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Enhanced recovery pathways in geriatric orthopaedics

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Enhanced recovery pathways in geriatric orthopaedics

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The Charlson Comorbidity Index and depression are associated with satisfaction after short-segment lumbar fusion in patients 75 years and older

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Background: The rate and volume of lumbar spinal fusion (LSF) surgery performed for patients aged 75 years and older increased in recent years. The purposes of our study were to identify factors associated with postoperative dissatisfaction and evaluate the predictive value of comprehensive geriatric assessment (CGA) for dissatisfaction at 2 years after elective short-segment (one- or two- level) LSF in patients aged 75 and older.
Methods: This was a retrospective study using a prospectively collected database of consecutive patients (aged 75 and older) who underwent elective short-segment transforaminal lumbar interbody fusion surgery for degenerative diseases from June 2018 to May 2020. Preoperative CGA consisting six domains was performed for each patient 1 day before the operative day. Univariate and multivariate analyses were performed to identify factors that predict for dissatisfaction with surgical treatment. The primary outcome was patient satisfaction with LSF surgery, as measured by the North American Spine Society (NASS) satisfaction scale. Secondary outcomes included postoperative complications, the length of stay, visual analog scale (VAS), and Oswestry Disability Index.
Results: A total of 211 patients were available for a follow-up at 2 years and included in our final study cohort with a mean age of 80.0 years. A total of 175 patients (82.9%) were included in the satisfied group, and 36 patients (17.1%) were included in the not dissatisfied group. In the dissatisfied group, there was a higher incidence of postoperative complications (30.6% vs. 14.3%, $p = 0.024$) and greater VAS scores for lower back (4.3 ± 1.9 vs. 1.3 ± 1.4, $p = 0.001$) and leg (3.9 ± 2.1 vs. 0.9 ± 1.3, $p = 0.001$). Multivariate regression analysis revealed that patients with greater CCI score [odd ratio (OR) 2.56, 95% CI, 1.12–5.76; $p = 0.030$ for CCI 1 or 2 and OR 6.20, 95% CI, 1.20–28.69; $p = 0.024$], and depression (OR 3.34, 95% CI, 1.26–9.20; $p = 0.016$) were more likely to be dissatisfied compared with patients with the CCI score of 0 and without depression.
Conclusions: Satisfaction after LSF in older patients (aged 75 and older) was similar to that of previously reported younger patients. Preoperative depression and higher CCI scores were independent risk factors for

postoperative dissatisfaction two years after LSF surgery. These results help inform decision-making when considering LSF surgery for patients aged 75 and older.

KEYWORDS

elderly, lumbar fusion surgery, comprehensive geriatric assessment, dissatisfaction, depression, comorbiditiy

Introduction

With the rapid population aging, the incidence of lumbar degenerative disease is increasing, severely deteriorating the patient's quality of life (QoL), and increasing socioeconomic burdens (1). Lumbar spinal fusion (LSF) surgery is the standard treatment for lumbar degenerative disease. With the improvement of surgical techniques, the rate and volume of LSF surgery increased in recent years. Martin et al. (2) reviewed the National Inpatient Sample database and found that aggregate hospital costs increased by 177%, and the volume of elective lumbar fusion increased 62.3% from 2004 to 2015 in the United States, especially for elderly patients. A recent study using Finnish nationwide data showed that the increase in lumbar spinal fusions was highest among women over 75 years, with a 4-fold increase (3). Previous studies found that age did not impact on patient-reported outcomes (4–6). However, patients aged 75 and older may be more likely to refuse surgery than younger patients due to fear of high rates of morbidity and mortality. With the increase of age, the physiological function reserves of elderly patients decrease, especially changes in cardiopulmonary function and the nervous system (7). These may lead to reduced ability of older patients to tolerate surgical stress. Comprehensive assessments are needed to select patients who are more likely to benefit from surgical treatment when designing the treatment plans for high-risk patients.

Patient-reported outcome (PRO) measures of pain, disability, and health-related QoL are commonly used to evaluate the effect of LSF. Sivaganesan et al. (8) reported that 23% of patients with clinically relevant pain improvement nevertheless remained dissatisfied with surgery. Patient satisfaction is essential to evaluate the quality and effectiveness of medical care. Reimbursement of healthcare systems is linked to patient-reported satisfaction in many countries. Improving postoperative satisfaction is necessary for the current healthcare environment. Patient characteristics such as smoking status, psychological distress, low level of education, unemployment status and symptoms duration were associated with postoperative dissatisfaction in previous studies (9–13). The comprehensive geriatric assessment (CGA) is an effective tool for assessing a patient's functional age. The CGA evaluates an elderly patient's medical, psychosocial, functional, and environmental resources and links them with an overall plan of treatment and follow-up. Preoperative assessment can identify patients with physiologic dysfunction, including frailty, disability, depression, and malnutrition associated with poor clinical outcomes (14). The value of CGA in predicting long-term QoL and satisfaction has been demonstrated in previous studies on cancer surgery and hip fracture surgery (15–17); however, few studies on spine surgery included CGA in their analyses (18). Identifying the factors influencing older patient satisfaction after LSF surgery is critical to improve shared clinical decision-making. Thus, this study aimed to determine the level of satisfaction and identify factors associated with postoperative dissatisfaction 2 years after elective short-segment (one- or two- level) LSF in patients aged 75 and older.

Materials and methods

This was a retrospective study using a prospectively collected database. The ethical review committee of our hospital approved the study. Lumbar spine surgery is recommended for patients who have failed conservative treatment with medications or exercise for more than half a year, and the same experienced surgical team performed all surgeries. A midline incision was made for patients under general anesthesia. The nerve roots were decompressed by hemilaminectomy or laminectomy according to the preoperative lumbar symptoms, radicular symptoms and MRI. The vertebral pedicle screws of surgical segments were implanted under direct vision. To improve the fusion rates and restore the height of intervertebral height, cages filled with bone grafts were placed in the intervertebral space. We included consecutive patients (aged 75 and older) who underwent elective short-segment transforaminal lumbar interbody fusion surgery for degenerative diseases from June 2018 to May 2020. Patients undergoing surgery for lumbar trauma, tumors, infections were excluded.

Data collection

As published previously, we collected patients' demographic variables [age, sex, weight, body mass index (BMI), comorbidities, smoking status, and surgical history], American Society of Anesthesiologists (ASA), laboratory examination data (level of albumin, prealbumin and hemoglobin), primary

diagnosis and baseline PRO scores [visual analogue scale (VAS), Oswestry Disability Index (ODI)], and surgery-related variables (operative time, number of fused levels, and estimated blood loss).

We conducted preoperative CGA for each patient 1day before the operative day. Our CGA consisted of six domains [Zung Depression Rating Scale (ZDRS), Activities of Daily Living (ADL), Instrumental Activities of Daily Life (IADL), Mini-Mental Status Examination (MMSE), Mini Nutritional Assessment (MNA), and Charlson Comorbidity Index (CCI)]. The severity of comorbidities was evaluated using CCI (19) and ASA grades. Functional status and dependency were evaluated using ADL (20) and IADL (21) scales. Cognitive function and psychological disorders were evaluated using the MMSE (22) and ZDRS (23, 24), respectively. The six domains of our CGA with their corresponding cutoff values are summarized in Table 1.

Outcome measures

The primary outcome was patient satisfaction with LSF surgery at a 2-year follow-up, measured by the North American Spine Society (NASS) satisfaction scale. Answer choices of the satisfaction scale were as follows: (1) The treatment met my expectations; (2) I did not improve as much as I had hoped, but I would undergo the same treatment for the same outcome; (3) I did not improve as much as I had hoped, and I would not undergo the same treatment for the same outcome; and (4) I am the same or worse than before treatment. Patients who chose (1) and (2) were considered satisfied with surgical care and outcomes, and patients with the other answer choices were classified as dissatisfied and regretting the choice of surgical treatment (12). Secondary outcomes included VAS scores of lower back and leg pain, ODI, the incidence of complications, and the length of hospital stay.

TABLE 1 Cutoff values for the six domains of our comprehensive geriatric assessment.

Domains	Cutoff values for a deficit or disability
CCI	No applicable
ADL	Independent: 100 points; mild disability: 61–99 points; severe disability: ≤60 points
IADL	Independent: 100 points; mild disability: 61–99 points; severe disability: ≤60 points
MNA	Malnutrition: ≤18 points
MMSE	Cognitive impairment: ≤23 points
Zung depression	Depression: ≥50 points

CCI, Charlson Comorbidity Index; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MNA, Mini Nutritional Assessment; MMSE, Mini-Mental Status Examination.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and analyzed using the 2-tailed Student's *t*-test or Mann-Whitney *U* test depending on the variable type. Categorical variables were expressed as frequencies with percentages and analyzed using Fisher's exact or chi-square tests. All variables with a *p*-value <0.1 detected in univariate analyses were entered into multivariate logistic analyses for dissatisfaction. All statistical analyses were performed using SPSS Statistics 25 (SPSS, version 22.0, Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Results

A total of 218 consecutive patients (75 years or older) underwent short-segment LSF surgery for lumbar degenerative diseases from June 2018 to May 2020. All patients received preoperative assessments by a multidisciplinary team including experienced surgeons, internists, and anesthesiologists. Of the included 218 patients, three patients died of other diseases after the patient had been discharged home and four patients were lost to follow-up. A total of 211 patients were available for a follow-up at 2 years and included in our final study cohort with a mean age of 80.0. (Figure 1). Among these, 121 (57.3%) patients had a NASS satisfaction score of 1 at 2-year follow-up, 54 (25.6%) patients had a score of 2, 22 (10.4%) patients had a score of 3, and 14 (6.6%) patients had a score of 4 (Figure 2). A total of 175 patients (82.9%) were satisfied after 2 years of LSF surgery and included in the satisfied group, and 36 (17.1%) were dissatisfied and included in the not dissatisfied group. There were no significant differences between groups in baseline demographic characteristics, primary diagnosis, comorbidities, or laboratory data (Table 2). Compared to satisfied patients, dissatisfied patients showed a higher incidence of depression (25.0% vs. 9.1%, $p = 0.002$) and a higher rate of greater CCI scores ($p = 0.017$). There were no significant differences in ASA level ($p = 0.383$), ADL ($p = 0.631$), IADL ($p = 0.682$), MNA ($p = 0.910$), MMSE ($p = 0.132$), or procedure-related variables (Table 3). Table 4 presents the study population's postoperative clinical outcomes and VAS scores. In the dissatisfied group, there was a higher incidence of postoperative complications (30.6% vs. 14.3%, $p = 0.024$), greater ODI (44.0 ± 26.3 vs. 20.3 ± 17.2, $p = 0.001$) and VAS scores for lower back (4.3 ± 1.9 vs. 1.3 ± 1.4, $p = 0.001$) and leg (3.9 ± 2.1 vs. 0.9 ± 1.3, $p = 0.001$). There were no differences between the two groups in postoperative deep vein thrombosis, surgical site infection, and urinary retention.

Five factors (CCI score, depression, preoperative serum albumin, complications) with a *p*-value <0.1 in univariate analyses were included in multivariate logistic analyses. Multivariate regression analysis revealed that patients with greater CCI score [odds ratio, (OR) 2.56, 95% CI, 1.12–5.76; $p = 0.030$ for CCI 1 or 2 and OR 6.20, 95% CI, 1.20–28.69;

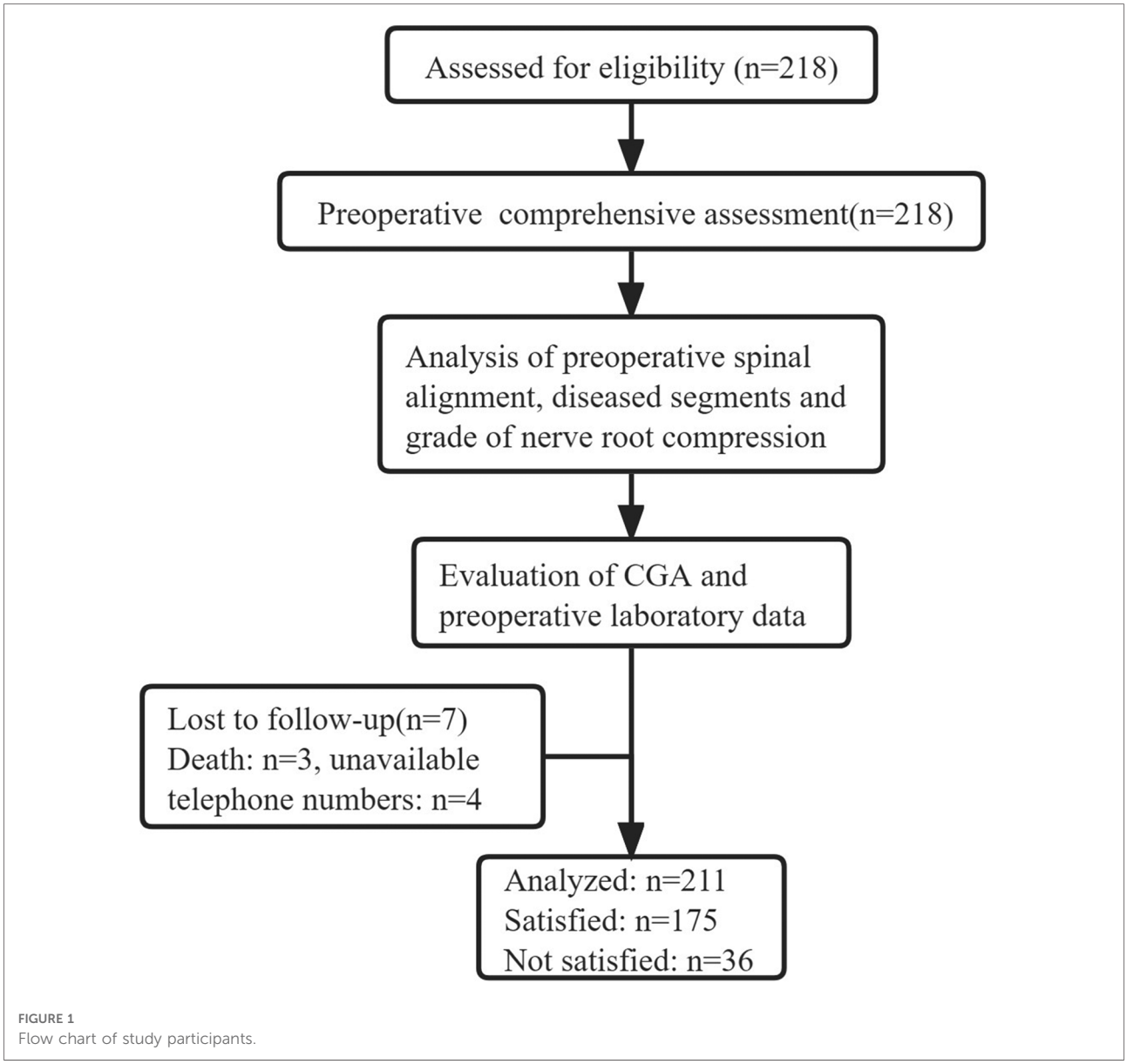

FIGURE 1
Flow chart of study participants.

