Study Characteristics [Title/Abstract]) OR Epidemiologic Studies [Title/Abstract]) OR Case-Control Studies [Title/Abstract])) OR “Retrospective Studies”[MeSH])).

2.2. Study Selection. All studies that described the management of chronic neck pain and included outcome evaluations over a period of at least 6 months were reviewed. All randomized trials in all languages with appropriate statistical analyses were included. Study type: randomized controlled trial (RCT). Patients: all patients with neck pain secondary to cervical disc herniation, spondylosis, cervical, or postsurgery syndrome treated with cervical epidural injections of local anesthetic alone or in conjunction with a steroid. Intervention: cervical interlaminar injections of anesthetic (lidocaine) and steroid (betamethasone). Outcome: for pain relief, a 50% decrease from the baseline pain score or a change of at least 3 points on an 11-point pain scale was considered clinically significant. For functional status improvement, a change of ≥30% in disability score or 50% improvement from baseline was considered clinically significant. A study was judged to be positive if the effectiveness of the therapy was demonstrated through comparison with a control group or from baseline to follow-up. A negative study was defined as one in which no difference was seen as a result of the treatment or in which there was no measurable improvement from baseline. Reference point measurements were at 6 months, 1 year, and 2 years. Book chapters, case reports, and reports without a definitive diagnosis were excluded. Studies in which patients had acute trauma, fractures, malignancies, and inflammatory diseases were also excluded.

2.3. Data Collection. Two investigators independently performed the initial search and completed study screening and data extraction according to the selection criteria. Disagreements were resolved through discussion between 2 investigators; a third investigator was consulted in cases where a consensus could not be reached. Data synthesis and analysis, including assessment of study quality, were performed by the 2 investigators, with a third investigator consulted as needed.

2.4. Methodological Quality of Studies. Cochrane review and the Interventional Pain Management Techniques Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) criteria were used to evaluate the quality of each individual article for RCTs. Studies meeting at least 9 of the 13 Cochrane review inclusion criteria were considered to be of high quality; those meeting 5–8 criteria were deemed to be of moderate quality; and those meeting <5 criteria were low-quality studies that were excluded. Studies meeting the IPM-QRB inclusion criteria with a score of 32–48 were considered to be of high quality and were included in the analysis; those with a score of 16–31 were judged as being of moderate quality; and those

Table 1: Qualitative modified approach to grading of evidence.

Level	Strength of evidence	Description
I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials
II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate- or low-quality randomized controlled trials
III	Fair	Evidence obtained from at least one relevant moderate- or low-quality randomized controlled trial with multiple relevant observational studies OR Evidence obtained from at least one relevant high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies
IV	Limited	Evidence obtained from multiple moderate- or low-quality relevant observational studies
V	Consensus-based	Opinion or consensus of a large group of clinicians and/or scientists

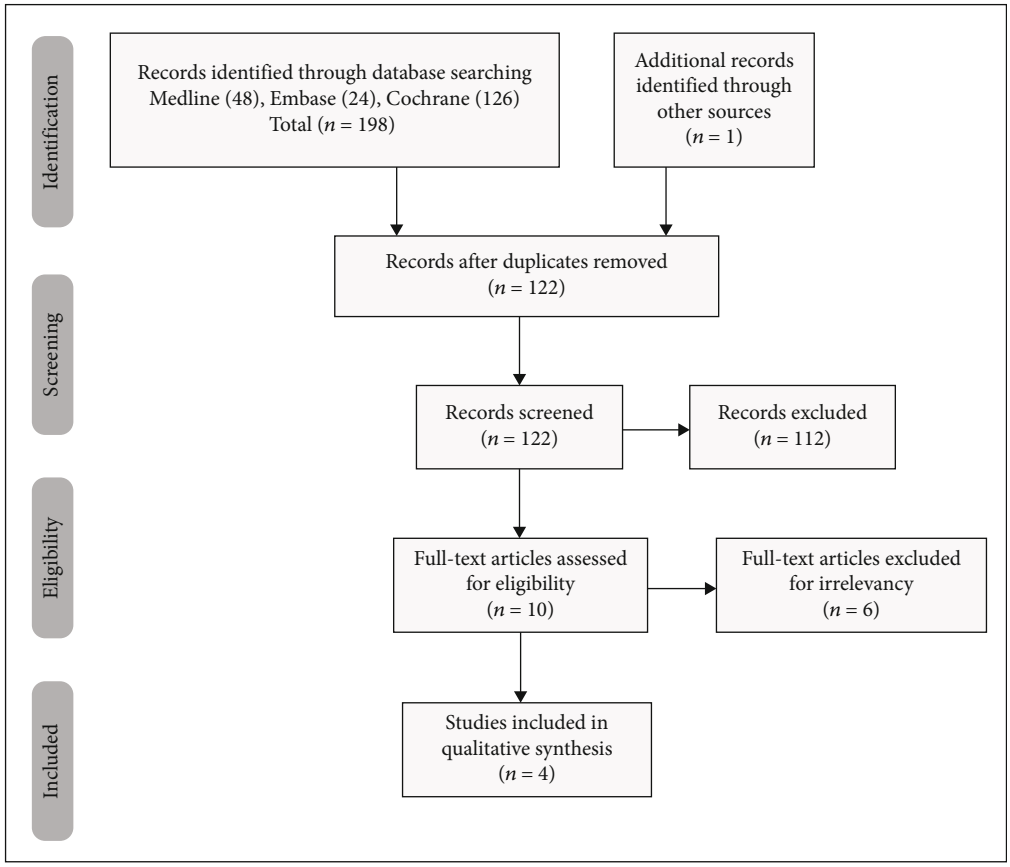


Figure 1: Flow diagram illustrating published literature evaluating epidural injection in neck pain.

meeting the inclusion criteria but with a score < 16 were low-quality studies that were excluded.

The methodologic quality and internal validity of each publication, as well as the quality of evidence, were independently assessed in an unblinded, standardized manner by 2 investigators. In the case of any disagreements, a third investigator performed the assessment and a consensus was reached. Outstanding issues were resolved through a discussion involving all investigators. The evidence was analyzed based on best-evidence synthesis principles and was modified and collated according to multiple criteria including Cochrane review and United States Preventive Services Task Force criteria (Table 1). The analysis was conducted based on 5 levels of evidence ranging from

Table 2: Methodologic quality assessment according to Cochrane review criteria.

	Manchikanti 2012 (36)	Manchikanti 2013 (37)	Manchikanti 2014 (38)	Manchikanti 2018 (39)
Adequate randomization	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	Y	Y
Patient blinded	Y	Y	Y	Y
Care provider blinded	Y	Y	Y	Y
Outcome assessor blinded	N	N	N	N
Dropout rate described	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y
Groups similar at baseline with respect to most important prognostic indicators	N	Y	N	N
Cointerventions avoided or similar	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y
Other sources of potential bias unlikely	Y	Y	Y	Y
Score	11/13	12/13	11/13	11/13

Y: yes; N: no; U: unclear.

strong to opinion- or consensus-based. The results of best evidence as determined by the evidence level were used. If there were any conflicts of interest (e.g., authorship), the investigator in question was recused from the review of evidence.

2.5. Statistical Analysis. The single-arm meta-analysis was performed using Comprehensive Meta-analysis v3.0 (Biostat, Englewood, NJ, USA). The I^2 statistic was used to assess the heterogeneity of included studies. Data were displayed as forest plots to evaluate treatment effects. Pain and functional status improvement data from the included studies are reported as standardized mean differences with 95% confidence interval. All analyses were based on treatment modality and the injected solution. Short- and long-term improvement was defined as any improvement at 6 months and after 6 months, respectively.

3. Results

3.1. Study Selection. A flow diagram of the study selection process according to PRISMA guidelines is shown in Figure 1. Based on the search criteria, 10 publications were considered for inclusion; 6 of these were excluded because of duplicate publications or lack of data. Ultimately, 4 RCTs [31, 32, 34, 36] were included in the present analysis.

3.2. Methodologic Quality and Risk of Bias Assessment. The results of the methodologic quality and risk of bias assessments for each of the included studies are shown in Tables 2 and 3. According to Cochrane review and IPM-QRB criteria [37, 38], all of the RCTs were of high quality.

3.3. Study Characteristics. The characteristics and outcomes of the included studies are shown in Table 4. The studies were not heterogeneous. One RCT [36] followed up patients treated with epidural injections of a steroid ($n = 30$) or without the steroid ($n = 30$) for 1 year; 50% pain relief associated with a 50% functional improvement was considered significant. Work status was also an outcome measure; at the 1-year follow-up, the effectiveness in terms of pain relief and functional improvement was 71.5%. The second RCT [32] included 120 patients, and the interventions and outcome measures for each group were similar to those in the first RCT. The rates of effectiveness for pain relief and functional improvements were 72% and 68% in patients who received epidural injections without and with the steroid, respectively. The third and fourth RCTs had similar interventions and outcome measures as the first 2, but the follow-up time was 2 years. One study [34] showed improvements in pain and function after an average of 6 treatment sessions over a period of 2 years. In the other study [31], patients receiving epidural injections without the steroid experienced 65.6 ± 37.8 weeks of pain relief over a period of 2 years compared to 59.4 ± 34.2 weeks in those receiving injections that included the steroid, with no significant difference between groups.

3.4. Analysis of Study Quality. The quality of evidence of the included studies was assessed using a modified version of evidence grading [39] with high evidence (level I) from multiple relevant high-quality RCTs. All studies reported pain relief and functional improvement in patients who received epidural injections with or without the steroid. Conventional meta-analysis was not feasible because there were no significant differences between patients receiving epidural injections with lidocaine alone vs lidocaine + steroid. To assess pain relief and functional improvement,

Table 3: Methodologic quality assessment using the Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment instrument.

	Manchikanti 2012 (36)	Manchikanti 2013 (37)	Manchikanti 2014 (38)	Manchikanti 2018 (39)
I. Trial design and guidance reporting				
1. Consort or spirit	3	3	3	3
II. Design factors				
2. Type and design of trial	2	2	2	2
3. Setting/physician	2	2	2	2
4. Imaging	3	3	3	3
5. Sample size	2	3	3	2
6. Statistical methodology	1	1	1	1
III. Patient factors				
7. Inclusiveness of population	2	2	2	2
8. Duration of pain	2	2	2	2
9. Previous treatments	2	2	2	2
10. Duration of follow-up with appropriate interventions	2	3	3	2
IV. Outcomes				
11. Outcome assessment criteria for significant improvement	4	4	4	4
12. Analysis of all randomized participants in the groups	2	2	2	2
13. Description of dropout rate	2	2	2	2
14. Similarity of groups at baseline for important prognostic indicators	1	0	1	1
15. Role of cointerventions	1	1	1	1
V. Randomization				
16. Method of randomization	2	2	2	2
VI. Allocation concealment				
17. Concealed treatment allocation	2	2	2	2
VII. Blinding				
18. Patient blinding	1	1	1	1
19. Care provider blinding	1	1	1	1
20. Outcome assessor blinding	0	0	0	0
VIII. Conflicts of interest				
21. Funding and sponsorship	2	2	2	2
22. Conflicts of interest	3	3	3	3
Score	42	43	44	42

we performed a single-arm meta-analysis of the data from the 4 studies [31, 32, 34, 36].