$p = 0.024$], and depression (OR 3.34, 95% CI, 1.26–9.20; $p = 0.016$) were more likely to be dissatisfied with surgical treatment compared with patients with the CCI score of 0 (Table 5). Increasing CCI score was significantly associated with a higher rate of dissatisfaction (Figure 3). However, preoperative serum albumin and postoperative complications were not significantly associated with dissatisfaction.

Discussion

Patients of advanced age had a higher incidence of postoperative complications, readmission, and hospital costs after spinal surgery due to the presence of frailty and comorbidities (25–27); these findings suggest that comprehensive assessment is needed to select patients more likely to benefit from surgical treatment. Preoperative patient expectations, postoperative pain control levels, functional recovery, and cost of hospitalization are influenced by satisfaction. The NASS scale is a commonly used evaluation tool for patient-reported outcomes considering patient expectations and postoperative outcomes actuality. The objective of the present study was to measure the satisfaction of patients aged 75 years and older using the NASS scale and to identify independent risk factors for dissatisfaction with short-segment lumbar fusion surgery.

Previously, it was demonstrated that older age was not a risk factor for worse PRO, and elderly patients could also benefit

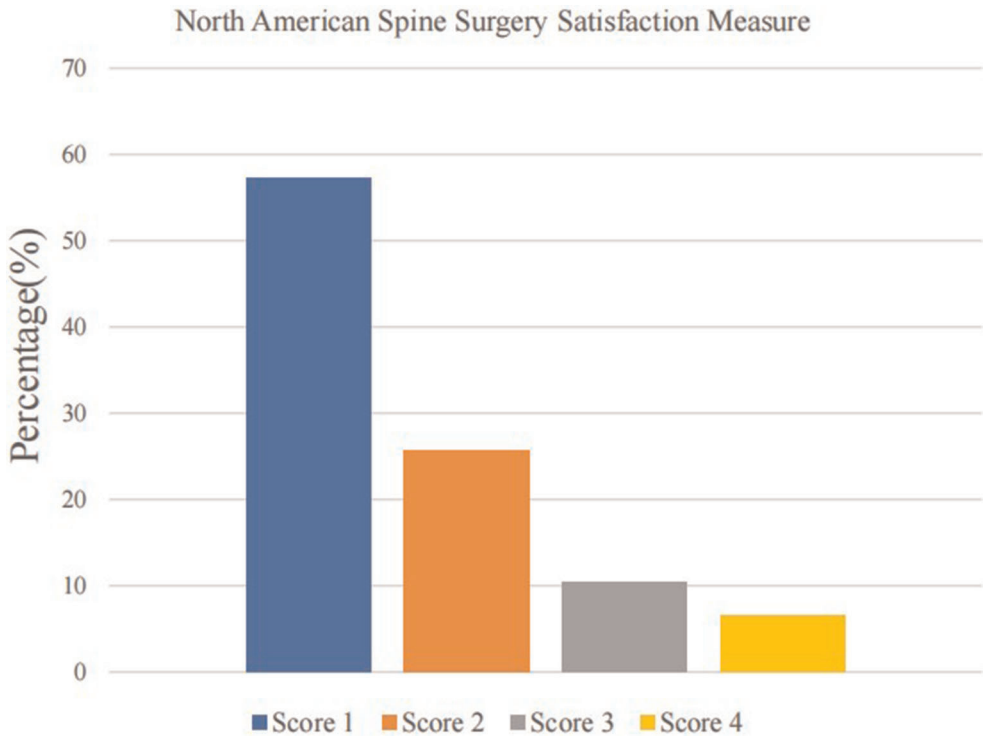

FIGURE 2
North American Spine Surgery Satisfaction measure.

from spinal fusion and show a good satisfaction rate (6, 28, 29). Our study found that 82.9% of patients were satisfied, and 6.6% were most dissatisfied with surgical treatment at the 2-year follow-up point. These results were similar to previous studies. Mummaneni et al. reviewed 502 patients (mean age of 61 years) undergoing surgery for degenerative lumbar spondylolisthesis and found that 82% of patients were satisfied with and 10.3% of patients were most dissatisfied with their surgery (12). Another study of patients over 80 years conducted by Hikata et al. found that 77.5% of patients were satisfied with surgical treatment (29). Our study validates previous findings that LSF surgery effectively improve QoL in patients aged 75 years and older.

The predictive value and details of CGA were extensively reported in various disciplines (18, 30, 31). Several studies evaluated the value of CGA and found that preoperative ASA grade, frailty, depression, and CCI scores were significantly associated with postoperative complications and PRO following spinal surgery (32, 33). The present study found that higher CCI scores and depression were independently associated with postoperative dissatisfaction. The CCI is a convenient tool that allows physicians to assess comorbidity severity and predict mortality risk for surgery patients (19). In a prospective observational study, Whitmore et al. (33) found that increasing CCI score was associated with an increased likelihood of major and minor complications. In another study of patients with single-level fusion surgery, the CCI score was a risk factor for less improvement in the Japanese Orthopedic Association lumbar score (34). Moreover, the CCI was also reported to be independently associated with length of hospital stay and unplanned readmission after lumbar spine surgery (35). Some researchers used other satisfaction evaluation tools to demonstrate the relationship between satisfaction and CCI and found the same conclusion. Benjamin et al. (36) conducted a retrospective review of 17,853 consecutive spinal patients and found that overall comorbid disease burden was a significant negative predictor for high Press Ganey satisfaction scores. Another study reported that high CCI was associated with lower Hospital Consumer Assessment of Healthcare Providers and Systems score of satisfaction (37). In the present study, we compared the baseline characteristics of the satisfied group with the dissatisfied group and found that no specific disease was associated with dissatisfaction. It is worth noting that the impact of comorbidities on satisfaction is multifaceted, and this finding highlights the importance of comprehensive assessments in patients aged 75 and older.

The ZDRS is a 20-item questionnaire with well-established reliability and validity (23). Depression, as measured using the Zung depression scale, was another domain of CGA

TABLE 2 Baseline characteristics and laboratory data of patients in the two groups.

Variable	Total (n = 211)	Satisfied (n = 175)	Not Satisfied (n = 36)	p-value
Female n/ (%)	126 (59.7%)	108 (61.7%)	18 (50.0%)	0.192
Age (year)	80.0 ± 3.5	79.9 ± 3.5	80.0 ± 3.4	0.935
Height (cm)	160.8 ± 7.5	160.6 ± 7.5	162.0 ± 7.5	0.295
Weight (kg)	63.9 ± 9.2	64.0 ± 9.2	63.5 ± 8.9	0.774
BMI (kg/m^2)	24.8 ± 3.6	24.9 ± 3.7	24.2 ± 3.1	0.311
Co-Morbidities n/ (%)				
Hypertension	140 (66.4%)	117 (66.9%)	23 (63.9%)	0.731
Coronary heart disease	52 (24.6%)	42 (24.0%)	10 (27.8%)	0.632
Diabetes disease	53 (25.1%)	41 (23.4%)	12 (33.3%)	0.212
Knee arthritis	27 (12.8%)	22 (12.6%)	5 (13.9%)	0.829
Digestive disease	26 (12.3%)	20 (11.4%)	6 (16.7%)	0.384
Old cerebral infarction	14 (6.6%)	11 (6.3%)	3 (8.3%)	0.653
Pulmonary disease	3 (1.4%)	2 (1.1%)	1 (2.8%)	0.450
Osteoporosis	44 (20.9%)	35 (20%)	9 (25%)	0.501
Urological diseases	18 (8.5%)	15 (8.6%)	3 (8.3%)	0.963
Smoker	14 (6.6%)	12 (6.9%)	2 (5.6%)	0.775
Drinker	15 (7.1%)	13 (7.4%)	2 (5.6%)	0.435
Diagnosis				0.151
LSS	77 (36.5%)	60 (34.3%)	17 (47.2%)	
DDD	89 (37.9%)	79 (45.1%)	10 (27.8%)	
Lumbar	45 (21.3%)	36 (20.6%)	9 (25.0%)	
Spondylolisthesis				
Duration of symptoms (year)	6.4 ± 9.2	6.2 ± 9.5	6.9 ± 7.4	0.629
VAS (lower back)	5.1 ± 2.0	5.1 ± 2.1	5.2 ± 1.6	0.828
VAS (leg)	6.7 ± 2.3	6.7 ± 2.3	6.4 ± 2.3	0.411
ODI	54.5 ± 12.4	54.6 ± 12.7	53.9 ± 11.4	0.781
Laboratory data				
Serum albumin (g/L)	37.5 ± 3.8	37.7 ± 3.8	36.5 ± 3.6	0.075
Prealbumin (g/L)	219 ± 55	219 ± 55	218 ± 57	0.881
Hemoglobin (g/L)	126 ± 15	127 ± 14	123 ± 17	0.119

BMI, Body Mass Index; LSS, lumbar spine stenosis; DDD, Degenerative Disc Disease; VAS, Visual Analogue Scale; ODI, Oswestry Dability Index.

TABLE 3 CGA scores and procedure-related variables of patients in the two groups.

Variable	Satisfied (n = 175)	Not Satisfied (n = 36)	p-value
ASA			0.383
1 or 2	77 (44.0%)	13 (36.1%)	
3 or 4	98 (56.0%)	23 (63.9%)	
CCI			**0.017**
0 (%)	96 (54.9%)	11 (30.5%)	
1 or 2	74 (42.3%)	22 (61.1%)	
3 and 3+	5 (2.8%)	3 (8.3%)	
Level of dependence in the ADL			0.631
Independent	31 (17.7%)	7 (19.4%)	
Mild disability	102 (58.3%)	18 (50.0%)	
Severe disability	42 (24.0%)	11 (30.6%)	
Level of dependence in the IADL			0.682
Independent	39 (22.2%)	6 (16.7%)	
Mild disability	53 (30.3%)	13 (36.1%)	
Severe disability	83 (47.4%)	17 (47.2%)	
Zung depression scale			**0.002**
Depression	16 (9.1%)	9 (25%)	
No depression	159 (90.9%)	27 (75%)	
MNA			
Malnutrition	47 (26.9%)	10 (27.8%)	0.910
No malnutrition	128 (73.1%)	26 (72.2%)	
MMSE			0.132
Cognitive impairment	42 (24.0%)	13 (36.1%)	
Normal cognition	133 (76.0%)	23 (63.9%)	
No. of levels			0.923
1	50 (28.6%)	10 (27.8%)	
2	125 (71.4%)	26 (72.2%)	
Operative time (min)	199.7 ± 61.4	212.9 ± 56.1	0.237
EBL	334.1 ± 260.0	390.1 ± 261.0	0.234

ASA, American Society of Anesthesiologists Physical Classification System; CCI, Charlson Comorbidity Index; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MNA, Mini Nutritional Assessment; MMSE, Mini-Mental Status Examination; EBL, Estimated Blood Loss.
Bold values implies statistical significance.

associated with postoperative dissatisfaction in elderly patients (aged 75 years and older). The association between preoperative depression and postoperative outcomes was demonstrated in previous studies (9, 10). In a retrospective study of 8,585 patients, Zakaria et al. (38) found that preoperative depression (measured using the Patient Health Questionnaire-2) predicted worse satisfaction and inability to return to work. In another retrospective study, Levin et al. (9) analyzed the association between depression using the PHQ-9 and postoperative satisfaction after lumbar fusion. These results showed that patients with preoperative depression were more likely to be dissatisfied with physicians and nurses. The ZDSR was also identified to be effective in predicting postoperative satisfaction in patients undergoing revision lumbar surgery (39). Depressed patients (particularly those more than 75 years) may be more sensitive to preoperative mental stress and postoperative pain. It is necessary for these patients to understand their expectations and fully provide them with emotional support. Changes in depressive symptoms may have a more significant effect than preoperative depression on satisfaction and changes in other PRO after spine surgery (40).

In some previous studies, patient satisfaction showed a clear correlation with achieving clinical improvement in pain and

TABLE 4 Postoperative outcomes of patients in both groups.

Variables	Satisfied (n = 175)	Not Satisfied (n = 36)	*p*-value
NASS Satisfaction Measure	1.3 ± 0.5	3.4 ± 0.5	**0.001**
VAS of lower back	1.3 ± 1.4	4.3 ± 1.9	**0.001**
VAS of leg	0.9 ± 1.3	3.9 ± 2.1	**0.001**
Length of hospital stay	17.2 ± 7.5	18.3 ± 6.6	0.413
Complications	25 (14.3%)	11 (30.6%)	**0.024**
Urinary retention	4 (2.3%)	2 (5.6%)	0.282
Deep vein thrombosis	2 (1.1%)	2 (1.1%)	0.077
Nausea/vomiting	9 (5.1%)	4 (11.1%)	0.175
Urinary Infection	1 (0.6%)	0 (0%)	0.649
Acute cerebral infarction	1 (0.6%)	0 (0%)	0.649
Pneumonia	2 (1.1%)	1 (2.8%)	0.450
Hematoma	2 (1.1%)	0 (0%)	0.519
Delirium	2 (1.1%)	2 (5.5%)	0.077
Myocardial infarction	1 (0.6%)	1 (2.8%)	0.213
Surgical site infection	3 (1.7%)	1 (2.8%)	0.670
Constipation	3 (1.7%)	2 (5.5%)	0.168

NASS, North American Spine Surgery; VAS, Visual Analogue Scale.
Bold values implies statistical significance.

TABLE 5 Multivariate logistic analysis for risk factors associated with dissatisfaction.

Variable	OR	95% CI	*p*-value
Depression	3.40	1.26–9.20	**0.016**
CCI score of 1or 2	2.56	1.12–5.76	**0.030**
CCI score of 3+	6.20	1.20–28.69	**0.024**

CCI, Charlson Comorbidity Index; LL, Lumbar Lordosis.
Bold values implies statistical significance.

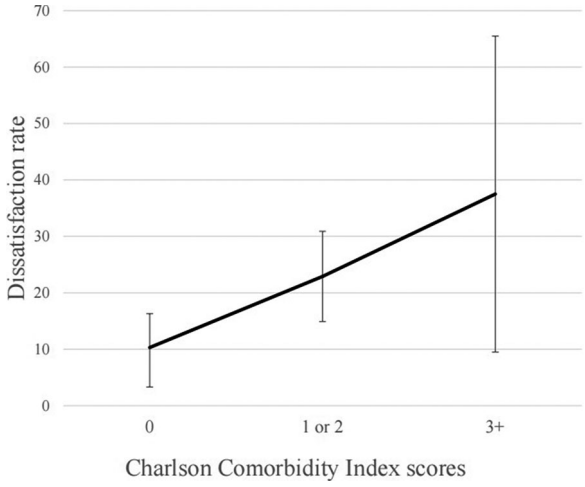

FIGURE 3
Association between CCI and dissatisfaction rate.

disability after surgery (12, 29, 41). Nevertheless, Yoo et al. (42) found that actual postoperative results had a stronger correlation with patient satisfaction than the expectation-actuality discrepancy and postoperative improvement. In the present study, we found no difference in preoperative pain level and functional disability between the satisfied and unsatisfied groups, while the unsatisfied group had significantly higher postoperative pain scores. These findings suggest that surgeons should focus on achieving the best clinical outcome through surgery regardless of the duration and extent of the patient's preoperative symptoms.

Another postoperative outcome that should be noted is the incidence of postoperative complications. Consistent with several previous studies (12, 37, 43), multivariate regression analysis revealed that complication was not an independent risk factor for postoperative dissatisfaction in our patient cohort. Some reasons may potentially explain this finding. First, there were no severe postoperative complications such as myocardial infarction, cerebral infarction, or paralysis in our enrolled patients, and all patients with complications were discharged from the hospital after medical and surgical treatment. Second, the impact of confounding factors was amplified due to the small sample size. Moreover, preoperative comorbidities may have potential implications for postoperative complications, and these variables have a synergistic effect on postoperative satisfaction.

Several limitations in our study should be noted. First, this was a retrospective, single-center study evaluating the impact of CGA on satisfaction and postoperative CGA was not performed for patients. Prospective studies are needed to identify the changes in CGA score after surgery and the impact of improvement of preoperative depression on outcomes. Second, the small sample size of our study may decrease our findings' robustness. Third, only six CGA domains, pain level, and functional status were included, and QoL scales (e.g., Short Form 36 Health Status Survey, PHQ-9) that may be associated with satisfaction were evaluated. Finally, this study had a short follow-up time of 24 months. Indeed, satisfaction is an outcome that can fluctuate with the follow-up time. Long-term and continuous follow-up will help to identify changes in satisfaction over time. Despite these limitations, this is the first study to examine the value of the CGA for predicting surgical outcomes in patients aged 75 and older. Our findings could be implemented in clinical practice to improve shared decision-making when considering LSF for patients aged 75 and older.

Conclusions

The results of this study indicate that the satisfaction after LSF in older patients (aged 75 and older) was similar to that of previously reported younger patients. Multivariate analysis revealed that preoperative depression and higher CCI scores

were independent risk factors for postoperative dissatisfaction two years after LSF surgery. Preoperative assessment using the Zung depression scale and CCI help inform decision-making when considering LSF surgery for patients aged 75 and older.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

S-KW and G-GZ contributed to the conception of the study. HM made an important contribution to the revision of the manuscript. PW and X-YL contributed significantly to analysis and manuscript preparation. S-KW and J-BC performed the data analyses and wrote the manuscript; CK and S-BL helped perform the analysis with constructive discussions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Buser Z, Ortega B, D'Oro A, Pannell W, Cohen JR, Wang J, et al. Spine degenerative conditions and their treatments: national trends in the United States of America. *Global Spine J.* (2018) 8:57–67. doi: 10.1177/2192568217696688

2. Martin BI, Mirza SK, Spina N, Spiker WR, Lawrence B, Brodke DS. Trends in lumbar fusion procedure rates and associated hospital costs for degenerative spinal diseases in the United States, 2004 to 2015. *Spine.* (2019) 44:369–76. doi: 10.1097/brs.0000000000002822

3. Ponkilainen VT, Huttunen TT, Neva MH, Pekkanen L, Repo JP, Mattila VM. National trends in lumbar spine decompression and fusion surgery in Finland, 1997–2018. *Acta Orthop.* (2021) 92:199–203. doi: 10.1080/17453674.2020.1839244

4. Khan JM, Basques BA, Harada GK, Louie PK, Chen I, Vetter C, et al. Does increasing age impact clinical and radiographic outcomes following lumbar spinal fusion? *Spine J.* (2020) 20:563–71. doi: 10.1016/j.spinee.2019.11.003

5. Liao JC, Chen WJ. Surgical outcomes in the elderly with degenerative spondylolisthesis: comparative study between patients over 80 years of age and under 80 years-a gender-, diagnosis-, and surgical method-matched two-cohort analyses. *Spine J.* (2018) 18:734–9. doi: 10.1016/j.spinee.2017.08.250

6. Karsy M, Chan AK, Mummaneni PV, Virk MS, Bydon M, Glassman SD, et al. Outcomes and complications with age in spondylolisthesis an evaluation of the elderly from the quality outcomes database. *Spine.* (2020) 45:1000–8. doi: 10.1097/brs.0000000000003441

7. Sun LY, Spence SD, Benton S, Beanlands RS, Austin PC, Eddeen AB, et al. Age, not sex, modifies the effect of frailty on long-term outcomes after cardiac surgery. *Ann Surg.* (2022) 275:800–6. doi: 10.1097/sla.0000000000004060

8. Sivaganesan A, Khan I, Pennings JS, Roth SG, Nolan ER, Oleisky ER, et al. Why are patients dissatisfied after spine surgery when improvements in disability and pain are clinically meaningful? *Spine J.* (2020) 20:1535–43. doi: 10.1016/j.spinee.2020.06.008

9. Levin JM, Winkelman RD, Smith GA, Tanenbaum JE, Benzel EC, Mroz TE, et al. Impact of preoperative depression on hospital consumer assessment of healthcare providers and systems survey results in a lumbar fusion population. *Spine.* (2017) 42:675–81. doi: 10.1097/brs.0000000000002101

10. Levin JM, Boyle S, Winkelman RD, Tanenbaum JE, Abdullah KG, Steinmetz MP, et al. Patient-reported allergies are associated with preoperative psychological distress and less satisfying patient experience in a lumbar spine surgery population. *Clin Spine Surg.* (2018) 31:E368–E74. doi: 10.1097/bsd.0000000000000665

11. Chapin L, Ward K, Ryken T. Preoperative depression, smoking, and employment status are significant factors in patient satisfaction after lumbar spine surgery. *Clin Spine Surg.* (2017) 30:E725–E32. doi: 10.1097/bsd.0000000000000331

12. Mummaneni PV, Bydon M, Alvi MA, Chan AK, Glassman SD, Foley KT, et al. Predictive model for long-term patient satisfaction after surgery for grade I degenerative lumbar spondylolisthesis: insights from the Quality Outcomes Database. *Neurosurg Focus.* (2019) 46:E12. doi: 10.3171/2019.2.Focus18734

13. Lubelski D, Feghali J, Nowacki AS, Alentado VJ, Planchard R, Abdullah KG, et al. Patient-specific prediction model for clinical and quality-of-life outcomes after lumbar spine surgery. *J Neurosurg Spine.* (2021) 34:580–8. doi: 10.3171/2020.8.Spine20577

14. Robinson TN, Eiseman B, Wallace JI, Church SD, McFann KK, Pfister SM, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. *Ann Surg.* (2009) 250:449–55. doi: 10.1097/SLA.0b013e3181b45598

15. Whittle AK, Kalsi T, Babic-Illman G, Wang Y, Fields P, Ross PJ, et al. A comprehensive geriatric assessment screening questionnaire (CGA-GOLD) for older people undergoing treatment for cancer. *Eur J Cancer Care (Engl).* (2017) 26:1–16. doi: 10.1111/ecc.12509

16. Choi JY, Kim JK, Kim KI, Lee YK, Koo KH, Kim CH. How does the multidimensional frailty score compare with grip strength for predicting outcomes after hip fracture surgery in older patients? A retrospective cohort study. *BMC Geriatr*. (2021) 21:234. doi: 10.1186/s12877-021-02150-9

17. Parks RM, Hall L, Tang SW, Howard P, Lakshmanan R, Winterbottom L, et al. The potential value of comprehensive geriatric assessment in evaluating older women with primary operable breast cancer undergoing surgery or non-operative treatment—a pilot study. *J Geriatr Oncol*. (2015) 6:46–51. doi: 10.1016/j.jgo.2014.09.180

18. Parker SG, McCue P, Phelps K, McCleod A, Arora S, Nockels K, et al. What is comprehensive geriatric assessment (CGA)? An umbrella review. *Age Ageing*. (2018) 47:149–55. doi: 10.1093/ageing/afx166

19. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. (1987) 40:373–83. doi: 10.1016/0021-9681(87)90171-8

20. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe M. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. (1963) 185:914–9. doi: 10.1001/jama.1963.03060120024016

21. Jitapunkul S, Kamolratanakul P, Age SEJ. The meaning of activities of daily living in a Thai elderly population: development of a new index. *Age Ageing*. (1994) 23:97–101. doi: 10.1093/ageing/23.2.97

22. Folstein MF, Folstein SE, Mchugh P. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. (1975) 12:0–198. doi: 10.1016/0022-3956(75)90026-6

23. Thurber S, Snow M, Honts CRJA. The Zung Self-Rating Depression Scale: convergent validity and diagnostic discrimination. *Assessment*. (2002) 9:401–5. doi: 10.1177/1073191102238471

24. Trief PM, Grant W, Fredrickson B. A prospective study of psychological predictors of lumbar surgery outcome. *Spine*. (2000) 25:2616–21. doi: 10.1097/00007632-200010150-00012

25. Walid MS, Sanoufa M, Robinson JS. The effect of age and body mass index on cost of spinal surgery. *J Clin Neurosci*. (2011) 18:489–93. doi: 10.1016/j.jocn.2010.07.132

26. Claus CF, Tong D, Lytle E, Bahoura M, Garmo L, Li CX, et al. Age as a predictor for complications and patient-reported outcomes in multilevel transforaminal lumbar interbody fusions analyses from the michigan spine surgery improvement collaborative (MSSIC). *Spine*. (2021) 46:356–65. doi: 10.1097/brs.0000000000003792

27. Pugely AJ, Martin CT, Gao YB, Mendoza-Lattes S. Causes and risk factors for 30-day unplanned readmissions after lumbar spine surgery. *Spine*. (2014) 39:761–8. doi: 10.1097/brs.0000000000000270

28. Becker P, Bretschneider W, Tuschel A, Ogon M. Life quality after instrumented lumbar fusion in the elderly. *Spine*. (2010) 35:1478–81. doi: 10.1097/BRS.0b013e3181c62294

29. Hikata T, Ishii K, Matsumoto M, Kobayashi K, Imagama S, Ando K, et al. Risk factor for poor patient satisfaction after lumbar spine surgery in elderly patients aged over 80 years. *Clin Spine Surg*. (2021) 34:E223–E8. doi: 10.1097/bsd.0000000000001101

30. Wilhelmson K, Hammar IA, Westgard T, Henrikson LH, Dahlin-Ivanoff S. Positive effects on activities of daily living one year after receiving comprehensive geriatric assessment—results from the randomised controlled study CGA-swed. *BMC Geriatr*. (2022) 22:1–10. doi: 10.1186/s12877-022-02862-6

31. Chang SY, Son J, Park SM, Chang BS, Lee CK, Kim H. Predictive value of comprehensive geriatric assessment on early postoperative complications following lumbar spinal stenosis surgery A prospective cohort study. *Spine*. (2020) 45:1498–505. doi: 10.1097/brs.0000000000003597

32. McGirt MJ, Bydon M, Archer KR, Devin CJ, Chotai S, Parker SL, et al. An analysis from the Quality Outcomes Database, Part 1. Disability, quality of life, and pain outcomes following lumbar spine surgery: predicting likely individual patient outcomes for shared decision-making. *J Neurosurg Spine*. (2017) 27:357–69. doi: 10.3171/2016.11.Spine16526