3.5. Pain and Functionality at 6 Months, 1 Year, and 2 Years. Four studies [31, 32, 34, 36] were included in this single-arm meta-analysis of pain relief and functional improvement (Figures 2(a) and 2(b)). Treatment with lidocaine alone or with the steroid resulted in decreases of 4.46 and 4.29 points, respectively, in pain scores (Figures 3(a) and 3(b)) and of 15.8 and 14.46 points, respectively, in functional scores (Figures 2(a) and 2(b)) at 6 months. Similar trends were observed at the 1-year follow-up: pain scores decreased by 4.27 and 4.14 points (Figures 4(a) and 4(b)), while functional scores decreased by 15.94 and 14.44 points (Figures 5(a) and 5(b)) in patients with neck pain who received lidocaine without or with the steroid, respectively. In the 3 studies that reported 2-year follow-up data [31, 32, 34], patients with neck pain treated with lidocaine or lidocaine + steroid showed 4.2- and 4.14-point decreases, in pain score (Figures 6(a) and 6(b)) and 15.92- and 14.89-point decreases, respectively, in functional scores (Figures 7(a) and 7(b)).

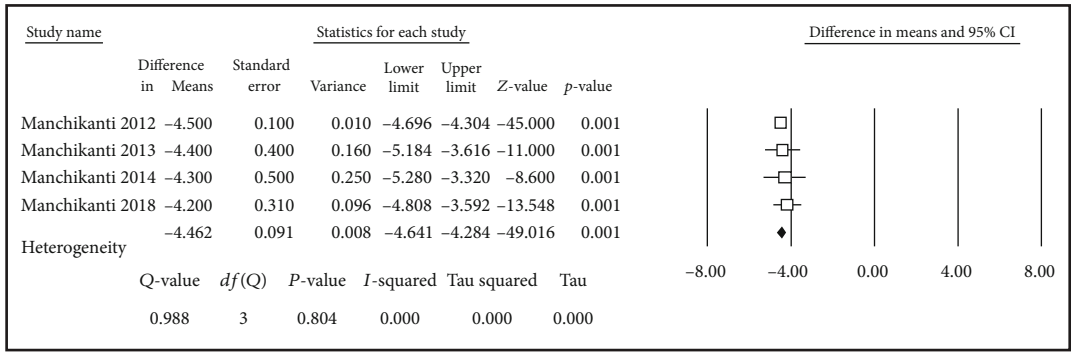
4. Discussion

This systematic review and single-arm meta-analysis of 4 RCTs provided evidence that cervical epidural injections with lidocaine alone or in combination with the steroid

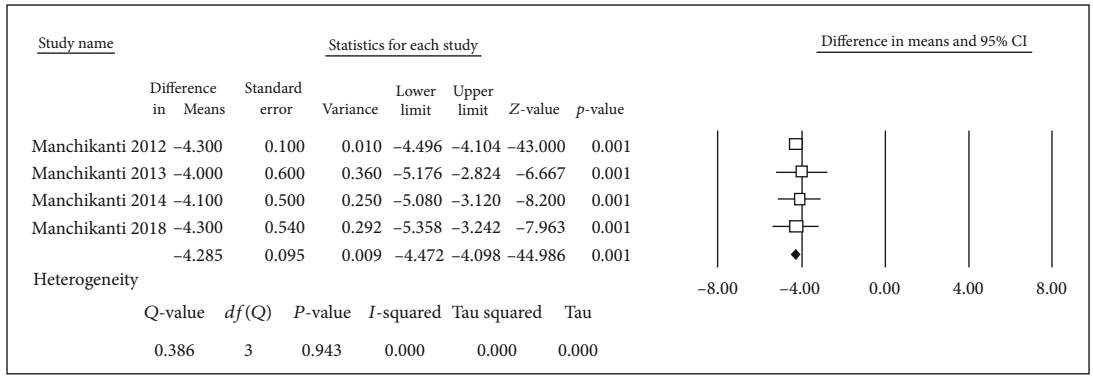
Table 4: Characteristics of included studies on cervical epidural injections in neck pain.

Study/study type Methodologic quality scoring	Participants and interventions	Outcome measure	Follow-up period	Conclusions
Manchikanti et al. (36)/RCT Quality scores: Cochrane = 11/13; IPM – QRB = 42/48	$N = 60$ Epidural injections without steroid, $n = 30$ Epidural injections with steroid, $n = 30$ Group I: cervical interlaminar epidural injections with 5 ml of 0.5% lidocaine Group II: cervical interlaminar epidural injections with 4 ml of 0.5% lidocaine mixed with 1 mL or 6 mg of nonparticulate betamethasone	NDI, NRS, opioid intake, work status	1 year	Cervical interlaminar epidural injections had an efficacy of 71.5% for pain reduction and improvement in functional status for neck pain.
Manchikanti et al. (37)/RCT Quality scores: Cochrane = 12/13; IPM – QRB = 43/48	$N = 120$ Epidural injections without steroid, $n = 60$ Epidural injections with steroid, $n = 60$ Group I: cervical interlaminar epidural injections with 5 ml of 0.5% lidocaine Group II: cervical interlaminar epidural injections with 4 ml of 0.5% lidocaine mixed with 1 ml or 6 mg of nonparticulate betamethasone	NDI, NRS, opioid intake, work status	2 years	Cervical interlaminar epidural injections for chronic neck pain was effective in 72% of patients in group I and 68% of patients in group 2.
Manchikanti et al. (38)/RCT Quality scores: Cochrane = 11/13 IPM – QRB = 44/48	$N = 120$ Epidural injections without steroid, $n = 60$ Epidural injections with steroid, $n = 60$ Group I: cervical interlaminar epidural injections with 5 mL of 0.5% lidocaine Group II: cervical interlaminar epidural injections with 4 ml of 0.5% lidocaine mixed with 1 ml or 6 mg of nonparticulate betamethasone	NDI, NRS, opioid intake, work status	2 years	Cervical epidural injections of local anesthetic with or without steroids were effective in 71% of patients.
Manchikanti et al. (39)/RCT Quality scores: Cochrane = 11/13 IPM – QRB = 42/48	$N = 116$ Epidural injections without steroid, $n = 58$ Epidural injections with steroid, $n = 58$ Group I: cervical interlaminar epidural injections with 5 ml of 0.5% lidocaine Group II: cervical interlaminar epidural injections with 4 ml of 0.5% lidocaine mixed with 6 mg of nonparticulate betamethasone	NDI, NRS, work status	2 years	Cervical interlaminar epidural injections for chronic neck pain alleviated pain relief and improved functional status by ≥50% in 69% of patients in group I and 71% of patients in group 2 at the 2-year follow-up.

IPM-QRB: Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment; NDI: Neck Disability Index; NRS: numeric rating scale; RCT: randomized controlled trial.

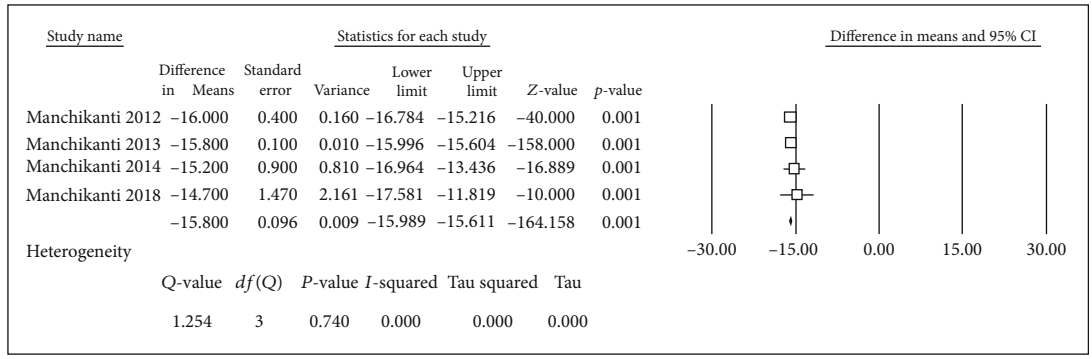


(a) Change in functional level using Neck Disability Index (NDI) from baseline at 6 months in patients treated with lidocaine

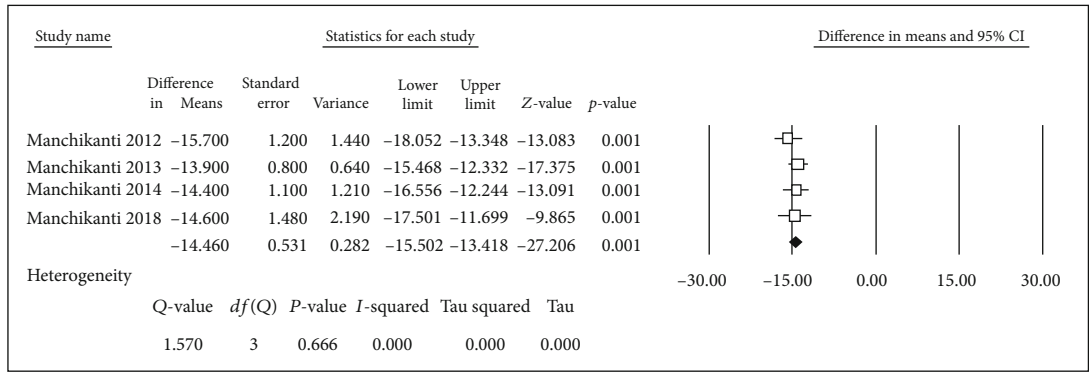


(b) Change in functional level using Neck Disability Index (NDI) from baseline at 6 months in patients treated with lidocaine + steroids

Figure 2: Change in functional level using Neck Disability Index (NDI).

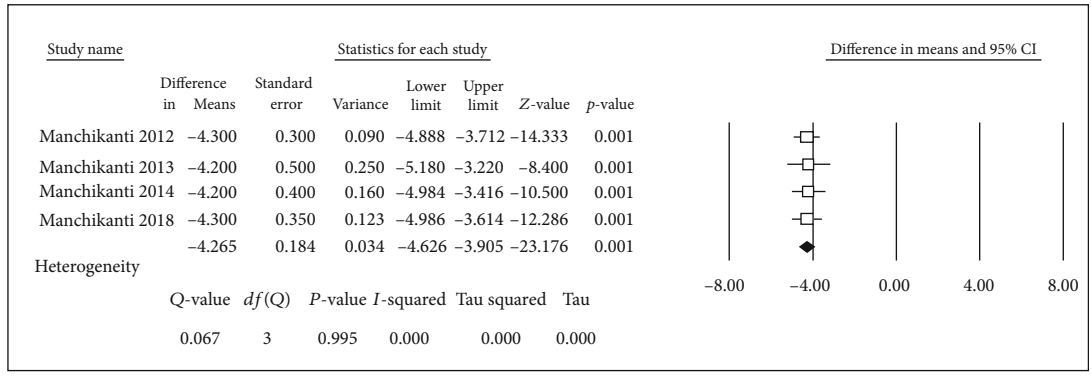


(a) Change in pain score level using numeric rating scale (NRS) from baseline at 6 months in patients treated with lidocaine

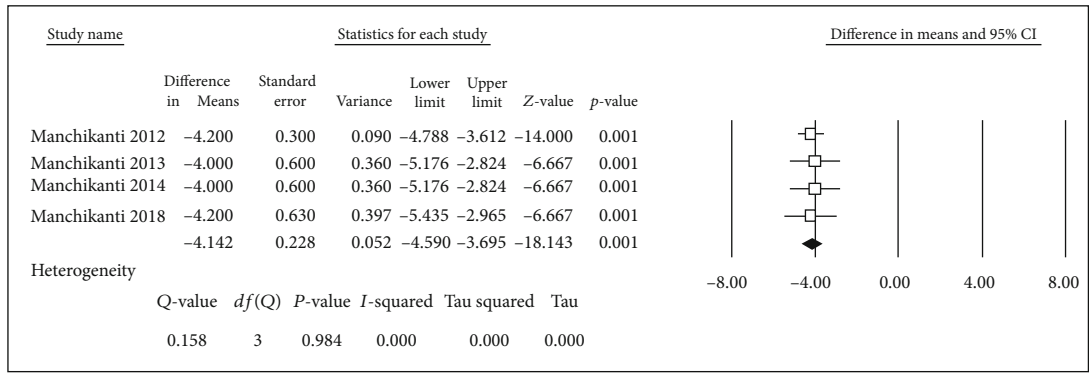


(b) Change in pain score level using numeric rating scale (NRS) from baseline at 6 months in patients treated with lidocaine + steroids

Figure 3: Change in pain score level using numeric rating scale (NRS).