33. Whitmore RG, Stephen JH, Vernick C, Campbell PG, Yadla S, Ghobrial GM, et al. ASA Grade and Charlson Comorbidity Index of spinal surgery patients: correlation with complications and societal costs. *Spine J*. (2014) 14:31–8. doi: 10.1016/j.spinee.2013.03.011

34. Shinonara K, Ugawa R, Arataki S, Nakahara S, Takeuchi K. Charlson comorbidity index is predictive of postoperative clinical outcome after single-level posterior lumbar interbody fusion surgery. *J Orthop Surg Res*. (2021) 16:E12. doi: 10.1186/s13018-021-02377-7

35. Pitter FT, Lindberg-Larsen M, Pedersen AB, Dahl B, Gehrchen M. Readmissions, length of stay, and mortality after primary surgery for adult spinal deformity A 10-year danish nationwide cohort study. *Spine*. (2019) 44:E107–E16. doi: 10.1097/brs.0000000000002782

36. Hopkins BS, Patel MR, Yamaguchi JT, Cloney MB, Dahdaleh NS. Predictors of patient satisfaction and survey participation after spine surgery: a retrospective review of 17,853 consecutive spinal patients from a single academic institution. Part 1: press ganey. *J Neurosurg Spine*. (2019) 30:382–8. doi: 10.3171/2018.8.Spine18594

37. Hopkins BS, Patel MR, Yamaguchi JT, Cloney MB, Dahdaleh NS. Predictors of patient satisfaction and survey participation after spine surgery: a retrospective review of 17,853 consecutive spinal patients from a single academic institution. Part 2: HCAHPS. *J Neurosurg Spine*. (2019) 30:389–96. doi: 10.3171/2018.8.Spine181024

38. Zakaria HM, Mansour TR, Telemi E, et al. Use of Patient Health Questionnaire-2 scoring to predict patient satisfaction and return to work up to 1 year after lumbar fusion: a 2-year analysis from the Michigan Spine Surgery Improvement Collaborative. *J Neurosurg Spine*. (2019) 31:794–801. doi: 10.3171/2019.6.Spine1963

39. Adogwa O, Parker SL, Shau DN, Mendenhall SK, Bydon A, Cheng JS, et al. Preoperative Zung depression scale predicts patient satisfaction independent of the extent of improvement after revision lumbar surgery. *Spine J*. (2013) 13:501–6. doi: 10.1016/j.spinee.2013.01.017

40. Rahman R, Ibaseta A, Reidler JS, Andrade NS, Skolasky RL, Riley LH, et al. Changes in patients' depression and anxiety associated with changes in patient-reported outcomes after spine surgery. *J Neurosurg Spine*. (2020) 32:871–90. doi: 10.3171/2019.11.Spine19586

41. Geoghegan CE, Mohan S, Cha EDK, Lynch CP, Jadczak CN, Singh K. Achievement of a minimum clinically important difference for back disability is a suitable predictor of patient satisfaction among lumbar fusion patients. *World Neurosurg*. (2021) 152:E94–E100. doi: 10.1016/j.wneu.2021.05.036

42. Yoo JS, Patel DV, Mayo BC, et al. Postoperative satisfaction following lumbar spinal fusion surgery: patient expectation versus actuality. *J Neurosurg Spine*. (2019) 31:676–82. doi: 10.3171/2019.5.Spine19213

43. Chotai S, Parker SL, Sivaganesan A, Sielatycki JA, Asher AL, McGirt MJ, et al. Effect of complications within 90 days on patient-reported outcomes 3 months and 12 months following elective surgery for lumbar degenerative disease. *Neurosurg Focus*. (2015) 39:E8. doi: 10.3171/2015.8.Focus15302

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Treatment of three-level cervical spondylotic myelopathy using ACDF or a combination of ACDF and ACCF

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Objectives: This study aims to compare the outcomes between two anterior decompression and fusion techniques to treat multilevel cervical spondylotic myelopathy (MCSM).

Methods: After the screening for eligibility, a total of 66 patients were admitted to this study. These participants underwent anterior surgeries due to MCSM in our hospital between June 2016 and July 2018. All participants underwent either the anterior cervical discectomy and fusion (ACDF) surgery (ACDF group) or the combination of ACDF and anterior cervical corpectomy and fusion (ACCF), which was the anterior cervical hybrid decompression and fusion (ACHDF) surgery group. All the patients were followed up ≥18 months, the average latest followed up time was 23.64 (±2.69) months. The length of hospitalization, operation time, blood loss, visual analog scale (VAS), Japanese Orthopaedic Association (JOA) score, improvement rate, Hounsfield units (HU) of C3–C7, cobb angle, and anterior column height of fusion levels pre and post operation were analyzed.

Results: There were no statistical differences between the ACDF and ACHDF groups regarding the length of hospitalization, operation time, blood loss, HU of C3–C7, VAS, JOA score, improvement rate, cobb angle, and anterior column height in fusion levels in pre-operation and 3 months after operation (all $P > 0.05$). However, compared with the ACHDF group, the ACDF group achieved significantly better improvement in the anterior column height of fusion levels in the final 18–29 months post-operatively ($P < 0.05$).

Conclusions: Both approaches of ACDF alone and a combination of ACDF and ACCF can achieve satisfactory outcomes in the treatment of MCSM, but ACDF has better outcomes in maintaining anterior column height of fusion levels.

KEYWORDS

ACDF, ACCF, cervical spondylotic myelopathy, anterior decompression, fusion, anterior column height

Introduction

Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord dysfunction (1). CSM often presents with clinical symptoms and signs of impaired upper motor neurons. Multilevel cervical spondylotic myelopathy (MCSM) is a pathological change that affects three or more segments in the cervical intervertebral disc and the surrounding tissues. MCSM often goes with hyperosteogeny, facet joint degeneration or hypertrophy, and ossification of the peripheral ligament (2). It may reduce patients' ability to do daily activities or even lead to paralysis, which not only reduces patients' quality of life, but also causes a substantial social-economic burden. The outcome of conservative treatment is usually insufficient to treat this condition. Immediate surgical intervention is always required once MCSM is diagnosed.

MCSM is generally caused by pathologies that directly compress the spinal cord on the ventral side of the spinal column. Clinically, there are several surgical procedures used to treat MCSM, with two basic approaches (3). The first is the anterior approach, which aims to directly relieve the compression, including anterior cervical discectomy with fusion (ACDF), anterior cervical corpectomy and fusion (ACCF), anterior cervical hybrid decompression and fusion surgery (ACHDF, the combination of ACDF and ACCF), anterior approach with zero-profile devices and artificial disc replacement (ADR). The second one is to widen the spinal canal indirectly by using the bowstring effect *via* a posterior approach including laminoplasty and laminotomy. Due to the pathologies of MCSM, the anterior approach is an effective but less invasive surgical procedure for patients whose compression is less severe. With the advantages of techniques and the popularization of surgical approaches, anterior surgery is becoming increasingly common for treating MCSM.

Among various techniques in the anterior approach, the zero-profile devices and ADR are newly developing devices which are not widely used for MCSM due to the relatively high surgical skill requirement of these devices and a narrow application range (4–7). Multiple segmental ACCF greatly changes the cervical spine structure and causes massive injuries (8). Studies have shown that ACCF in MCSM has no significant advantages over other procedures in terms of surgical outcomes (9–11). Currently, the two main anterior procedures used to treat MCSM are multi-segmental ACDF and the combination of ACDF and ACCF. These two approaches have demonstrated similar effectiveness and safety (8). However, there have been few comparisons between these two procedures as to which one delivers better outcomes for patients. Thus, the current study aimed to compare ACDF alone with the combination of ACDF and ACCF in treating three-level MCSM, with the purpose of determining the best procedure.

Patients and methods

Data collection

The patients who underwent anterior surgeries for MCSM with intervertebral disc herniation in our hospital between June 2016 and July 2018 were reviewed in our study. This research was approved by the Ethics Committee of the Third Hospital of Hebei Medical University; all patients agreed to participate in this study for publishing of data and images. Inclusion criteria were as follows: (1) the imagelogical examination showed three or more levels of compression; (2) fatigue or pain in the neck and shoulder, upper limb numbness, loss of muscle tone, or other symptoms caused by peripheral nerve injury in context of excluding other systemic diseases; (3) hypertonia, hyperreflexia, positive pathological; signs or symptoms of upper motor neuron injury. The exclusion criteria were as follows: (1) diagnosed with multi-segmental cervical spondylotic radiculopathy; (2) cervical surgery history; (3) cervical vertebral fracture, spinal cord injury; (4) cervical tumor, inflammation; (5) serious ossification of the posterior longitudinal ligament. To ensure the patients' maximum benefits, the patients with severe compression to the spinal cord which is difficult to decompress using the ACDF surgery, and those patients with the compression came from the posterior vertebral body, were chosen to perform ACDF and ACCF combined surgery.

Surgical procedures

The operation level was determined by medical history, physical examination, and radiological examination. Before the operation, all the patients underwent tracheoesophageal push training to prevent post-operation sputum and dysphagia. Under general anesthesia, a Smith-Robinson incision was made on the right side of the neck. In the ACDF group (**Figure 1**), after the discectomy, the suitable poly ether ether ketone (PEEK) cages were implanted. In the ACHDF group (**Figure 2**), the severe compression levels were followed by vertebral corpectomy, and titanium mesh cages (TMC) were implanted with autogenous bone. Then, a single-level ACDF was implemented on the adjacent level. Both groups were fixed by a titanium plate with screws (eight in the ACDF surgery and six in the ACHDF surgery) that fit the centrum. All the surgeries were performed by the same surgeon.

Radiological parameters

The radiological parameters were the cobb angle of fusion segments, the height of the anterior column in sagittal x-ray, and Hounsfield units (HU) values in computed tomography (CT). All data were measured by two researchers and the

average value of two measurements was analyzed. Another expert was asked to evaluate the data to ensure accuracy. The cobb angle of fusion segments was measured as the angle between the upper endplate of the upper fusion vertebrae and the lower endplate of the lower fusion vertebrae (12). The height of the anterior column was measured as the average value of the anterior-inferior intersection of the lower vertebral body and the anterior-superior intersection of the upper vertebral body (**Figure 3**). The HU values (13) were measured using an elliptical region of interest function in the median sagittal position of the cervical spine (**Figure 4**).

Clinical assessment

Clinical parameters include the Japanese Orthopaedic Association (JOA) and visual analog scale (VAS), length of hospitalization, operation time, blood loss and improvement rate. All the patients underwent preoperative evaluation, and were followed up for 23.64 (±2.69) months on average.

Statistical analysis

All data were analyzed by SPSS 21.0 (IBM, Armonk, New York, United States) software. Continuous variables are presented as mean ± standard deviation (SD) when normally distributed, and as median (interquartile ranges, IQR) when the distribution was skewed. Independent *t*-tests were performed to compare radiological and clinical parameters for independent samples. Chi-square test was performed for categorical data. For continuous variables but not normally distributed, Mann-Whitney U-test was applied. Repeated measure ANOVA and the generalized estimating equation

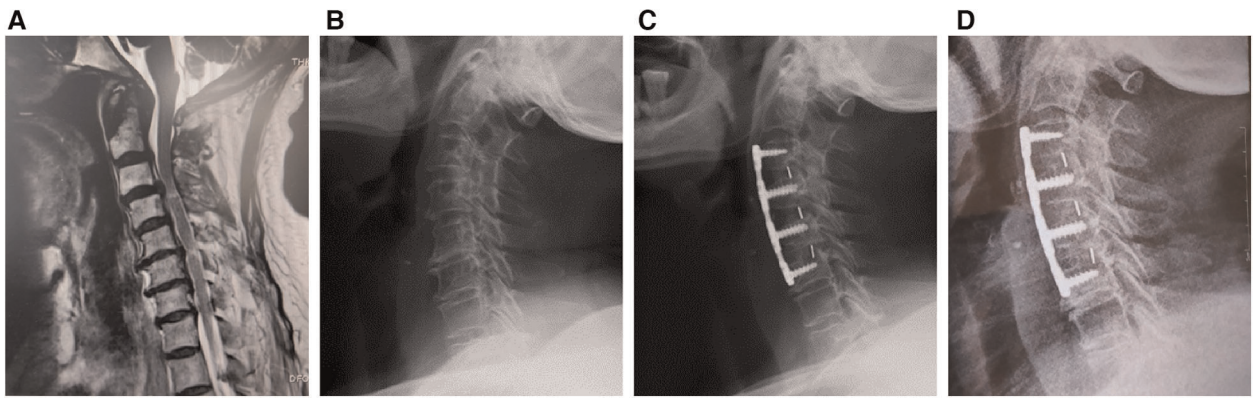

FIGURE 1
Male, 69-year-old, underwent three-level anterior cervical discectomy and fusion (ACDF) surgery. (**A**) The pre-operational magnetic resonance imaging (MRI), (**B**) the x-ray of pre-operation, (**C**) operation after 3 months, and (**D**) the final follow-up.