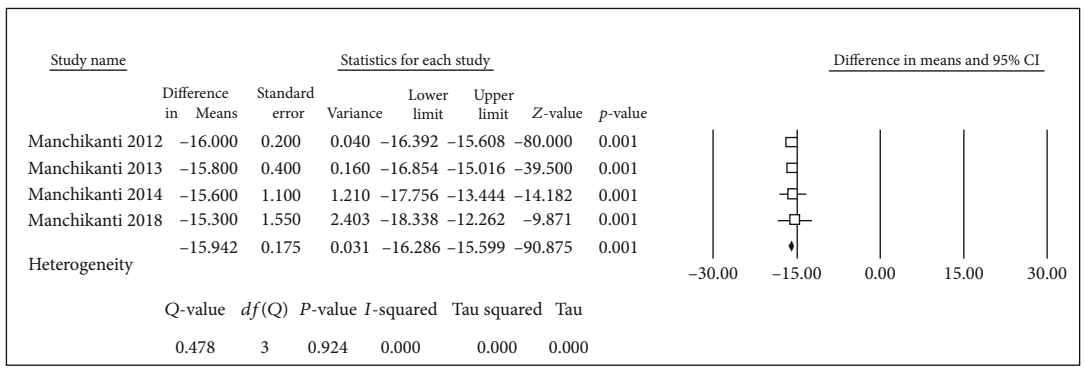


(a) Change in pain score level using numeric rating scale (NRS) from baseline at 12 months in patients treated with lidocaine

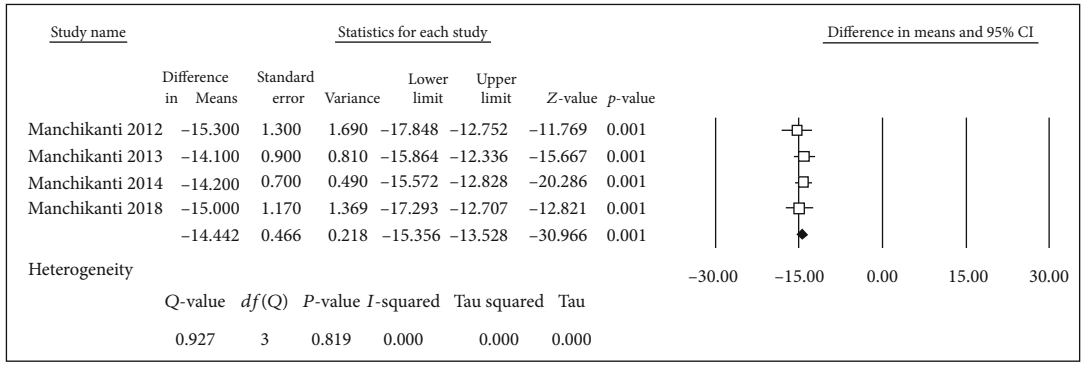


(b) Change in pain score level using numeric rating scale (NRS) from baseline at from baseline at 12 months in patients treated with lidocaine + steroids

Figure 4: Change in pain score level using numeric rating scale (NRS).

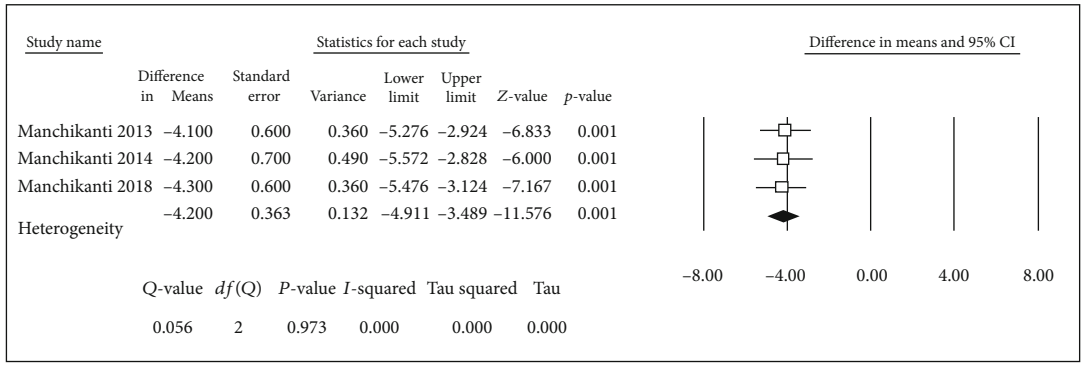


(a) Change in functional level using Neck Disability Index (NDI) from baseline at 12 months in patients treated with lidocaine

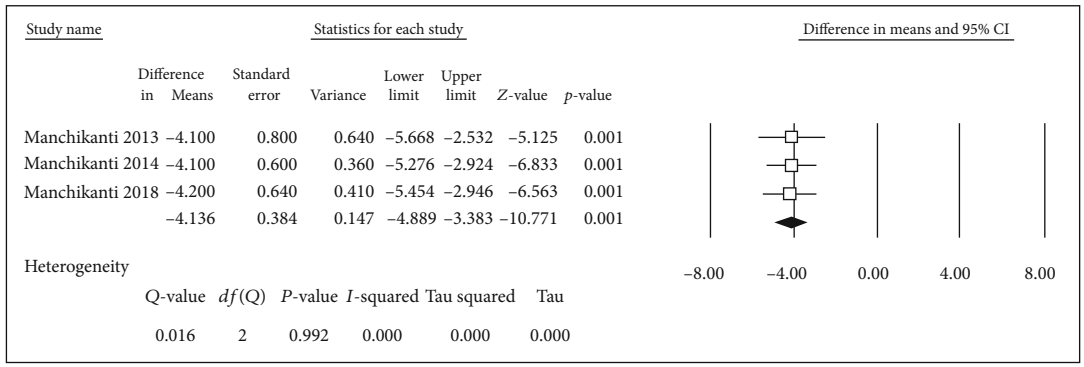


(b) Change in functional level using Neck Disability Index (NDI) from baseline at 12 months in patients treated with lidocaine + steroids

Figure 5: Change in functional level using Neck Disability Index (NDI).

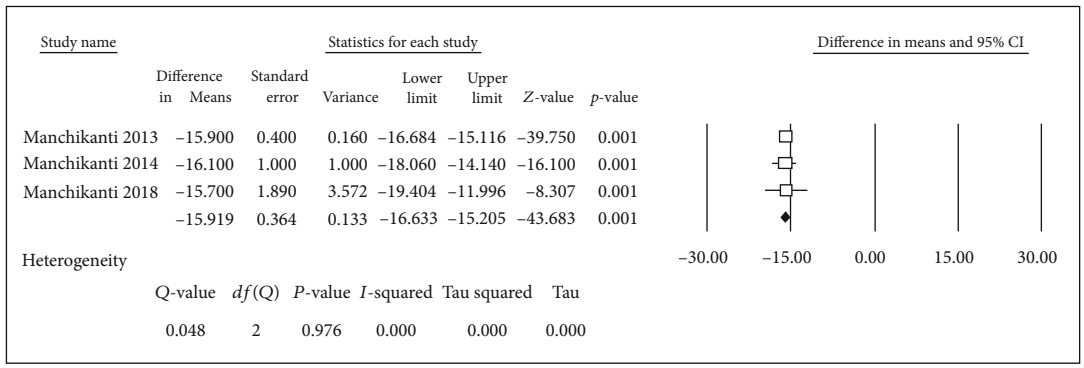


(a) Change in pain score level using numeric rating scale (NRS) from baseline at 24 months in patients treated with lidocaine

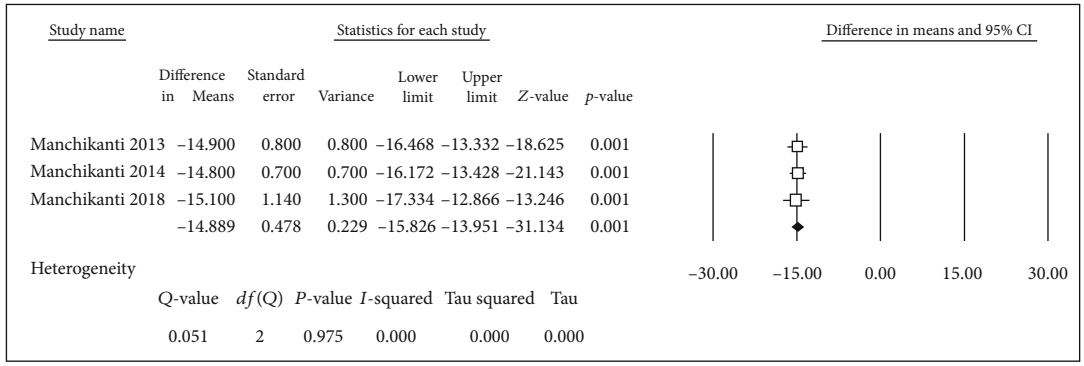


(b) Change in pain score level using numeric rating scale (NRS) from baseline at 24 months in patients treated with lidocaine + steroids

Figure 6: Change in pain score level using numeric rating scale (NRS).



(a) Change in functional level using Neck Disability Index (NDI) from baseline at 24 months in patients treated with lidocaine



(b) Change in functional level using Neck Disability Index (NDI) from baseline at 24 months in patients treated with lidocaine + steroids

Figure 7: Change in functional level using Neck Disability Index (NDI).

betamethasone alleviated pain and improved functionality in patients with neck pain. According to Cochrane review and IPM-QRB criteria, all studies were of high quality. Furthermore, the studies included descriptions of sample size and employed similar injection approaches and pharmacologic agents, which increased the reliability and consistency, respectively, of reported outcomes. All of the studies demonstrated that both treatments were effective for the management of neck pain secondary to cervical disc herniation, spondylosis, or postsurgery syndrome. One of the studies [36] included 1-year follow-up data and the other 3 [31, 32, 34] followed up patients for 2 years, which reduced the bias in outcome reporting. Additionally, opioid intake by the patients was significant decreased by the 2 two treatments. However, there was no significant difference between the 2 treatments in terms of efficacy in any of the RCTs.