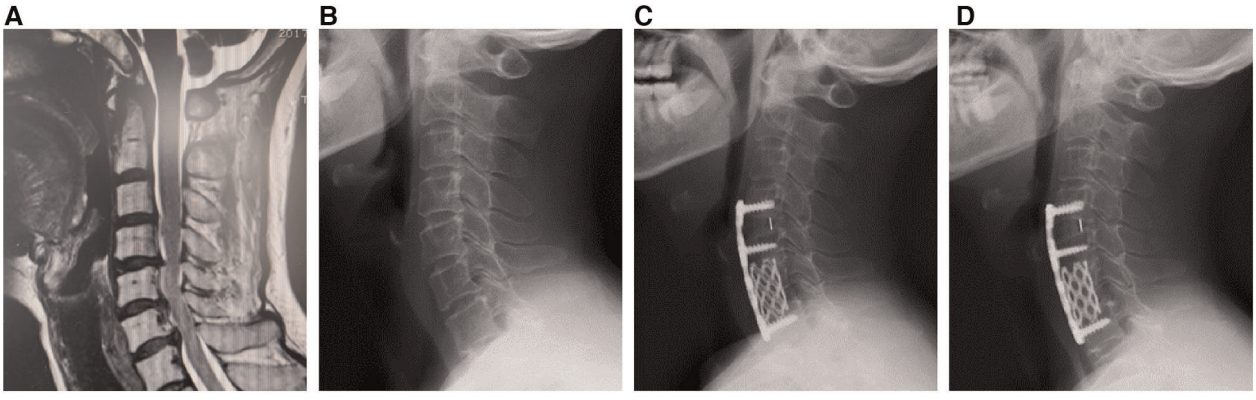

FIGURE 2
Female, 50-year-old, underwent one-level anterior cervical discectomy and fusion (ACDF) and one-level anterior cervical corpectomy and fusion (ACCF) surgery. (**A**) The pre-operational MRI, (**B**) the x-ray of pre-operation, (**C**) operation after 3 months, and (**D**) the final follow-up.

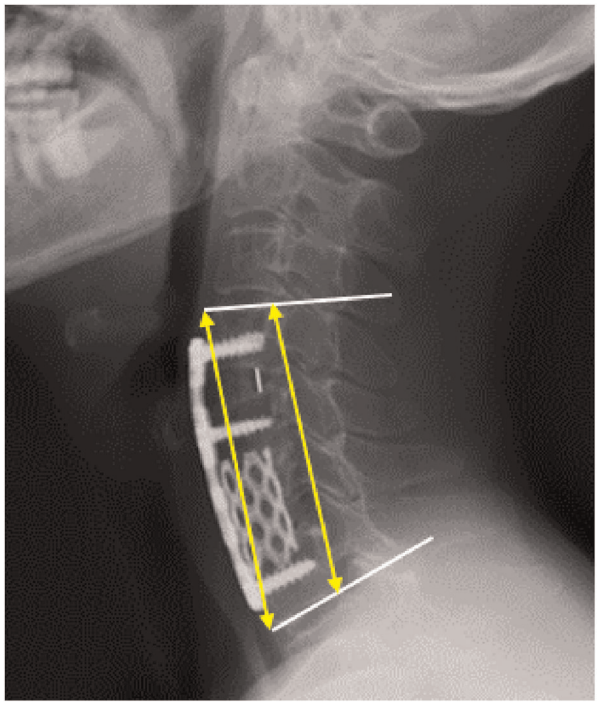

FIGURE 3
The height of the anterior column (the mean value of two yellow arrows) and the cobb angle of fusion segments (the angle of two white lines).

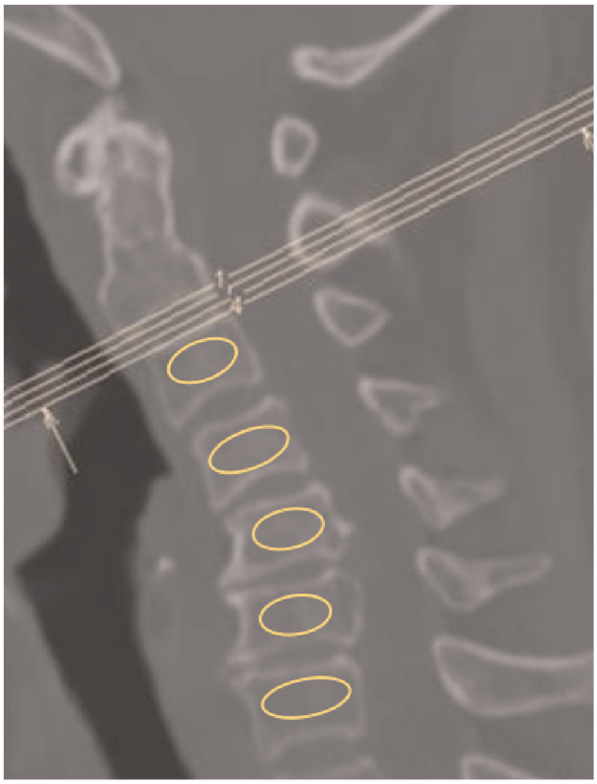

FIGURE 4
Using an elliptical region of interest function to evaluate the hounsfield units (HU) value in median sagittal computed tomography (CT) scan of the cervical spine, select the largest possible range of cancellous bone without including cortical bone.

were used to compare the repeated measurement data. $P < 0.05$ was considered statistically significant.

Results

A total of 66 patients were enrolled in this study, and none of these patients experienced any severe complications. The general data between the ACDF and ACHDF groups did not show statistical differences in gender, age, BMI, complications, tobacco and alcohol addiction, course of the disease, and operation sections (Table 1). The HU values of cervical vertebrae C3–C7 were used to evaluate the bone mineral density and resistance to external forces in the two groups. In the ACDF group, the HU values were 321.91, 311.48, 310.83, 276.20, and 246.96 from C3 to C7 respectively. While in the ACHDF group the HU values were 337.93, 320.69, 320.80, 271.58 and 262.93 from C3 to C7 respectively (Table 2). In each vertebral segment, there were no statistical differences regarding to the HU values between the ACDF and ACHDF groups ($P > 0.05$).

Comparisons of the length of hospitalization, operation time, blood loss, VAS, JOA score, and improvement rate showed no statistical differences between the ACDF and ACHDF groups ($P > 0.05$). In both ACDF group and ACHDF

TABLE 1 Comparison of general data between the two groups of ACDF and ACHDF.

	ACDF ($n = 43$)	ACHDF ($n = 23$)	Z value	P value
Gender (female/male)	16/27	12/11	–	0.241
Age (year)	56.4 (±9.62)	57.3 (± 9.21)	–	0.712
BMI	25.35 (IQR = 3.60)	25.26 (IQR = 2.93)	−0.040	0.968
Diabetes	4	6	–	0.070
Hypertension	12	10	–	0.201
Smoking	2	3	–	0.220
Drinking	6	4	–	0.711
Course of the disease (month)	3 (IQR = 10.84)	7 (IQR = 45.00)	−1.647	0.099
Operation sections				0.534
C3–C6	20	8	–	
C4–C7	20	14	–	
C3–C4/C5–C7	3	1	–	

ACDF, the anterior cervical discectomy and fusion surgery; ACHDF, the anterior cervical hybrid decompression and fusion surgery (the combination of ACDF and ACCF); BMI, body mass index; IQR, interquartile ranges.

TABLE 2 The comparison of HU in C3–C7 of the two groups of ACDF and ACHDF.

	ACDF ($n = 43$)	ACHDF ($n = 23$)	Z value	P value
C3	321.91 (IQR = 96.92)	337.93 (IQR = 109.93)	−0.828	0.408
C4	311.48 (IQR = 103.48)	320.69 (IQR = 112.73)	−0.357	0.721
C5	310.83 (IQR = 69.13)	320.80 (IQR = 104.40)	−1.204	0.228
C6	276.20 (IQR = 104.29)	271.58 (IQR = 108.02)	−0.101	0.920
C7	246.96 (IQR = 78.33)	262.93 (IQR = 112.81)	−1.151	0.250

ACDF, the anterior cervical discectomy and fusion surgery; ACHDF, the anterior cervical hybrid decompression and fusion surgery (the combination of ACDF and ACCF); HU, Hunsfield units; IQR, interquartile ranges.

group, post-operation VAS and JOA scores showed improvements compared to pre-operative scores. The median VAS score decreased from 2 to 1 in the ACDF group, and from 3 to 1 in the ACHDF group. The JOA score of the ACDF group increased from 8 to 14, while in the ACHDF group increased from 8 to 13 (Table 3).

The anterior column height in the ACDF group was 76.96 (±9.72) mm, 80.89 (±9.26) mm, and 79.85 (±9.20) mm pre-operation, 3 months after surgery, and the last follow-up respectively. In the ACHDF group, the anterior column height was 73.10 (±8.62) mm, 76.56 (±7.30) mm, and 75.27 (±7.41) mm pre-operation, 3 months after surgery, and the last follow-up, respectively. The anterior column height at the final follow-up was lower compared to 3 months after surgery in both groups. However, there was a significant improvement when compared to the pre-operation ($P < 0.05$). In the last follow-up, the anterior column height was significantly higher in the ACDF than in the ACHDF groups ($P < 0.05$), indicating that the ACDF group was better than the ACHDF group. Although the improvement of the cobb angle showed statistical differences between the last follow-up and pre-operation within the ACDF group and not in the ACHDF group, there was no statistical difference between the ACDF and ACHDF groups (Table 4).

TABLE 3 The comparison of length of hospitalization (days), operation time (min), blood loss (ml), VAS, JOA score and improvement rate (%) of the two groups of ACDF and ACHDF.

	ACDF ($n = 43$)	ACHDF ($n = 23$)	Z value	P value
Hospitalization (days)	12.11 (±4.02)	13.65 (±3.27)	–	0.121
Operation time (min)	133.63 (±34.22)	136.09 (±41.40)	–	0.797
Blood loss (ml)	200 (IQR = 200)	200 (IQR = 200)	−0.314	0.754
VAS (pre-operation)	2 (IQR = 4)	3 (IQR = 3)	−0.979	0.328
VAS (last follow-up)	1 (IQR = 2)*	1 (IQR = 2)*	−0.170	0.865
JOA (pre-operation)	8 (IQR = 2)	8 (IQR = 2)	−0.868	0.385
JOA (last follow-up)	14 (IQR = 1)*	13 (IQR = 2)*	−1.749	0.080
Improvement rate (%)	62.50 (IQR = 14.44)	50.00 (IQR = 25.56)	−1.619	0.105

ACDF, the anterior cervical discectomy and fusion surgery; ACHDF, the anterior cervical hybrid decompression and fusion surgery (the combination of ACDF and ACCF); VAS, visual analog scale; JOA, Japanese orthopaedic association; IQR, interquartile ranges.
*Means statistically significant between pre-operation and last follow-up in the same group.

TABLE 4 The comparison of cobb angle (degree) and anterior column height (mm) of the two groups of ACDF and ACHDF.

	ACDF ($n = 43$)	ACHDF ($n = 23$)	P value
Cobb (pre-operation)	8.67 ± 9.54	10.09 ± 10.86	0.587
Cobb (3 months)	12.53 ± 5.95**	12.87 ± 6.92**	0.838
Cobb (last follow-up)	11.58 ± 5.89*,***	11.48 ± 6.73***	0.949
Height (pre-operation)	76.96 ± 9.72	73.10 ± 8.62	0.116
Height (3 months)	80.89 ± 9.26**	76.56 ± 7.30**	0.057
Height (last follow-up)	79.85 ± 9.20*,***	75.27 ± 7.41*,***	*0.044*

ACDF, the anterior cervical discectomy and fusion surgery; ACHDF, the anterior cervical hybrid decompression and fusion surgery (the combination of ACDF and ACCF).
*Means statistically significant between pre-operation and last follow-up in the same group.
**Means statistically significant between pre-operation and 3-month follow-up in the same group.
***Means statistically significant between the 3-month follow-up and last follow-up in the same group.

Discussion

The surgical methods for MCSM

MCSM is a multi-factor caused disease, including intervertebral disc degeneration, narrowing of the disc space, and osteophyte formation that changes the curvature of the cervical spine to be straight or reverse. The nerve damage is progressive and can cause disability. Conservative treatment is generally ineffective, and immediate surgical intervention is required (14). Many surgical procedures are used, including anterior, posterior, and combined anterior-posterior approaches (15). The anterior approach includes ACDF, ACCF, the combination of ACDF and ACCF, and with the use of zero-profile devices and ADR. The posterior approach includes laminectomy with or without fusion and laminoplasty (16). The combined anterior-posterior approaches include the first or second stage surgery and is only used to provide a greater effect on deformity correction. Due to the higher mortality and morbidity rates (17), the combined anterior-posterior surgery is not preferred by surgeons. Our previous study has shown that the combined anterior-posterior with posterior instrumented fixation is a good choice to treat adjacent segmental disease caused by ACCF (18).

The anterior approach was proposed by Smith and Robinson in 1958 (19) and was acknowledged by spinal surgeons. The anterior approach can remove the compression by excising the herniated disc, the osteophyte behind the vertebrae, and the posterior longitudinal ligament, especially in single-level cervical spondylosis (20). To date, the consensus on the best approach to treat MCSM has not been achieved due to the complex pathogenesis and compression from the front and rear of the cervical vertebrae. For patients with compression from the front, anterior approach surgeries are usually selected, including ACCF, ACDF, and the combination of ACDF and ACCF.

Long-segments ACCF is not the first choice usually. The direct vision is available using ACCF, with a large operative field and thorough decompression, but the damage and change to the anterior and middle columns are large, which cannot be ignored. In addition, multilevel segment fixation without enough bone structure induces more stress that may lead to screws loosening, displacement and other postoperative complications (21).

A multilevel ACDF surgery can alleviate the compression by removing the disc, osteophyte, and posterior longitudinal ligament directly. The surgery retains the structural stability of columns and restores physiological curvature. Multilevel ACDF also fits skipped-level cervical spondylosis patients to protect the normal disc (22), and is even chosen for cervical kyphosis. Moreover, ACDF is clinically favored due to a minimal barrier to entry and short learning curve for trainee surgeons. However, the ACDF approach also has certain drawbacks, such as tunnel vision, a limited operational field, and the inability to alleviate compression below the targeted disc level.

The combination of ACDF and ACCF is a technique that combines one segment of ACDF with ACCF to maximize the benefits of the two surgical methods. With a broader view of the severe segments and less damage to the mild segments, ACCF releases compression that comes from the vertebral bodies while ACDF removes moderate compression that comes from the diseased disc. However, our data show that ACDF has better outcomes in maintaining anterior column height in fusion levels when compared with a combination of ACDF and ACCF (**Table 4**).