The cervical spine has two natural spaces in structure, namely, the cervical foramen and the cervical intervertebral space. Therefore, cervical injection treatment involves an epidural injection through the cervical intervertebral plate and an epidural injection through the cervical intervertebral foramen. The former is commonly used to treat central or paracentral or multisegment disc herniation, while the latter is primarily used for single-segment disc herniation [40–42]. Both have some complication rates, and many studies comparing interlamellar and transforaminal approaches to neck pain have shown a greater risk of neurological complications [19, 43–47], including infarction of the spinal cord, brainstem, brain, or cerebellum [40]. Potential complications of the interlamina approach include needle placement, infection, or the need for additional medication [2].

The most common causes of neck pain are cervical intervertebral herniation, spondylosis, or stenosis; facet joint, vertebral body, meningeal, blood vessel, nerve sheath, or nerve pathology; and postsurgery syndrome [32, 48–51]. Axial neck pain is associated with disc herniation, facet joint degeneration, cervical spondylosis, or ligamentous diseases. Given the relationship between axial neck pain and disc herniation with radiculitis and spinal stenosis, cervical epidural injections are used to manage axial neck pain [38]. Some patients have a long history of neck pain, which is difficult to manage from a clinical standpoint. Conservative treatments for chronic neck pain include oral analgesics or anti-inflammatory drugs or physical therapy, which can eliminate pain symptoms in some patients by up to 80% [9, 52–64]. Nevertheless, a subset of patients requires decompression surgery although this is not always an option because of the high cost and surgical contraindications. Besides surgery, cervical epidural injections are a valid treatment approach [10, 65, 66] that were shown to be effective in many studies [12, 19, 41, 43, 47].

Dexamethasone is a nonparticulate steroid while triamcinolone and betamethasone are particulate steroids [67]. The use of steroids is linked to the risk of spinal cord injury [67–70]. No significant differences in efficacy have been reported between the 2 types of steroid for the treatment of cervical radiculopathy [71]. Steroids can suppress ectopic discharges from inflamed nerves, improve blood flow, and induce the lysis of iatrogenic and inflammatory adhesions and proinflammatory cytokines.

A washout function has also been ascribed to local anesthetics [40, 72]. Thus, it is possible that the reason there were no differences observed between treatment with anesthetic alone or in conjunction with a steroid in the 4 RCTs is that both agents play the same roles in pain relief and functional improvement. In the evaluation of epidural anesthesia plus corticosteroids for the treatment of cervical arm radiculolargia [73], continuous epidural control of chronic cervical-arm pain was better compared with a single injection. Although both injections use corticosteroids. Thus, local anesthetics have an independent or additive effect.

5. Conclusions

This systematic review and single-arm meta-analysis of 4 RCTs showed strong (level I) evidence for the efficacy of fluoroscopic cervical epidural injections of a local anesthetic alone or combined with a steroid in the treatment of neck pain secondary to cervical disc herniation, spondylosis, stenosis, or postsurgery syndrome. Given the risks and adverse effects associated with both types of drug and potential interaction effects, additional studies are needed to determine whether the 2 treatments are equally effective, in which case the use of steroids can be avoided.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Bang-zhi Li, Wen-hai Tang, Ming-guo Liu, and Sheng-xue Bao have contributed equally to this work.

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Research Article

Finite Element Analysis of a Novel Fusion Strategy in Minimally Invasive Transforaminal Lumbar Interbody Fusion

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Purpose. To evaluate the biomechanics of a novel fusion strategy (hybrid internal fixation+horizontal cage position) in minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF). *Methods.* MIS-TLIF finite element models for three fusion strategies were created based on computed tomography images, namely, Model-A, hybrid internal fixation (ipsilateral pedicle screw and contralateral translaminar facet screw fixation)+horizontal cage position; Model-B, bilateral pedicle screw (BPS) fixation +horizontal cage position; and Model-C, BPS fixation+oblique 45° cage position. A preload of 500 N and a moment of 10 Nm were applied to the models to simulate lumbar motion, and the models' range of motion (ROM), peak stress of the internal fixation system, and cage were assessed. *Results.* The ROM for Models A, B, and C were not different ($P > 0.05$) but were significantly lower than the ROM of Model-INT ($P < 0.0001$). Although there were subtle differences in the ROM ratio for Models A, B, and C, the trend was similar. The peak stress of the internal fixation system was significantly higher in Model-A than that of Models B and C, but only the difference between Models A and B was significant ($P < 0.05$). The peak stress of the cage in Model-A was significantly lower than that of Models B and C ($P < 0.01$). *Conclusion.* Hybrid internal fixation with horizontal single cage implantation can provide the same biomechanical stability as traditional fixation while reducing peak stress on the cage and vertebral endplate.

1. Introduction

Lumbar degenerative disease (LDD) is the most common cause of mechanical low back pain, lower limb pain, and intermittent claudication [1]. When conservative treatment fails, lumbar interbody fusion is the standard surgical treatment for LDD [2, 3]. Although a satisfactory outcome can be expected with conventional open lumbar fusion surgery, extensive destruction of the posterior muscular-ligamentous complex can lead to significant postoperative pain, muscular atrophy, and functional disability in most patients [4, 5]. Compared to traditional open surgery, minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) uses tubular retractors for the surgical approach, which can significantly reduce tissue damage and preserve the physiological function of muscle tissue [6, 7]. Therefore, MIS-TLIF has been widely used for the treatment of LDD [8, 9]. However, there are still controversies about the internal fixation method and the implantation position of the cage for MIS-TLIF in clinical practice. Bilateral pedicle screw (BPS) fixation and oblique fusion cage placement are often used for lumbar fusion. However, the excessive rigidity of BPS fixation can cause device-related osteoporosis, absorption of grafted bone,

Table 1: Summary of material properties used in finite element models.

Material properties	Young's modulus (MPa)	Poisson's ratio	Cross section area (mm^2)
Cortical bone	12000	0.3	—
Cancellous bone	100	0.2	—
Endplate	4000	0.3	—
Posterior bone	3500	0.25	—
Articular cartilage	25	0.25	—
Annulus fibrosus	6	0.40	—
Nucleus pulposus	1	0.50	—
ALL	7.8	—	22.4
PLL	1	—	7.0
LF	1.7	—	14.1
ITL	1	—	0.6
CL	7.5	—	10.5
ISL	1	—	14.1
SSL	8	—	10.5
Cage (PEEK material)	3500	0.3	
Screws and rods (titanium alloy material)	110000	0.3	

ALL: Anterior longitudinal ligament; PLL: Posterior longitudinal ligament; LF: Ligament flavum; ISL: Interspinous ligament; SSL: Supraspinous ligament; ITL: Intertransverse ligament; CL: Joint capsule ligament.

and degeneration of adjacent segments [10, 11]. The oblique implantation of the cage into the intervertebral space may cause the risk of nerve compression due to the displacement and withdrawal of the cage along the original implantation way [12, 13]. Therefore, various improvement methods have been proposed. Of these, preliminary clinical evaluation has been performed for hybrid internal fixation (ipsilateral pedicle screw fixation and contralateral translaminar facet screw fixation) [14], as well as for horizontal placement of the fusion cage in the intervertebral space [15, 16]. However, there is still a lack of theoretical research on their combined application in MIS-TLIF.

The finite element analysis (FEA) can provide detailed data that is not influenced by complicated clinical factors, which is ideal to evaluate spinal biomechanics [17, 18]. Therefore, the FEA method was used in this study to compare the effects of hybrid internal fixation combined with cage horizontal placement fusion strategy and traditional fusion strategy on the biomechanics of the lumbar spine and to provide a theoretical basis for the application of this new fusion strategy in MIS-TLIF.

2. Materials and Methods

2.1. Lumbar Spine FE Model. Computed tomographic (CT) images of the lumbar spine, used as inputs for the development of the model, were obtained from a healthy 24-year-old male (70 kg, 176 cm, and no history of lumbar spine disease). Images were obtained using a Philips Brilliance 64 Slice CT scanner (Philips Medical Systems, Inc., OH, USA) at a slice interval of 0.625 mm. Images were saved in DICOM format and imported into Mimics research software (version 19.0; Materialise, Inc., Belgium) for preprocessing and to build a preliminary three-dimensional model of the L4-L5 lumbar segment. The file (format: .stl) generated by Mimics software was imported into Geomagic Wrap 2017 software (3D Systems, Inc., USA) for optimization and smoothing of the model. The file generated by the Geomagic software (.stp format) was imported into SolidWorks (version 2017, Dassault Systems, Inc., USA) to assemble the different components of the model: bones, annulus, nucleus pulposus, screws, and cages. The reconstructed model was saved (.X_T file). Finally, the. X_T file was imported into ANSYS software (version 20.0; ANSYS, Inc., USA) for finite element analysis.

Due to the complex shape of the lumbar vertebrae model, the 3D tetrahedral elements were employed to mesh the FE model except for the ligaments. The vertebral body was divided into the outer cortical bone and inner cancellous bone. The thickness of cortical bone was 1.0 mm and the thickness of bone endplate was 0.5 mm [19], and the endplates were set on the superior and inferior surfaces of each vertebral body. The intervertebral disc was divided into nucleus pulposus and annulus fibrosus. According to the lumbar model, there was no separation between the annulus fibrosus and the nucleus pulposus under load, and no separation between the vertebral body and the disc under load; therefore, the interfacing of the nucleus pulposus and the annulus fibrosus and interfacing of the disc and the vertebral body were set as binding. The interfaces of vertebrae and cages were also assigned to tie constraints [19]. There were ligaments around the lumbar vertebral body, which can limit the range of motion of the vertebral body of the spine. However, because the model of the ligament is too slender and irregular in shape, a spring element is used in the model to simulate the ligament of the intervertebral body. The ligaments of the lumbar spine were included: the anterior longitudinal ligament (ALL), posterior longitudinal ligament

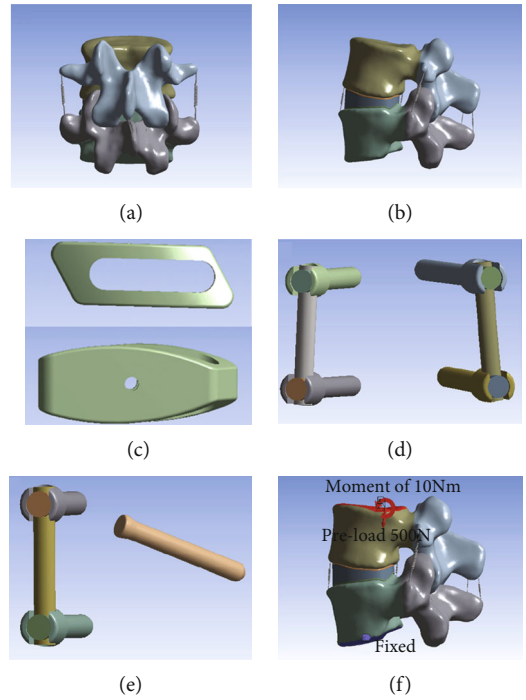


Figure 1: (a) Anterior-posterior and (b) lateral views of the L4-L5 reference model (Model-INT). (c) Model of the Z-Cage (size: 12 × 10 × 32 mm). (d) Model of the pedicle screws (size: 6.0 × 45 mm) and titanium rods (size: 5.5 × 40 mm). (e) Model of the translaminar facet screws (size: 4.5 × 50 mm). (f) A preload of 500 N and a moment of 10 Nm were applied to the models to simulate lumbar motion.

(PLL), ligament flavum (LF), interspinous ligament (ISL), supraspinous ligament (SSL), intertransverse ligament (ITL), and joint capsule ligament (CL). The material properties were based on the previously reported values [20, 21]. Material properties used in the model (Model-INT), including Young's modulus, Poisson's ratio, and the cross-sectional areas of structures, are summarized in Table 1. The resultant reference model (Model-INT) is shown in Figures 1(a) and 1(b).

2.2. MIS-TLIF FE Model. The L4-L5 functional spinal unit was selected to evaluate the MIS-TLIF technique as it is the most frequent site of LDD requiring surgical treatment [22]. The steps of the MIS-TLIF procedure are as follows.

First, the left L4 lower articular process, part of the L5 upper articular process, the ligament flavum, and the posterolateral annulus fibrosus were removed. The nucleus pulposus tissues in the intervertebral disc could then be removed. A cage (size: 12 × 10 × 32 mm, Figure 1(c)) was fabricated based on the Z-Cage (WeGo Company, Shandong, China), using polyetheretherketone ($E = 3.6$ GPa). The pedicle screws (size: 6.0 × 45 mm, Figure 1(d)), translaminar facet screws (size: 4.5 × 50 mm, Figure 1(e)), and titanium rods (size: 5.5 × 40 mm) were fabricated based on the Premier Lumbar Internal Fixation System (WeGo Company, Shandong, China). All fixation components were made of titanium alloy ($E = 110$ Gpa).

All the MIS-TLIF FE models were constructed based on the validated Model-INT: Model-A, hybrid internal fixation +horizontal single cage implantation (Figures 2(a)–2(c)); Model-B, BPS fixation+horizontal single cage implantation (Figures 2(d)–2(f)); and Model-C, BPS fixation+oblique 45° single cage implantation (Figures 2(g)–2(i)). Unilateral pedicle screw fixation was not evaluated owing to a previous report showing poor biomechanical stability with this type of fixation [23].

Figures 2(a)–2(c) Model-A, with hybrid internal fixation (ipsilateral pedicle screw fixation and contralateral translaminar facet screw fixation)+horizontal single cage implantation. (d)–(f) Model-B, with BPS fixation+horizontal single cage implantation. (g)–(i) Model-C, with BPS fixation+45° oblique single cage implantation.

2.3. Loading and Boundary Conditions. All nodes of the L5 lower endplate and the two lower facet surfaces were set to be fully constrained with 0 degrees of freedom to ensure no displacement or rotation of L5 under external forces. A 500 N preload was applied to the upper endplate of L4 to simulate loading by the upper body weight (Figure 1(f)). A moment of 10 Nm was then applied to simulate the following physiological motions, as per previous studies [24, 25]: lumbar flexion (FL), extension (EX), left lateral bending (LLB), right lateral bending (RLB), left rotation (LR), and right rotation (RR). ROM is an important indicator of lumbar stability [26]. To compare the ROM between models, the ROM ratio was calculated using the Model-INT as the reference: $((\text{Model} - \text{INT} - \text{Model} - \text{A/B/C}) \div \text{Model} - \text{INT}) \times 100\%$. The ROM and ROM ratio were calculated for each of the six directions of loading motions. The peak stress in the internal fixation system and cage was used as an index of the risk of fixation failure [27].

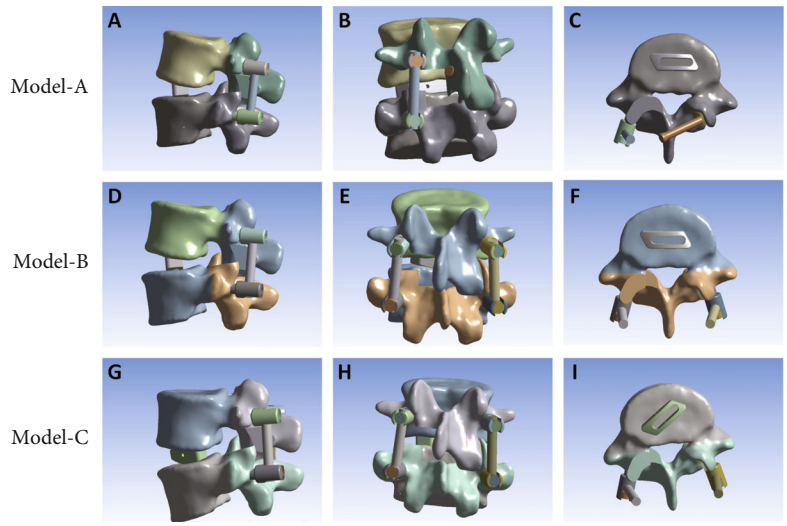


Figure 2: (a)–(c) Model-A, with hybrid internal fixation (ipsilateral pedicle screw fixation and contralateral translaminar facet screw fixation)+horizontal single cage implantation. (d)–(f) Model-B, with BPS fixation+horizontal single cage implantation. (g)–(i) Model-C, with BPS fixation+45° oblique single cage implantation.

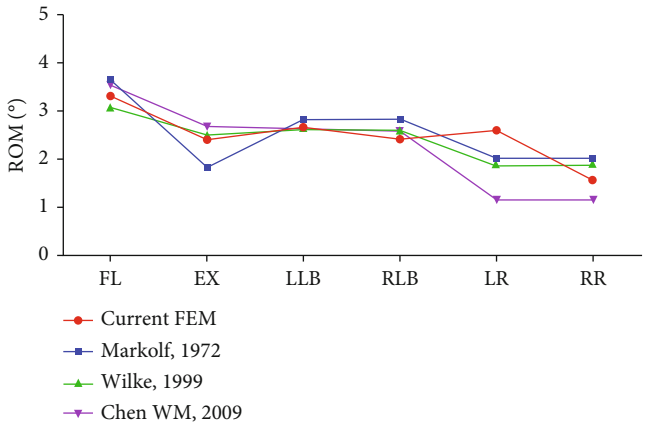


Figure 3: Range of motion Model-INT compared to previously reported values under the same conditions of loading. FL: Lumbar flexion; EX, Extension; LLB: Left lateral bending; RLB: Right lateral bending; LR: Left rotation; RR: Right rotation; ROM: Range of motion.

2.4. Statistical Analysis. Statistical analysis and graphing were performed using GraphPad Prism (version 7.0; GraphPad Software Inc., La Jolla, CA, USA). One-way analysis of variance (ANOVA) was used to evaluate differences in ROM, ROM ratio, and peak stress between the different internal fixation techniques and cage implantation position, with a P value <0.05 considered significant.

3. Results

3.1. Reliability of the Model-INT Model. The reliability of the Model-INT was confirmed by ROM under preload conditions of a 500 N force and a moment of 10 Nm, which were comparable to values previously reported in experimental results [28–30] (Figure 3).

3.2. Range of Motion. The ROM for all models (-INT, A, B, and C) under the six loading motions (FL, EX, LLB, RLB, LR, and RR) is shown in Figure 4(a). The reference values (Model-INT) were as follows: FL, 3.32°; EX, 2.43°; LLB, 2.66°; RLB, 2.42°; LR, 2.62°; and RR, 1.59°. The ROM for Models A, B, and C were not different ($P > 0.05$) but were significantly lower than the ROM of Model-INT ($P < 0.0001$ for all loading motions). The ROM ratio ranged between 71.07 and 97.53% for Models A, B, and C across all six loading motions (Figure 4(b)). Although there were subtle differences in the ROM ratio for Models A, B, and C, the trend in the ROM ratio was similar across all six loading motions. It can be found that the novel fusion strategy can achieve postoperative stability similar to the traditional fusion strategy.

3.3. Peak Stress in the Internal Fixation System. The peak stress in the internal fixation system for all loading motions is shown in Figure 5(a). The range of peak stress was as follows: Model-A, 83.26 MPa (EX) to 189.81 MPa (LR); Model-B, 48.56 MPa (EX) to 100.09 MPa (RR); and Model-C, 58.10 MPa (EX) to 136.05 MPa (RLB). The peak stress was significantly higher in Model-A than in Models B and C. Specifically, the peak stress in Model-A was higher (fold-increase) than in Models B and C, respectively, in LLB (1.80- and 2.05-fold), LR (2.07- and 1.64-fold), and RR (1.79- and 2.28-fold). In addition, the peak stress in the internal fixation system was significantly lower in Model-B than in Models C and A in FL, EX, RLB, and LR. As shown in Figure 5(b), although the average peak stress in Model-A was significantly higher than that of Models B and C, only the difference between Models A and B was significant ($P < 0.05$). By comparing the values of Models B and C, it can be found that under the same internal fixation method, the horizontal placement of the cage reduces the peak stress of the internal fixation system.

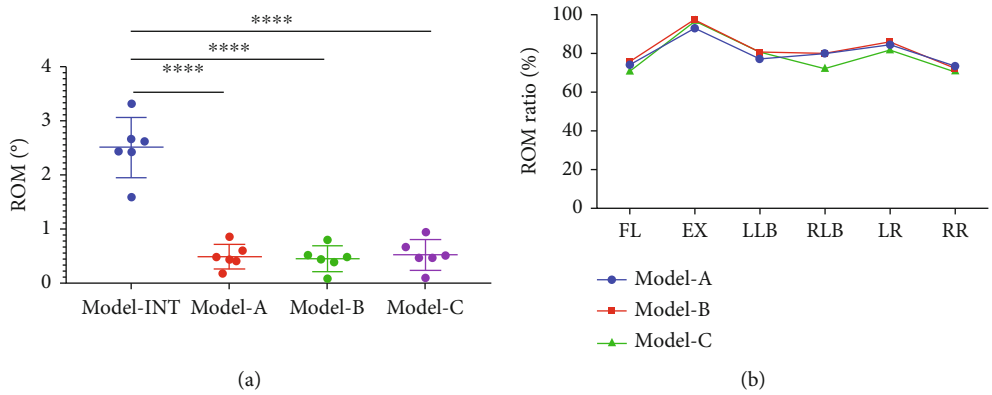


Figure 4: (a) The ROM values of Models A, B, and C were not different ($P > 0.05$) but they were significantly lower than the Model-INT for all loading motions (****$P < 0.0001$). (b) The ROM ratio ranged between 71.07 and 97.53% for Models A, B, and C, but the model of the ROM ratio curves was highly similar. FL: Lumbar flexion; EX: Extension; LLB: Left lateral bending; RLB: Right lateral bending; LR: Left rotation; RR: Right rotation; ROM: Range of motion.