The effect of restoring the anterior column height and curvature on patient outcomes

Upon imaging, MCSM frequently exhibits a reduction in disc height, which indicates compression and narrowing of the nerve root canal. Loss of anterior column height can cause folds in the posterior longitudinal ligament and ligamentum flavum, squeezing the spinal cord. If the height loss cannot be restored during surgery, the volume of the spinal canal will not be regained. Therefore, it is necessary to gain height and regain the curvature during the surgery to obtain satisfactory outcomes (23). Aiming to enlarge the nerve root canal and restore the tension of surrounding tissues, reconstruction of the anterior column with bone grafting can effectively remove compressive factors and immediately increase the anterior column height.

In our study, both multilevel ACDF and the combination of ACDF and ACCF can increase the anterior column height and improve VAS and JOA scores (**Table 3**). The height of the ACDF and ACHDF groups was lower in the final follow-up than in the 3-month follow-up, but without statistical difference. This result possibly relates to an adaptive response to the implant which can cause a small amount of subsidence of the anterior cervical column (24). Additionally, our study showed that the anterior column height in the ACHDF group was significantly lower compared to the ACDF group in the final follow-up. Also, the HU values did not show statistical differences between the ACDF and ACHDF groups. Previous reports showed that HU values were associated with compressive tolerance and represent bone mineral density in detecting the degree of osteoporosis (25), meaning that osteoporosis in the ACDF and ACHDF groups can be ignored. The difference in column height is most likely due to TMC compressing cancellous bone more firmly over the entire vertebral body than in the interbody fusion cage (26). According to other studies, a vertical reduction of more than 3 mm in the intervertebral disc space is related to severe narrowing of the neuroforamen (27). There is a risk of secondary surgical revision if the continuous subsidence and loss of curvature lead to a secondary compression to the nerve roots and spinal cord, while some studies showed that there is no relationship between subsidence and clinical outcomes (28). Despite the fact that three patients experienced screw issues, it has been believed that inadequate bone fusion causes implant problems rather than subsidence (12). The preservation of the endplate, the degree of osteoporosis, and the length of the implantation materials can impact the patient's prognosis by influencing the column height at the fusion segments (29).

The restoration of cervical curvature is an important indicator of the efficacy of anterior cervical spine surgery. The maintenance of cervical spine curvature is a critical factor in preventing the deterioration of neurological function (23, 30). Most healthy cobb angle of C2–C7 ranges from 20° to 25°. This physiological pronation angle has a cushioning effect on the spinal cord. MCSM often causes the straightening or even reversal of the cervical spine. These changes would further aggravate the degeneration of the adjacent discs, small joints, and tissues. Studies on the vascular supply to the spinal cord have found that the decreased anterior-posterior diameter of the spinal cord is strongly correlated with the decreased spinal

cord blood volume, and spinal cord ischemia induces neural function disorders (31). Axial symptoms also occur in patients with reverse cervical curvature. In the current study, the cobb angle was improved in both ACDF and ACHDF groups compared with the pre-operation. In the ACHDF group, the cobb angle showed no statistical differences compared with pre-operation. This result may be due to the difference of subsidence. The subsidence of the anterior intervertebral height was more than that of the posterior intervertebral height when ACCF was performed with the TMC (12). However, another study showed the opposite results (28). We speculate that it might be associated with the immediate cervical curvature of the patients when the fusion device is implanted. In addition, the depth of implant insertion, the degree of fit between the implant and the endplate, and the potential influence of the ACDF segment on the ACCF segment remain controversial and need to be further investigated.

It is worth noting that this is a single-center retrospective study. Due to the relatively small number of severe MCSM cases, the sample size is small, and the number of patients in the ACDF and ACHDF groups is unbalanced. Therefore, a multi-center prospective study is expected to further confirm our findings. Additionally, because of the short follow-up period, the exact timing of when the differences in anterior column height occurred is unknown. Therefore, further investigation of the maintenance of cobb angle and the height over a long period is required.

Conclusion

ACDF alone and the combination of ACDF and ACCF procedures have similar treatment outcomes in the treatment of MCSM. Compared with the combination of ACDF and ACCF procedures, ACDF alone can better maintain anterior column height.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the Third. Hospital of Hebei Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

XT: Data collection, methodology, and manuscript drafting. HZ: Data collection and statistical analysis. FYH: Data interpretation and manuscript editing. SR: Data interpretation and manuscript editing. ZL: Refining statistical methods. WD: Study design and supervision. SY: Study supervision, data interpretation, manuscript editing and finalization. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Badhiwala JH, Ahuja CS, Akbar MA, Witiw CD, Nassiri F, Furlan JC, et al. Degenerative cervical myelopathy - update and future directions. *Nat Rev Neurol.* (2020) 16(2):108–24. doi: 10.1038/s41582-019-0303-0

2. Xiao SW, Jiang H, Yang LJ, Xiao ZM. Anterior cervical discectomy versus corpectomy for multilevel cervical spondylotic myelopathy: a meta-analysis. *Eur Spine J.* (2015) 24(1):31–9. doi: 10.1007/s00586-014-3607-1

3. Ghogawala Z, Terrin N, Dunbar MR, Breeze JL, Freund KM, Kanter AS, et al. Effect of ventral vs. dorsal spinal surgery on patient-reported physical functioning in patients with cervical spondylotic myelopathy: a randomized clinical trial. *Jama.* (2021) 325(10):942–51. doi: 10.1001/jama.2021.1233

4. Shi S, Liu ZD, Li XF, Qian L, Zhong GB, Chen FJ. Comparison of plate-cage construct and stand-alone anchored spacer in the surgical treatment of three-level

cervical spondylotic myelopathy: a preliminary clinical study. *Spine J*. (2015) 15 (9):1973–80. doi: 10.1016/j.spinee.2015.04.024

5. Chen Y, Chen H, Wu X, Wang X, Lin W, Yuan W. Comparative analysis of clinical outcomes between zero-profile implant and cages with plate fixation in treating multilevel cervical spondilotic myelopathy: a three-year follow-up. *Clin Neurol Neurosurg*. (2016) 144:72–6. doi: 10.1016/j.clineuro.2016.03.010

6. Mao N, Wu J, Zhang Y, Gu X, Wu Y, Lu C, et al. A comparison of anterior cervical corpectomy and fusion combined with artificial disc replacement and cage fusion in patients with multilevel cervical spondylotic myelopathy. *Spine*. (2015) 40(16):1277–83. doi: 10.1097/BRS.0000000000000957

7. Joaquim AF, Riew KD. Multilevel cervical arthroplasty: current evidence. A systematic review. *Neurosurg Focus*. (2017) 42(2):E4. doi: 10.3171/2016.10.FOCUS16354

8. Badhiwala JH, Leung SN, Ellenbogen Y, Akbar MA, Martin AR, Jiang F, et al. A comparison of the perioperative outcomes of anterior surgical techniques for the treatment of multilevel degenerative cervical myelopathy. *J Neurosurg Spine*. (2020) 12:1–8. doi: 10.3171/2020.4.SPINE191094

9. Lian XF, Xu JG, Zeng BF, Zhou W, Kong WQ, Hou TS. Noncontiguous anterior decompression and fusion for multilevel cervical spondylotic myelopathy: a prospective randomized control clinical study. *Eur Spine J*. (2010) 19(5):713–9. doi: 10.1007/s00586-010-1319-8

10. Katz AD, Mancini N, Karukonda T, Cote M, Moss IL. Comparative and predictor analysis of 30-day readmission, reoperation, and morbidity in patients undergoing multilevel ACDF versus single and multilevel ACCF using the ACS-NSQIP dataset. *Spine*. (2019) 44(23):E1379–e87. doi: 10.1097/BRS.0000000000003167

11. Wang T, Wang H, Liu S, An HD, Liu H, Ding WY. Anterior cervical discectomy and fusion versus anterior cervical corpectomy and fusion in multilevel cervical spondylotic myelopathy: a meta-analysis. *Medicine*. (2016) 95 (49):e5437. doi: 10.1097/MD.0000000000005437

12. Ji C, Yu S, Yan N, Wang J, Hou F, Hou T, et al. Risk factors for subsidence of titanium mesh cage following single-level anterior cervical corpectomy and fusion. *BMC Musculoskelet Disord*. (2020) 21(1):32. doi: 10.1186/s12891-019-3036-8

13. Liang X, Liu Q, Xu J, Ding W, Wang H. Hounsfield unit for assessing bone mineral density distribution within cervical vertebrae and its correlation with the intervertebral disc degeneration. *Front Endocrinol*. (2022) 13:920167. doi: 10.3389/fendo.2022.920167

14. Traynelis VC, Arnold PM, Fourney DR, Bransford RJ, Fischer DJ, Skelly AC. Alternative procedures for the treatment of cervical spondylotic myelopathy. *Spine*. (2013) 38:S210–S31. doi: 10.1097/BRS.0000000000000009

15. Yeh KT, Lee RP, Chen IH, Yu TC, Peng CH, Liu KL, et al. Laminoplasty with adjunct anterior short segment fusion for multilevel cervical myelopathy associated with local kyphosis. *J Chin Med Assoc*. (2015) 78(6):364–9. doi: 10.1016/j.jcma.2015.03.009

16. Zhu B, Xu Y, Liu X, Liu Z, Dang G. Anterior approach versus posterior approach for the treatment of multilevel cervical spondylotic myelopathy: a systemic review and meta-analysis. *Eur Spine J*. (2013) 22(7):1583–93. doi: 10.1007/s00586-013-2817-2

17. Yeh KT, Chen IH, Lee RP, Yu TC, Peng CH, Liu KL, et al. Two surgical strategies for treating multilevel cervical spondylotic myelopathy combined with kyphotic deformity. *Medicine*. (2020) 99(7):e19215. doi: 10.1097/MD.0000000000019215

18. Yang S, Yang D, Ma L, Wang H, Ding W. Clinical efficacy of laminectomy with instrumented fixation in treatment of adjacent segmental disease following ACCF surgery: a retrospective observational study of 48 patients. *Sci Rep*. (2019) 9(1):6551. doi: 10.1038/s41598-019-43114-9

19. He J, Wu T, Ding C, Wang B, Hong Y, Liu H. Bibliometric and visualized analysis of the top 100 most-cited articles on anterior cervical surgery. *EFORT Open Rev*. (2021) 6(12):1203–13. doi: 10.1302/2058-5241.6.210074

20. Shah KC, Dominy C, Tang J, Geng E, Arvind V, Pasik S, et al. Significance of hospital size in outcomes of single-level elective anterior cervical discectomy and fusion: a nationwide readmissions database analysis. *World Neurosurg*. (2021) 155: e687–e94. doi: 10.1016/j.wneu.2021.08.122

21. Li Z, Liu H, Yang M, Zhang W. A biomechanical analysis of four anterior cervical techniques to treating multilevel cervical spondylotic myelopathy: a finite element study. *BMC Musculoskelet Disord*. (2021) 22(1):278. doi: 10.1186/s12891-021-04150-7

22. Shang Z, Zhang Y, Zhang D, Ding W, Shen Y. Clinical and radiological analysis of bryan cervical artificial disc replacement for "skip" multi-segment cervical spondylosis: long-term follow-up results. *Med Sci Monit*. (2017) 23:5254–63. doi: 10.12659/MSM.904863

23. Xia C, Shi F, Chen C, Lv J, Chen Q. Clinical efficacy and safety of anterior cervical decompression versus segmental fusion and posterior expansive canal plasty in the treatment of multilevel cervical spondylotic myelopathy. *J Healthc Eng*. (2022) 2022:7696209. doi: 10.1155/2022/7696209

24. López-Oliva Muñoz F, García de las Heras B, Concejero López V, Asenjo Siguero JJ. Comparison of three techniques of anterior fusion in single-level cervical disc herniation. *Eur Spine J*. (1998) 7(6):512–6. doi: 10.1007/s005860050117

25. Schreiber JJ, Anderson PA, Rosas HG, Buchholz AL, Au AG. Hounsfield units for assessing bone mineral density and strength: a tool for osteoporosis management. *J Bone Joint Surg Am*. (2011) 93(11):1057–63. doi: 10.2106/JBJS.J.00160

26. Seaman S, Kerezoudis P, Bydon M, Torner JC, Hitchon PW. Titanium vs. polyetheretherketone (PEEK) interbody fusion: meta-analysis and review of the literature. *J Clin Neurosci*. (2017) 44:23–9. doi: 10.1016/j.jocn.2017.06.062

27. Lu J, Ebraheim NA, Huntoon M, Haman SP. Cervical intervertebral disc space narrowing and size of intervertebral foramina. *Clin Orthop Relat Res*. (2000) 370:259–64. doi: 10.1097/00003086-200001000-00026

28. Jang JW, Lee JK, Lee JH, Hur H, Kim TW, Kim SH. Effect of posterior subsidence on cervical alignment after anterior cervical corpectomy and reconstruction using titanium mesh cages in degenerative cervical disease. *J Clin Neurosci*. (2014) 21(10):1779–85. doi: 10.1016/j.jocn.2014.02.016

29. Niu C-C, Hai Y, Fredrickson BE, Yuan HA. Anterior cervical corpectomy and strut graft fusion using a different method. *Spine J*. (2002) 2(3):179–87. doi: 10.1016/S1529-9430(02)00170-5

30. Goto S, Kita T. Long-term follow-up evaluation of surgery for ossification of the posterior longitudinal ligament. *Spine*. (1995) 20(20):2247–56. doi: 10.1097/00007632-199510001-00012

31. Ellingson BM, Woodworth DC, Leu K, Salamon N, Holly LT. Spinal cord perfusion MR imaging implicates both ischemia and hypoxia in the pathogenesis of cervical spondylosis. *World Neurosurg*. (2019) 128:e773–e81. doi: 10.1016/j.wneu.2019.04.253

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Why does patients' discharge delay after vertebral augmentation? A factor analysis of 1,442 patients

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Objective: Vertebral augmentation techniques are widely used to treat osteoporotic vertebral compression fractures (OVCFs). Superior analgesic effects and shortened bed rest time means patients recover quickly, but prolonged unscheduled hospitalization can increase medical expenses and the risk of bed rest complications. The aim of this study was to investigate the reasons for prolonged hospitalization after vertebral augmentation surgery and to determine the relative risk factors.