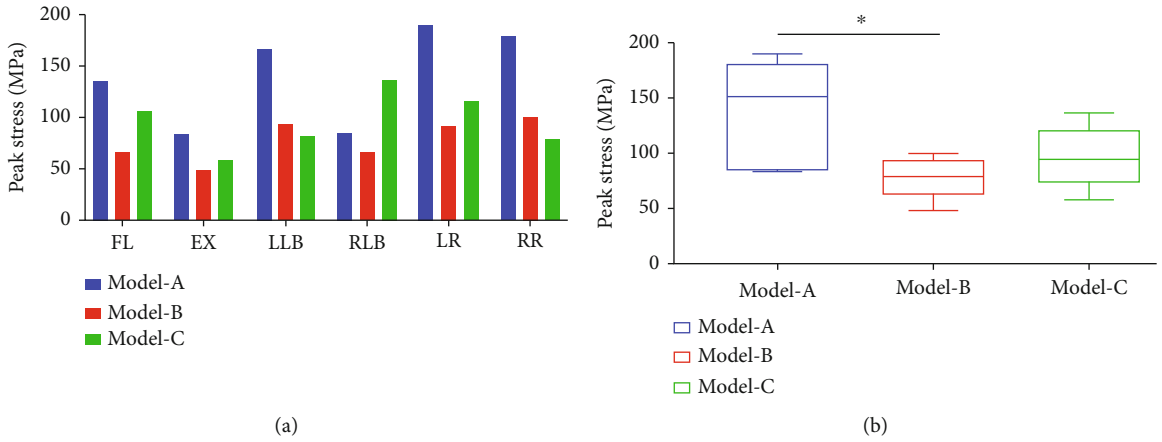


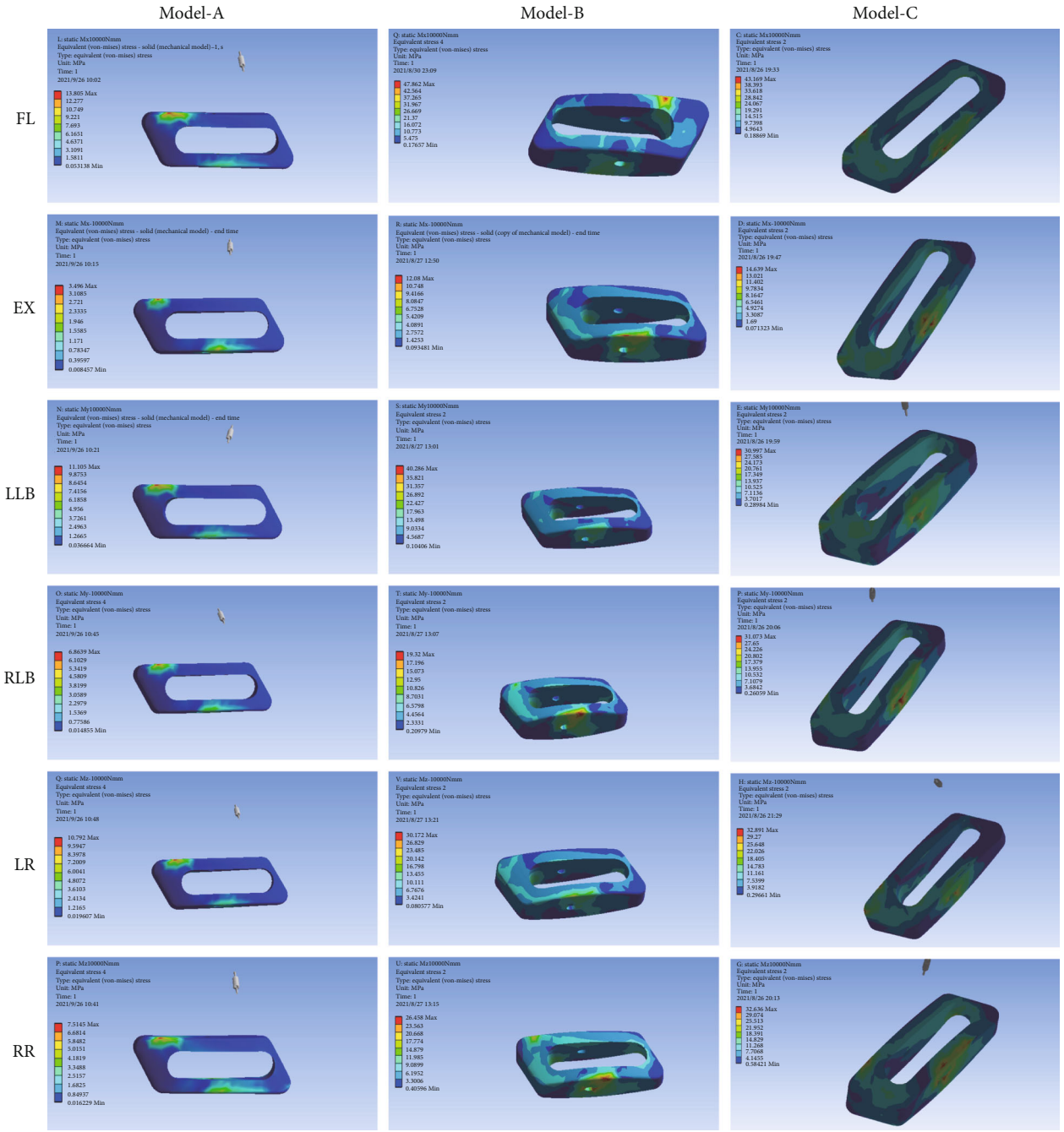
Figure 5: (a) The peak stress of the internal fixation system was higher in Model-A than in Models B and C for almost all loading motions, which was 83.26 MPa (EX) to 189.81 MPa (LR). (b) Although the average peak stress in Model-A was significantly higher than that of Models B and C, only the difference between Models A and B was significant (*$P < 0.05$). FL: Lumbar flexion; EX: Extension; LLB: Left lateral bending; RLB: Right lateral bending; LR: Left rotation; RR: Right rotation.

3.4. Peak Stress in the Cage. The cloud diagram of the stress in implanted cages is shown in Figure 6(a). It can be found that the peak stress appears in the area where the cage and the endplate are in contact, which is in line with the actual clinical situation. The peak stress in the cage predicts the stress on the endplate due to the interaction of these forces. The peak stress in the cage is shown in Figure 6(b). The peak stress in Model-B reached maximum values in FL (47.86 MPa) and LLB (40.29 MPa). In Model-C, maximum peak stress was created in EX (14.64 MPa), RLB (31.07 MPa), LR (32.64 MPa), and RR (32.89 MPa). The peak stress in the cage in Model-A was obviously lower than that of Models B and C. Compared to Model-B, the peak cage stress in Model-A was 29% in FL and 28% in LLB. Compared to Model-C, the peak cage stress in Model-A was 24% in EX, 22% in RLB, 33% in LR, and 23% in RR. As shown in Figure 6(c), the peak cage stress in Model-A was significantly different from the peak cage stress in Models B and C for all loading motions ($P < 0.01$), with no difference between Models B and C ($P > 0.05$).

4. Discussion

Modern intervertebral fusion is mostly achieved by implanting pedicle screws and intervertebral cages, which play an important role in promoting intervertebral fusion and maintaining early biomechanical stability of treated segments [31]. In clinical practice, the fusion strategy mainly depends on the experience and preferences of the surgeon. However, it also causes many implant-related complications. The excessive rigidity of BPS fixation can cause device-related complications [10, 11]. At the same time, cage-related complications have become increasingly prominent, including cage displacement, subsidence, and nonfusion, with these complications yet to be effectively solved [12, 13]. The purpose of our study is important in this regard, providing biomechanical evidence to assist surgeons in selecting the appropriate fusion strategy for different conditions.

We evaluated the biomechanics for two MIS-TLIF internal fixation modes (hybrid internal and BPS) and two cage implantation methods (horizontal and oblique 45°



(a)

Figure 6: Continued.

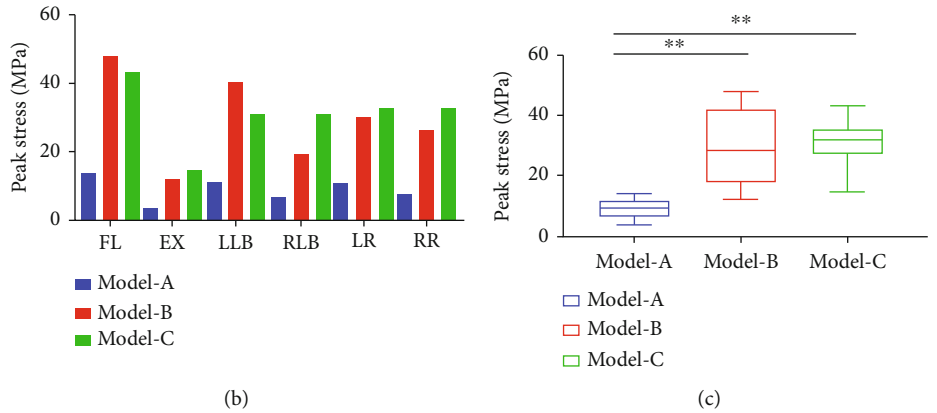


Figure 6: (a) The stress cloud diagrams showed that the peak stress of the implanted cage was concentrated in the area in contact with the vertebral endplate. (b) The peak stress in the implanted cage in Model-A was significantly lower than that of Models B and C for all loading motions. (c) The peak stress of the implanted cage in Model-A was significantly different from Models B and C ($^{**}P < 0.01$). FL: Lumbar flexion; EX: Extension; LLB: Left lateral bending; RLB: Right lateral bending; LR: Left rotation; RR: Right rotation.

implantation) using FEA. The ROM, ROM ratio, internal fixation system peak stress, and cage peak stress were estimated to identify the optimal internal fixation strategy for better biomechanical stability and a lower failure rate. Salient findings were as follows. First, with a horizontal cage placement, both hybrid (Model-A) and BPS (Model-B) internal fixation significantly reduced lumbar motions (Figure 4), achieving similar fixation strength, consistent with previous research conclusions [14, 32, 33]. However, the study found that the hybrid internal fixation bore greater peak stress than the BPS fixation (Figure 5), which may be closely related to the asymmetry in screw arrangement with the hybrid internal fixation. Since the predicted peak stress in the fixation components was much lower than the inherent yield strength of the titanium alloy material (877 ± 18.5 MPa) [34], the risk of failure of mixed internal fixation was not increased. Second, there was no significant difference in the fused segment stability for a horizontal (Model-B) and 45° oblique (Model-C) cage (Figure 4), but the horizontal cage position did reduce the peak stress in the internal fixation and (Figure 5). Thus, it could lower the risk of internal fixation failure. Previous clinical research has shown that horizontal placement of cages in lumbar fusion surgery can improve lumbar lordosis, restore spinal sagittal balance, and prevent fusion cage displacement [15, 16]. Theoretically, it is also less likely that a horizontally positioned cage would migrate from the intervertebral space than a cage placed at an oblique angle of 45°. It is extremely difficult that migration of the cage from its original position would allow rotation of the cage and exit from the intervertebral space. Third, the cloud diagram of stress distribution identified peak stress in the cage at the contact area between the cage and endplate. According to the principle of force interaction, it can be considered that the endplate is, therefore, subjected to the same magnitude of stress. This finding is consistent with clinical reality. The peak stress of the cage is significantly reduced in the hybrid internal fixation model (Model-A, Figure 6), which reflects the higher stress on the hybrid internal fixation than on BPS internal fixation (Model-B, Figure 5). The triangular structure of the hybrid internal fixation method provides excellent mechanical stability. Therefore, it can be inferred that the low peak stress of the cage reduces the stress shielding effect and reduces the risk of cage collapsing, which is especially suitable for application in older patients with osteoporosis.