Methods: A single-center retrospective study was conducted to enroll patients with OVCFs and accepted vertebral augmentation surgery from January 2017 to December 2017. Clinical information was collected from the Hospital Information System (HIS). The criterion of delayed discharge was postoperative hospitalization more than 3 days. Telephone interviews and medical history evaluations were conducted to confirm the exact reason for retention. The risk factors were analyzed by multiple logistic regression.

Results: Overall, 1,442 patients were included, and 191 (13.2%) stayed in the hospital for more than 3 days postoperatively. The reasons for delayed discharge were psychological factors (37.2%), residual pain (32.5%), cardiopulmonary complications (15.7%), nonspecific symptoms (8.4%), incision abnormalities (2.6%), thrombosis (2.1%), and postanesthesia reactions (1.6%). The multiple logistic model was significant; age (OR 1.028; 95% CI 1.009–1.046), preoperative stay (OR 1.192; 95% CI 1.095–1.298), operation type (OR 1.494; 95% CI 1.019–2.189), and the number of surgical segments (OR 2.238; 95% CI 1.512–3.312) showed statistical significance. In contrast, gender ($P > 0.1$) and chronic comorbidities ($P > 0.1$) were not predictors in this model.

Conclusion: Overall, 13.2% of OVCF patients who underwent vertebral augmentation surgery were not discharged within 3 days postoperatively, and several predictors were found. Preoperative communication and comprehensive evaluations are calling for more attention; physicians should adopt an appropriate medical process to enhance rehabilitation in geriatric orthopedics.

KEYWORDS

vertebral compression fracture, vertebral augmentation, vertebroplasty, delayed discharge, residual pain

Introduction

Osteoporosis has become a global disease of the elderly that develops with age and is thought to be the underlying cause of osteoporosis fractures (OFs). Osteoporosis vertebral compression fractures (OVCFs) are an important component of OFs, as approximately 520,000 incidents occurred in the European Union in 2010 (1). Symptomatic OVCFs cause severe pain, lead to inferior quality of life, and are related to increased mortality risk (2). Vertebral augmentation, including percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP), is commonly used to treat acute OVCFs. These methods require less operating time, are minimally invasive, and have higher cost-effectiveness compared with conservative treatments. Patients receiving PVP/PKP experienced pain relief and functional recovery. Reduction of hospitalization time can not only save medical resources and the financial burden of patients but also reduce bed rest time, which is one inducement of imbalanced bone turnover (3, 4). Research has shown that even short-term bed rest after trauma increased acute bone resorption, along with decreased muscle strength and aerobic capacity (5). Therefore, vertebral augmentation has a unique advantage in treating acute OVCFs in the elderly (6, 7).

The application of vertebral augmentation technology calls for the concept of rapid rehabilitation in geriatric orthopedics, including the removal of preoperative fear, surgical confidence, postoperative rehabilitation training, and functional recovery. However, we observed that some patients could not be discharged within the scheduled time and even undergo successful surgery, which may be caused by various factors. A randomized controlled trial reporting that 23% of acute OVCFs retained chronic low back pain after PVP (8) caused concern about residual symptoms. Meanwhile, severe cement leakages were reported, despite low complication morbidity (9). Furthermore, poor health conditions of the elderly increase the risk of acute onset of chronic diseases. All of the above-mentioned points out that prolonged bed rest will lead to more complications of being bedridden and a growing number of financial expenditures of patients (10).

Database searching found no relevant study on prolonged hospitalization or delayed discharge after PKP/PVP surgery. Therefore, the purpose of this study was to investigate the causes and predictors of delayed postoperative discharge to provide an informative clinical reference for the rehabilitation of patients with OVCFs.

Materials and methods

We retrospectively reviewed patients who accepted PVP or PKP in our spine surgery department from January 1, 2017, to December 31, 2017, and all of the participants were in-patients. This study was performed in line with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the ethics committee of Honghui Hospital affiliated with Xi'an Jiaotong University.

Inclusion and exclusion criteria

All patients had to meet the following inclusion criteria: (1) persistent back pain after slight exertion of energy or trauma and no evidence of relief; (2) clinical and imaging examinations, including x-ray, computed tomography, and magnetic resonance imaging presenting an OVCF related to the back pain; (3) osteoporosis diagnosis by dual-energy x-ray absorptiometry; and (4) complete information in the medical record system. The exclusion criteria are the following: (1) pathological fractures, including hemangioma and spinal metastasis; (2) chronic fractures, vertebrae osteonecrosis (like Kümmell disease), and intravertebral vacuum cleft in the vertebrae; (3) other coexisting traumas in addition to the spine (rib, limb, and sacrum fractures); and (4) severe comorbidities and other local or systematic disorders that may prolong the hospitalization.

To obtain the most consistent results according to the clinical situation, we did not limit the number of surgical segments or the age of participants. Preoperative examinations including lower limb arteriovenous ultrasound, blood routine, liver and kidney function, electrolyte, coagulation index, and infectious diseases were routinely performed. Patients with unstable comorbidities were consulted with relevant departments, and surgical treatment was performed only after excluding contraindications. All patients were informed of the treatment strategies by the physician, including operating procedures and prognosis.

Surgical procedures

PVP or PKP was chosen according to the specific fracture form and economic condition. PVP combined with the free-hand reduction was considered when the compression degrees of vertebrae anterior column were less than 30%; PKP and free-hand reduction were preferred in patients with greater than 30% compression. Patients who required a PVP due to poor economic conditions were informed about the risk and signed a consent form.

All procedures were conducted with standard procedures by senior spinal surgeons. Antibiotics were used intravenously 1 h prior to the procedure. The free-hand reduction was performed in a prone position, and a moderate restoration under x-ray was acceptable. Most of the patients were treated under infiltration anesthesia with 1% lidocaine, while a few others were treated

with general anesthesia (in consideration of strong fear of surgery). One or two trocars (KINETIC, China) were inserted into the pedicles of the object vertebrae under the surveillance of a C-arm x-ray (GE, American). The needles were inserted at the 3 or 9-o'clock position of pedicles with a specific inclination to approach the anterior third of the vertebrae body on anteroposterior and lateral radiographs. The vertebrae were then expanded by a balloon in PKP procedures. Pasta-like polymethylmethacrylate (PMMA, KINETIC, China) was injected until the cement approaching the posterior wall of the vertebrae or cement leakage was observed.

Patients remained in bed after surgery, and x-ray examination was undertaken within 12 h to ensure the cement location was good. Patients were advised to walk moderately with a plastic thoracolumbosacral orthosis (Hengshui Qianzhong Medical Equipment Co. Ltd., China) routinely on the second day after surgery. A 3-month brace stabilization was generally recommended.

Demographic data

To analyze the factors of delayed discharge after PKP/PVP, relevant clinical information covering gender, age, prehospital time, pre- and postoperative stays, preoperative bone mineral density (BMD), preoperative VAS, operation type, the number of surgical segments, and complete admitting/discharge diagnosis was obtained from the Hospital Information System (HIS). The third-day postoperatively VAS score was recorded to represent the pain relief at discharge. Diagnosis including cardiopulmonary diseases, hypertension, liver and kidney dysfunction, and diabetes was recorded as chronic comorbidities. Telephone interviews and medical history research were conducted to confirm the main reason for not being discharged on time.

Clinical outcomes

We used the following discharge criteria: (1) successful operation, no severe surgical complications such as cement embolism (in pulmonary arteries or cerebrovascular vessels) and intraspinal leakage (compressing the spinal cord or nerve root), which usually leads to urgent interventional thrombectomy or spinal decompression surgery; (2) visual analog scale (VAS) score decreased to below 4 (at most slight pain) (11–13); and (3) stable life signs, no acute comorbidities.

Subject to the requirements of local medicare policy and our hospital's clinical pathway, patients after vertebral augmentation surgery should be discharged within 3 days if they meet the above standard. Therefore, in this study, delayed discharge was considered to be postoperative hospitalization time over 3 days.

Statistical analyses

All statistical analyses were performed with Statistical Packages for Social Sciences V21.0 for Windows (SPSS Inc. Chicago, IL, USA). To describe the basic characteristics of the patients, quantitative variables were reported by means and standard deviations, while counts and percentages were recorded for qualitative variables. Chi-square tests and *t*-test/non-parametric tests were performed for univariate analyses, and P values <0.1 were considered significant temporarily. The Box–Tidwell test was used to verify whether a linear relationship existed between continuous independent variables and logit conversion values of dependent variables. Then, binary logistic analysis was performed to identify the predictors and odds ratios for delayed discharge, and P values <0.05 were considered significant.

Results

After filtering 1,877 patients who underwent PVP or PKP from January 1, 2017, to December 31, 2017, 1,442 patients (295 males and 1,147 females) with 1,549 treated vertebrae (1–4) were included in our study (**Figure 1**). The mean age of all patients was 71.95 ± 8.79 years (range 47–95). At a mean of 2.09 ± 1.33 days after injury, all patients came to the hospital and stayed for 4.01 ± 2.55 days in total, including 1.93 ± 1.58 days for preoperation and 2.06 ± 1.63 days for postoperation. The mean preoperative BMD and pre- and third-day postoperative VAS are shown in **Table 1**. Overall, 191 (13.2%) patients (mean age 73.58 ± 8.28) stayed in the hospital for more than 3 days after the surgery. The length of stay after the surgery was 5.09 ± 2.21 days (range 4–25), while the people discharged in 3 days had a shorter length of 1.59 ± 0.83 days (range 0–3) (**Table 1**).

After referring to the case history, we recorded chronic comorbidities including hypertension, diabetes mellitus, coronary heart disease, arrhythmia, cerebral infarction, and chronic obstructive pulmonary disease. Overall, 715 (49.6%) patients suffered one or more chronic comorbidities before hospitalization, and the rest of the patients simply had osteoporosis except for other local diseases, which were not recognized as comorbidities (**Table 1**).

We carried out phone interviews combined with medical history research in HIS, summarized the main reasons for the delay, and sorted these in **Figure 2**. In total, 71 (37.2%) of 191 patients met the discharge criteria but required extra treatment, mainly concerning their physical condition relating to trauma and surgery. We regarded these as psychological factors and gave them conservative treatment and nutrition support therapy until all these patients were discharged to communities or rehabilitation facilities. Sixty-two (32.5%)

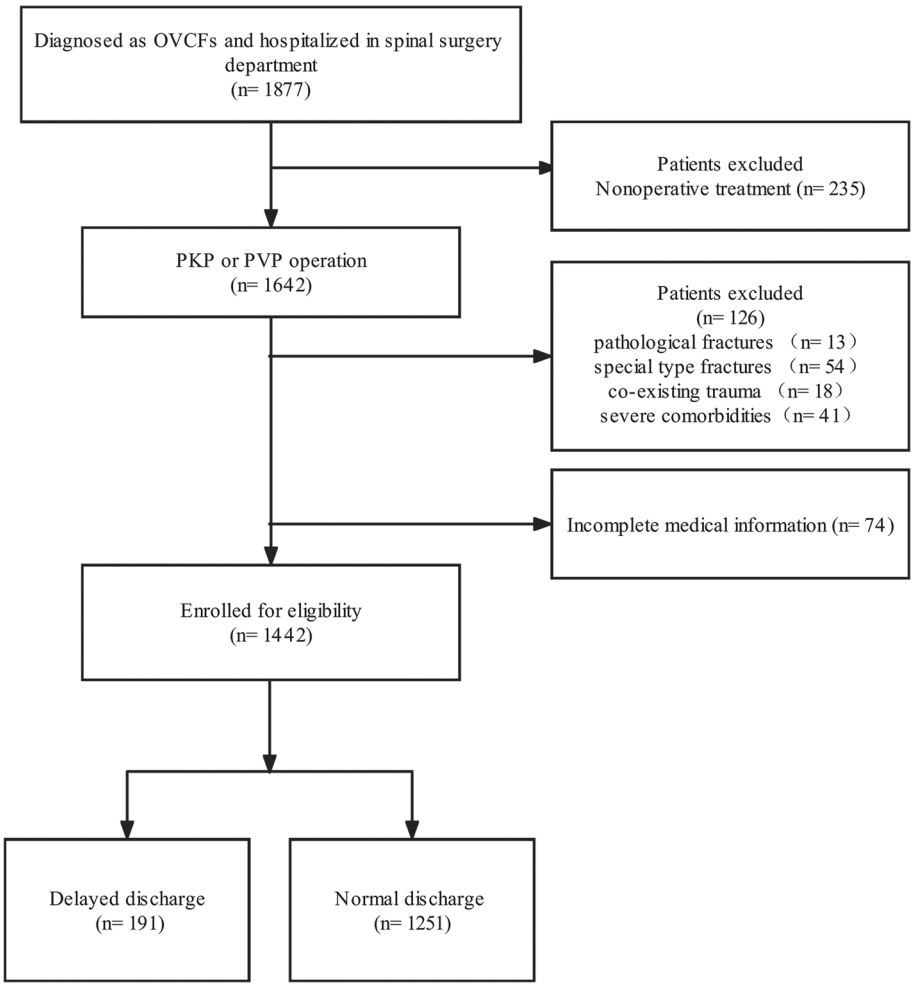

FIGURE 1
Study flowchart.