The limitations of our study need to be acknowledged. First, the FE model of L4-L5 segments was constructed from CT images of a young male adult without evidence of spinal disease. Therefore, structural changes in the spine caused by LDD were not considered. Second, the FE model does not consider the influence of paravertebral muscles, which may have a slight influence on the stability of the lumbar spine.

5. Conclusion

According to the results of our FEA, hybrid internal fixation and horizontal single cage implantation can achieve the same biomechanical stability as the traditional fixation method by open surgery while significantly reducing the peak stress in the cage and vertebral endplate. At the same time, the approach can reduce surgical damage as much as feasible, which is in line with the concept of minimally invasive surgery. Based on our results, we propose that the hybrid internal fixation and horizontal single cage implantation strategy is expected to become an ideal choice for MIS-TLIF.

Data Availability

The data used to support the findings of this study are included within the article.

Ethical Approval

Not applicable as this is a modeling study.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contributions

Keya Mao contributed to the conception of the study; Zhenchuan Han, Long Zhang, and Chao Ma performed the experiment; Jianheng Liu, Jiantao Li, Xiao Liu, and Qingzu Liu contributed significantly to the analysis and manuscript preparation; Zhenchuan Han and Bowen Ren performed the data analyses and wrote the manuscript; Peifu Tang helped perform the analysis with constructive discussions. Zhenchuan Han and Bowen Ren contributed equally to this work

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Research Article

Clinical Effect of Laminectomy with Lateral Mass Screw Fixation in Treating Cervical Schwannoma: A Retrospective Study

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Background. The objective of this study was to evaluate the clinical effectiveness and safety of laminectomy combined with lateral mass screw fixation in treating cervical intradural extramedullary schwannoma. *Methods*. We retrospectively collected and analyzed medical records of 38 patients who underwent resection of cervical intraspinal schwannoma between January 2012 and April 2019. Based on different surgical procedures, two groups were divided among all participants: laminectomy-only ($n = 21$) and laminectomy with instrumented fixation ($n = 17$); the minimum follow-up time was 1 year. The visual analogue scale (VAS) score and neck disability index (NDI) were utilized for pain assessment; the Japanese Orthopedic Association (JOA) score was carried out for the assessment of neurological impairment. Radiographic changes of Cobb angle were compared before and after the surgery. *Results*. Consequently, demographics were well matched in both groups, without any statistical difference ($P > 0.05$). Compared with preoperation, both surgical procedures significantly improved VAS, NDI, and JOA scores ($P < 0.001$), but no differences between them ($P > 0.05$). In terms of postoperative spinal instability/deformity, laminectomy-only caused more events than instrumented fixation, which is statistically significant ($P < 0.001$). *Conclusions*. In summary, laminectomy with lateral mass screw fixation is an effective and safe approach to treat cervical intraspinal schwannoma, which is likely to be a better choice than the laminectomy-only approach.

1. Introduction

Schwannomatosis is a distinct syndrome with the characterization of multiple peripheral nerve schwannomas, familial or sporadic [1]. Both neurofibromas and schwannomas are composed of neoplastic Schwann cells [2–4]. Spinal schwannomas are benign tumors, and most of them are extramedullary intradural [5–8]. However, there are anatomopathological differences between neurofibromas and schwannomas. Neurofibromas are areas of increased thickness of the nerve, often dumbbell-shaped and sited next to the intervertebral foramina. Schwannomas are well demarcated, encapsulated, typically round, and attached to the nerve roots [9].

Reportedly, 24% of all nerve sheath tumors in adults are schwannomas, which are the most frequent extramedullary, intradural spinal tumors [9]; intradural Schwannoma may rank up to a percentage of 83.67%. To our knowledge, the main symptoms caused by intradural extramedullary schwannoma are radiculopathy and neurogenic claudication, due to spinal cord compression with the growth of tumor [10, 11]. What is more, it usually causes motor loss and worsening sensory, as well as back pain spreading out from the tumor level [12, 13]. To date, surgical resection of the tumors by posterior laminectomy is still the first choice for the treatment of symptomatic intraspinal schwannomas [14]. However, the laminectomy-only approach might lead to the acceleration of spinal degeneration and progress to spinal instability and even form spinal deformity, due to the destruction of posterior column structure [15, 16].

Thus, the current study was focused on the assessment of clinical effectiveness and safety of posterior laminectomy plus lateral mass screw fixation in the treatment of cervical intraspinal schwannomas by comparing with a laminectomy-only approach, based on a minimum of 1-year follow-up.

Specifically, we only enrolled patients who had sustained cervical intradural extramedullary schwannomas to minimize the confounding factors.

2. Patients and Methods

2.1. Ethical Statement. This retrospective study has been approved by the local Ethical Committee of the Third Hospital of Hebei Medical University. This study was supported by all the participants with their informed consent provided. The methods that were used in this study were conducted according to related regulations and guidelines.

2.2. Participant Selection. In the current study, all participants were screened by medical records. The identified patients had experienced resection surgery to remove cervical intradural extramedullary schwannomas by total laminectomy, with or without instrumented fixation (Figure 1). All cases in this study received surgeries for the first time after being diagnosed with cervical spinal schwannomas; they did not have a previous history of the same diseases. No other tumors were found concurrent at the moment of surgery. During the period of follow-ups, diseases that were newly found and can change spinal stability have been excluded, such as severe osteoporosis, ankylosing spondylitis, and spine trauma. Patients undergoing reoperations were also excluded if performed due to recurrence. Our patients were usually followed up after surgery regularly, with postoperative 3rd month and 12th month and thereafter.

2.3. Clinical Assessment. Clinical assessment was conducted, and radiological changes were recorded preoperatively and postoperative 3rd month and 12th month and the last follow-up (1 year or longer). The visual analogue scale (VAS) score and neck disability index (NDI) were utilized for pain assessment; the Japanese Orthopedic Association (JOA, 17 points) score was carried out for the assessment of neurological impairment. Radiographic changes of Cobb angle were compared before and after the surgery. In addition, postoperative complications were recorded and compared. Furthermore, an analysis of patient satisfaction was performed as before [17, 18], according to the questionnaire including three levels of satisfaction—very satisfied, satisfied, and dissatisfied.

2.4. Statistical Analysis. Statistics was done with SPSS for Windows 18.0 (IBM SPSS Inc., Chicago, IL). Measurement data were presented as mean ± SD (standard deviation). The comparisons regarding VAS score, NDI, and JOA score between presurgery and postsurgery were conducted by analysis of variance (ANOVA), with SNK-q tests as post hoc tests. Student's *t*-tests were used to compare demographic data and surgical parameters. A chi-square test was used to compare categorical data between groups. Statistical significance was identified when $P < 0.05$.

3. Results

3.1. Demographics and Baseline Data. We retrospectively collected and analyzed medical records of 38 patients who underwent resection of cervical intraspinal schwannoma between January 2012 and April 2019. Based on different surgical procedures, two groups were divided among all participants: laminectomy-only ($n = 21$) and laminectomy with instrumented fixation ($n = 17$); the minimum follow-up time was 1 year. As shown in Table 1, the age of the laminectomy-only group was 49.4 years (19–72), while that of the lateral mass screw group was 47.8 years (17–75). There were 12 males and 9 females in the laminectomy-only group and 11 males and 6 females in the lateral mass screw group. Preoperative symptom duration was 7.3 ± 4.4 months and 6.9 ± 4.8 months in the laminectomy-only group and the lateral mass screw group, respectively. The follow-up period was 40.6 ± 21.5 months and 43.1 ± 19.8 months in the laminectomy-only group and the lateral mass screw group, respectively. There is no significant difference between these two follow-up periods ($P > 0.05$). Comparisons between the two groups above did not show any differences in terms of age, sex percentage, duration of symptom, follow-up, blood loss, and hospital stay (all $P > 0.05$). Blood transfusion was not compared between the two groups due to a lack of sufficient data.

However, the lateral mass screw group underwent longer surgical time and higher medical expenses in comparison with the laminectomy-only group ($P < 0.05$). The segmental distribution of cervical intraspinal schwannoma is shown in Figure 2. It revealed a similar distribution between the laminectomy-only group and the lateral mass screw group.

3.2. VAS Score and NDI. As exhibited in Table 2, the preoperative VAS score was 5.18 ± 2.01 and at the last follow-up was 1.02 ± 0.25 in the laminectomy-only group. The preoperative VAS score was 5.21 ± 2.13 and at the last follow-up 1.05 ± 0.22 in the lateral mass screw group. As shown in Table 3, preoperative NDI was 24.5 ± 13.8 and at the last follow-up 4.6 ± 2.5 in the laminectomy-only group, while they were 23.8 ± 14.6 and 4.3 ± 2.4, respectively, in the lateral mass screw group. Statistical analysis showed that VAS score and NDI have significantly improved in the laminectomy-only and lateral mass screw groups, compared with the preoperative ones (all $P < 0.001$). And yet, VAS score or NDI comparisons did not indicate any significant differences between the two groups above.

3.3. JOA Score. As Table 4 tells, in the laminectomy-only group, the preoperative JOA score was 7.1 ± 3.5 and postsurgery was 13.0 ± 2.6 at the last follow-up; in the lateral mass screw group, preoperative JOA score was 7.3 ± 4.1 and postsurgery 12.8 ± 2.5 at the last follow-up. Statistically, the within-group differences were significant regarding the JOA score between the postoperative and the preoperative ones ($P < 0.001$). No differences were found between the laminectomy-only and lateral mass screw groups, regardless of preoperation, postoperative 3rd month, postoperative one year, and the last follow-up (all $P > 0.05$).

3.4. Complications. Table 5 has summarized the main postoperative complications. Statistics has indicated that spinal instability, even deformity formation, only occurs in the

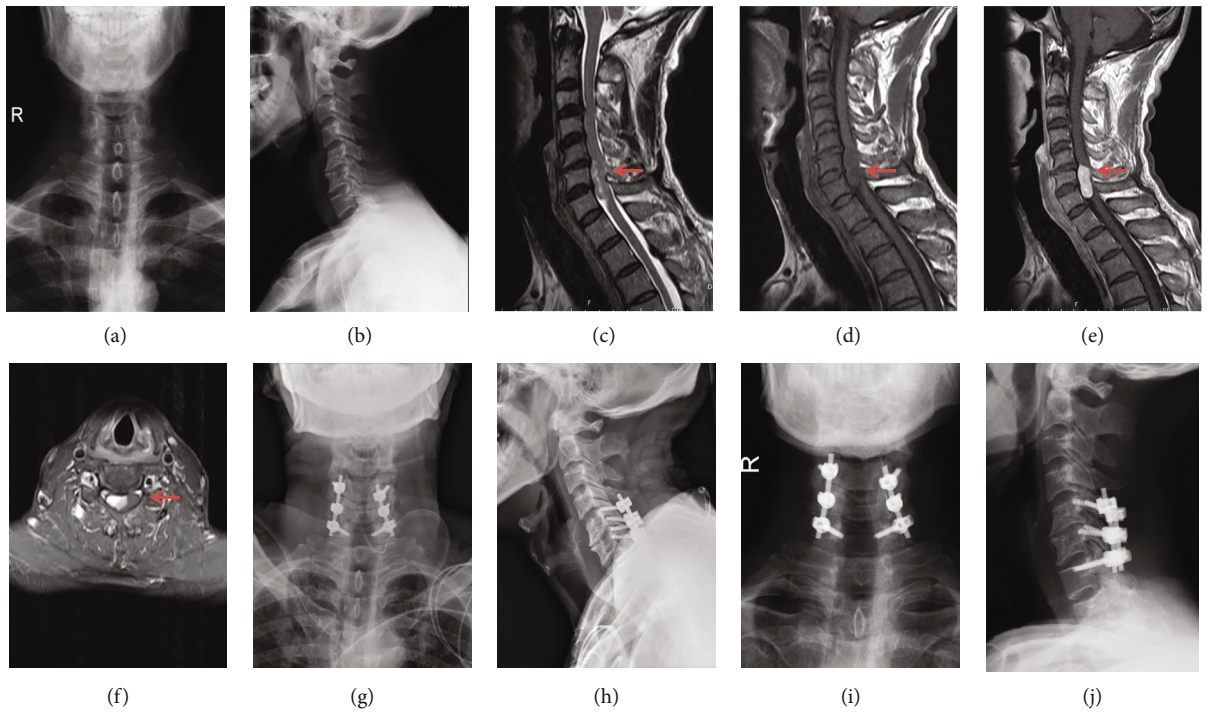

Figure 1: Radiological images before surgery, after surgery, and at the last follow-up. (a, b) Preoperative X-ray images; (c, d) preoperative T2- and T1-weighted MRI scan; (e, f) preoperative enhanced T1-weighted MRI scan; (g, h) postoperative X-ray immediately; (i, j) postoperative X-ray at the last follow-up.

Table 1: Demographic data and surgical information (mean ± SD).

Items	Laminectomy-only ($n = 21$)	Lateral mass screw ($n = 17$)	P value
Age (yr)	49.4 ± 18.3 (19-72)	47.8 ± 19.1 (17-75)	0.801
Sex	12/9 (M/F)	11/6 (M/F)	0.744*
Duration of symptom	7.3 ± 4.4 months	6.9 ± 4.8 months	0.797
Follow-up (months)	40.6 ± 21.5 (18-67)	43.1 ± 19.8 (20-72)	0.725
Blood loss (ml)	240 ± 180 (105-640)	283 ± 207 (123-955)	0.511
Surgical duration (min)	102.5 ± 31.9 (55-190)	129.7 ± 39.6 (68-220)	0.029
Hospital stay (days)	12.0 ± 4.8 (5-21)	10.5 ± 4.2 (6-18)	0.338
Medical expenses	¥ 14873 ± 3255	¥ 38875 ± 3662	<0.001

*By Pearson chi-square test; the other analyses were determined by independent t-tests.

laminectomy-only group, more than in the lateral mass screw group ($P < 0.001$). No differences were found between these two surgical procedures regarding the other complications (all $P > 0.05$).

3.5. Patient Satisfaction. Patient satisfaction grades are collected in Table 6; it did not show any significant difference between the laminectomy-only group and the lateral mass screw group regarding patient satisfaction grades ($\chi^2 = 646$, $P = 0.724$). Most patients were very satisfied with their surgical outcomes.

4. Discussion

Clinically, schwannomas are found the most common type of spinal intradural nerve sheath tumors, the second neurofibromas [19]. Because of sharing some similarities in symptoms and imaging characteristics, intradural extramedullary schwannoma and intervertebral disc diseases could be misdiagnosed to each other. Diagnosis of cervical radiculopathies due to disc herniation is straightforward with MRI or CT scan and electromyography. Schwannomas are relatively rare and often initially asymptomatic and yet can be progressive to manifest paresthesia, pain, numbness, and weakness. Schwannomas can also be misdiagnosed as other diseases, particularly neurological diseases. Navarro et al. [20] reported that a 19-year-old male patient with cervical intramedullary schwannoma was initially misdiagnosed as motor neuron disease. Thus, differential diagnosis is very important and should be cautious with schwannomas.

To date, total laminectomy has been regarded as an effective and safe technique in treating intraspinal

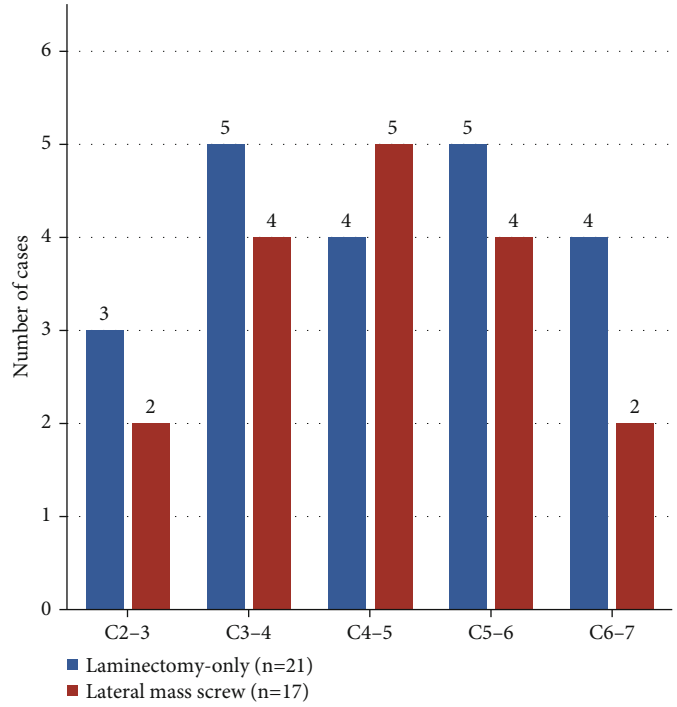

Figure 2: Distribution of cervical intraspinal schwannoma preoperatively.

Table 2: Comparison regarding VAS score (mean ± SD).

Groups	Pre	PO 3 months	1 year	Last follow-up	*P* value*
Laminectomy-only ($n = 21$)	5.18 ± 2.01	3.15 ± 1.42	1.21 ± 0.78	1.02 ± 0.25	<0.001
Lateral mass screw ($n = 17$)	5.21 ± 2.13	3.11 ± 1.33	1.16 ± 0.85	1.05 ± 0.22	<0.001
P value	0.966	0.932	0.856	0.712	—

VAS: visual analogue scale; Pre: preoperation; PO: postoperation. *Comparison within groups.

Table 3: Comparison regarding NDI (mean ± SD).

Groups	Pre	PO 3 months	1 year	Last follow-up	*P* value*
Laminectomy-only ($n = 21$)	24.5 ± 13.8	14.4 ± 11.9	8.2 ± 4.6	4.6 ± 2.5	0.0001
Lateral mass screw ($n = 17$)	23.8 ± 14.6	14.1 ± 12.1	7.2 ± 4.3	4.3 ± 2.4	0.0001
P value	0.884	0.941	0.513	0.720	—

NDI: neck disability index (50 points); Pre: preoperation; PO: postoperation. *Comparison within groups.

Table 4: Comparison regarding JOA score (mean ± SD).

Groups	Pre	PO 3 months	1 year	Last follow-up	*P* value*
Laminectomy-only ($n = 21$)	7.1 ± 3.5	10.2 ± 3.2	12.6 ± 2.8	13.0 ± 2.6	<0.001
Lateral mass screw ($n = 17$)	7.3 ± 4.1	10.5 ± 3.4	12.4 ± 3.1	12.8 ± 2.5	<0.001
P value	0.876	0.789	0.841	0.819	—

Pre: preoperation; PO: postoperation; JOA: Japanese Orthopedic Association (17 points); *comparison within groups.

schwannomas. However, mounting evidence has indicated an increasing rate of approach-related complications, including postoperative spinal instability or progression of spinal deformity [15, 21]. Compared with laminectomy-only, instrumented fixation possesses some evident advantages, especially for dumbbell tumors which are challenging for surgeons [22]. As such, instrumented fixation is imperative after total resection of a large cervical dumbbell schwannoma.

Furthermore, the advantages of instrumented fixation were also indicated by our findings in the current study. Overall, 38 patients undergoing resection of cervical

Table 5: Summary of postoperative complications.

Complications	Laminectomy-only ($n = 21$)	Lateral mass screw ($n = 17$)	P value*
New/worsening sensory symptom	2 (9.5%)	2 (11.8%)	0.758
New/worsening weakness	1 (4.8%)	1 (5.9%)	0.564
CSF leak	1 (4.8%)	1 (5.9%)	0.564
Wound infection	1 (4.8%)	0 (0.0%)	0.915
Spinal instability	6 (28.6%)	0 (0.0%)	<0.001
Spinal deformity	2 (9.5%)	0 (0.0%)	<0.001
Spinal instability/deformity	8 (38.1%)	0 (0.0%)	<0.001

CSF: cerebrospinal fluid. *By Fisher's exact test.

Table 6: Patient satisfaction grades.

Groups	Very satisfied	Satisfied	Dissatisfied	Statistic*
Laminectomy-only ($N = 21$)	15 (71.4%)	4 (19.1%)	2 (9.5%)	$\chi^2 = 0.646$
Lateral mass screw ($N = 17$)	11 (64.7%)	5 (29.4%)	1 (5.9%)	$P = 0.724$

*Pearson chi-square test between the laminectomy-only group and the lateral mass screw group.

intraspinal schwannomas were incorporated in this study. The patients were divided into two groups based on the different surgical procedures; one was a laminectomy-only group and the other was a laminectomy with instrumented fixation group. The follow-up period is long enough with a mean duration of over 40 months in both groups. Baseline data were well matched between the two groups without a difference. However, only a few patients experienced blood transfusion, and thus, no sufficient data can be compared. The segmental distribution of cervical intraspinal schwannoma was shown similar between the laminectomy-only group and the lateral mass screw group. Postoperatively, pain and neurological impairment significantly improved irrespective of a laminectomy-only group or lateral mass screw group. Seemingly, instrumented fixation did not differ from the laminectomy-only approach in terms of neurological improvement. However, the analyses of postoperative complications suggested that spinal instability and deformity were more likely to exist in the laminectomy-only group as compared with the lateral mass screw group, because the laminectomy-only approach generally leads to the destruction of posterior column structure including posterior ligament complex [15, 16]. We also compared some other postoperative complications including new/worsening sensory symptoms, new/worsening weakness, cerebrospinal fluid leak (4.8%-5.9%), and wound infection, but found no significant differences between the two surgical procedures. The demerits of the lateral mass screw group included longer surgical time due to more operation and higher medical expenses owing to the use of lateral mass screws in comparison with the laminectomy-only group. Some other postoperative complications have been reported in previous studies. Kobayashi et al. [23] reported a case of delayed hydrocephalus which was caused by the leak of cerebrospinal fluid after a cervical schwannoma was resected. Kumar et al. [24] reported that Horner's syndrome happened in the case after a cervical vagal schwannoma was removed.

There are some limitations and shortcomings in this work. First off, this is a retrospective study which might have generated the selection bias. Additionally, this study is a single-center report, not comprehensive enough. At last, this study does not have a large sample size, which could have compromised the power of test and thus is another shortcoming. Therefore, it would be much better if a prospective randomized clinical trial with a large sample size can be performed for further investigation in the future.

5. Conclusions

In conclusion, laminectomy with lateral mass screw fixation is an effective and safe approach in treating cervical intraspinal schwannoma, which is likely to be a better choice than laminectomy-only approach, particularly in terms of maintaining postoperative spinal stabilization.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

All authors declare no conflicts of interest regarding this study.

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