TABLE 1 Clinical information and characteristics of patients.

Variables	Delayed discharge	Normal discharge	Overall
Patients with surgery (*n*)	191 (13.2%)	1,251 (86.8%)	1,442 (100%)
Age (y)	73.58 ± 8.28	71.70 ± 8.84	71.95 ± 8.79
Gender (m/f)	49/142	246/1,005	295/1,147
Prehospital time (d)	2.19 ± 1.45	2.08 ± 1.32	2.09 ± 1.33
Preoperative time (d)	2.42 ± 1.45	1.86 ± 1.58	1.93 ± 1.58
Preoperative VAS	7.73 ± 0.97	7.52 ± 0.91	7.54 ± 0.92
Preoperative BMD (*T*-score)	−3.71 ± 0.59	−3.66 ± 0.69	−3.67 ± 0.68
Postoperative stay (d)	5.09 ± 2.22	1.59 ± 0.83	2.06 ± 1.63
Third-day postoperative VAS	2.90 ± 2.42	1.60 ± 1.03	1.77 ± 1.38
Chronic comorbidities (y/n)	100/91	615/636	715/727
Operation type (K/V)	153/38	903/348	1056/386
Number of segments (*n*)	1.17 ± 0.47	1.06 ± 0.26	1.07 ± 0.30

Data were mean ± SD or *N* (%); *n* = number, y = years, m/f = male/female, K/V = PKP/PVP, d = days, y/n = yes/no.

patients complained of residual pain (VAS value ≥4, range 4–9) from the former location or elsewhere after the surgery. Conservative analgesia therapies like oral NSAIDs or diclofenac lidocaine intramuscular injection were performed daily in these situations, and all these patients were relieved to varying degrees and then finally discharged. Cardiopulmonary complications, including acute heart failure, atrial fibrillation, and pneumonia, were the third reason that caused 30 (15.7%) patients to prolong their postoperative stay. They got emergency treatments and were transferred to specific departments with medical consultations. In addition, 16 (8.4%) experienced general discomfort, covering fever, stomachache, and headache and gradually recovered after symptomatic treatments and observations. Five (2.6%) incision abnormalities, four (2.1%) lower limb thromboses, and three (1.6%) postanesthesia reactions were recorded. No patient sustained severe cement leakage that needed reoperation including interventional therapy or spinal canal decompression.

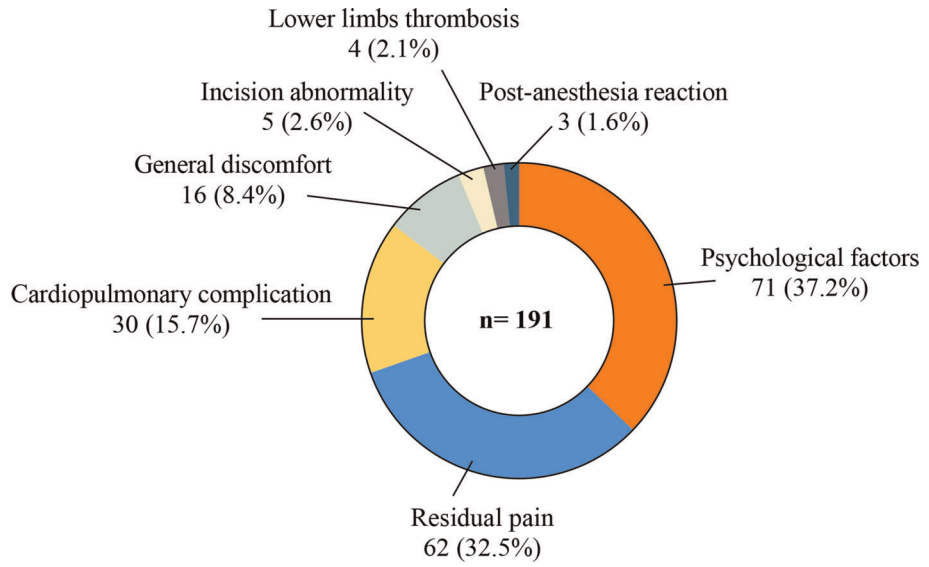

FIGURE 2
Reasons for delayed discharge.

We put gender, age, prehospital time, preoperative BMD, pre- and third-day postoperative VAS, preoperative stays, operation type, number of surgical segments, and chronic comorbidities into univariate analyses after all quantitative variables were proven to be nonnormally distributed. Gender, operation type, and chronic comorbidities were transformed into categorical data. As the results show in Table 2, age ($P < 0.05$), preoperative time ($P < 0.001$), preoperative VAS ($P < 0.05$), third-day postoperative VAS ($P < 0.001$), operation type ($P < 0.05$), and the number of surgical segments ($P < 0.001$) showed significance to delayed discharge, while prehospital time ($P = 0.484$), preoperative BMD ($P = 0.396$), and chronic comorbidities ($P > 0.1$) were not significant between the two groups. Gender ($P = 0.056$) approached statistical significance and was included in the multivariate analysis. A binary logistic analysis was performed to investigate the predictors of delayed discharge. Third-day postoperative VAS was excluded for direct relation to delayed discharge. The Box–Tidwell test showed a linear relationship between continuous independent variables and logit conversion values of dependent variables. Collinearity diagnostics showed negative results between the independent variables. Overall, the logistic model was significant ($\chi^2 = 56.796$, $P < 0.001$). Age (OR 1.028; 95% CI 1.009–1.046), preoperative time (OR 1.181; 95% CI 1.084–1.288), preoperative VAS (OR 1.271; 95% CI 1.070–1.510), operation type (OR 1.501; 95% CI 1.023–2.201), and the number of surgical segments (OR 2.231; 95% CI 1.503–3.310) showed statistical significance. Gender ($P = 0.103$) was not a predictor of delayed discharge of patients after PVP/PKP (Table 3).

TABLE 2 Univariate analysis of factors for delayed discharge.

Variables	χ^2/Z	P^* value
Gender	3.654	0.056
Chronic comorbidities	0.677	0.411
Operation type	5.305	0.021
Age	−2.574	0.010
Prehospital time	−0.700	0.484
Preoperative time	−6.089	<0.001
Preoperative VAS	−2.525	0.012
Third day postoperative VAS	−6.036	<0.001
Preoperative BMD	−0.849	0.396
Number of segments	−4.561	<0.001

VAS, visual analog scale.
*Statistics were analyzed using the chi-square test and Mann–Whitney *U* test.

TABLE 3 Multivariate logistic analysis for delayed discharge.

Variety of factors	*B*	S.E.	Wald χ^2	OR	CI 95%		*P* value
Gender	0.303	0.186	2.652	1.353	0.940	1.948	0.103
Age	0.027	0.009	8.898	1.028	1.009	1.046	**0.003**
Preoperative time	0.167	0.044	14.292	1.181	1.084	1.288	**<0.001**
Preoperative VAS	0.240	0.088	7.451	1.271	1.070	1.510	**0.006**
Operation type	0.406	0.195	4.322	1.501	1.023	2.201	**0.038**
Number of segments	0.802	0.201	15.873	2.231	1.503	3.310	**<0.001**

Gender and operation type were transferred into categorical data; B, partial regression coefficient; S.E., standard error; OR, odds ratio; CI, confidence interval; *P* values in bold were statistically significant.

Discussion

OVCFs in patients with osteoporosis involve severe pain episodes. The efficacy of conservative bed rest treatment is still uncertain but can cause complications such as muscle weakness, atelectasis, thrombosis, and pressure ulcers (10). Previous research has reported that bone resorption increases from the second day of bed rest (3), implying the disadvantages of immobilization. Vertebral augmentation is widely used to restore OVCF patients more quickly; meanwhile, the procedure being performed as ambulatory surgery is growing (14), as minimally invasive and rapid surgical intervention measures are effective and acceptable for elderly patients with OVCFs. Delayed discharge is an important quality monitor in ambulatory surgeries, and prolonged postoperative hospitalization may be related to poor quality of care and patients' low acceptance of ambulatory surgery, which may affect its superior cost-effectiveness (15).

To our knowledge, two high-quality studies about PVP surgery were published in 2009, querying the effectiveness of PVP and causing considerable controversy (16, 17). However, further studies have been conducted in subsequent clinical trials with strictly formulated inclusion criteria; PVP achieved more significant pain relief and vertebral height recovery than sham surgery (6). Nevertheless, current studies have shown similar analgesic effects of PVP and PKP (18). In this study, we have to note that all patients enrolled were in-patients because PVP/PKP were not carried out as ambulatory surgeries in our hospital during that time. Even so, our clinical pathway for the PKP/PVP operation required unified surgical and discharge standards, and patients with permitted situations were advised to discharge within 3 days after the surgery. Therefore, we can still obtain meaningful results by using this discharge indicator and providing advice for clinical work.

This study showed postoperative information about in-patients after vertebral augmentation surgery. Under the unified discharge standards, 191 (13.2%) patients stayed in the hospital longer than 3 days postoperatively, which was considered delayed discharge. All of the above patients got relevant treatments and reassessment and were finally discharged in a few days (range 4–25 days postoperatively). According to telephone interviews and medical history analyses, the reasons for delayed discharge related to incidence were psychological factors (37.2%), residual pain (32.5%), cardiopulmonary complications (15.7%), general discomfort (8.4%), incision abnormalities (2.6%), thrombosis (2.1%), and postanesthesia reactions (1.6%) (**Figure 2**). To further analyze the factors influencing delayed discharge, age, gender, prehospital time, pre- and third-day postoperative VAS, preoperative BMD, preoperative time, operation type, the number of surgical segments, and chronic comorbidities were included in univariate and multifactor analyses.

As we present in **Table 3**, age (OR 1.028; 95% CI 1.009–1.046), preoperative time (OR 1.181; 95% CI 1.084–1.288), preoperative VAS (OR 1.271; 95% CI 1.070–1.510), operation type (OR 1.501; 95% CI 1.023–2.201), and number of surgical segments (OR 2.231; 95% CI 1.503–3.310) were independent risk factors for delayed discharge after vertebral augmentation surgery in in-patients. The results indicated that, with each additional year of age, each more VAS point preoperatively, each additional day of preoperative hospitalization, every additional surgical segment and PKP compared with PVP, the risk of delayed discharge increased by 2.8, 18.1, 27.1, 50.1 and 123.1%, respectively. However, there were no significant associations between delayed discharge and gender, preoperative BMD, prehospital time, or chronic comorbidities. All of the factors from the logistic analysis will be discussed in the following sections.

Psychological factors

As previously mentioned, psychological factors were the most common reason for delayed discharge in this study, accounting for 37.2%. All of these patients had successful surgery and significant pain relief (VAS < 4) and met the discharge criteria. However, they rejected the discharge advice and asked for further conservative treatment in the hospital. Patients tend to like more comprehensive therapy when a fracture incident led to surgery, even if the pain got prominent relief. Mental disorders were excluded, and the feasibility of discharge was told to the patients and agents. Conservative treatment such as antiosteoporosis medication (calcitonin or intravenous bisphosphonates) and functional rehabilitation exercises was conducted. A retrospective study investigated the disposition of hospitalized patients after PVP. Approximately one-half of the patients (44%) living at home before surgery were discharged to rehabilitation facilities after surgery (19). Other areas of research, such as day-surgery laparoscopic cholecystectomy, have reported some factors responsible for delayed discharge, including psychosocial factors (20). On the one hand, patients usually believe that they should get more professional care than unsupervised rehabilitation at home. On the other hand, elderly age and comorbidities may burden them. It is the clinician's responsibility to understand the patient's perception. Another study from Sweden (21) surveyed patients after ambulatory surgery and reported that psychological preparation, knowledge of recovery, rehabilitation assistance, and a sense of security were required when patients returned home. Meanwhile, poor preoperative conversations may result in inadequate preparation and excessive concerns; less home assistance also leads to rejection for returning home early, which indeed requires nursing strategies and rehabilitation

centers. In our opinion, adequate psychological preparation is a prerequisite for elderly OVCF patients facing surgery or discharge. Patients need to know more about the experience of rapid recovery, therapeutic schedule, postoperative matters, and long-term rehabilitation; perioperative care of nurses was also indispensable.

Residual pain

Back pain is the leading symptom of OVCFs, but it could also come from adjacent soft tissue injuries. Thus, it is rational that pain relief is a subjective measure of surgical efficacy. In this study, patients with other injuries (such as distant fractures) were excluded to reduce bias, but inconspicuous injuries adjacent to the vertebrae were hard to detect. Sixty-two patients in the study complained of medium-to-severe pain (VAS value ≥4, range 4–9) after surgery, which was considered residual pain. Analgesic therapy was used after confirming no missing vertebral fractures, and all these patients got different levels of relief when finally discharged.

From **Table 3**, we found that preoperative VAS (OR 1.271), the number of surgical segments (OR 2.231), operation type (OR 1.501), and preoperative time (OR 1.181) were independent risk factors that led to prolonged discharge, which might be together associated with residual pain. Generally, multiple fractures are likely combined with greater energy of trauma, thus resulting in enduring pain and higher preoperative VAS. Ten of 62 residual pain patients during follow-up claimed that they got great relief in thoracolumbar but felt significant pain in the posterior superior iliac. We supposed that the elderly with weak muscle tend to get extra injury in places other than the spine, especially in the posterior superior iliac for an accidental tumble, which needs further research. Yan et al. (22) believed that OVCF combined with thoracolumbar fascia injury was related to residual back pain after PVP, and the surgery always resolved spinal disorders but usually ignored peripheral soft tissue damage (23).

During the procedure, the leakage of bone cement around the vertebral body can also cause postoperative back pain (24). Although there were no spinal cord or nerve root compressions by cement, there was still a possibility of back pain derived from intervertebral disc leakage (24). We recorded no severe cement leakage incident, but leakages surrounding the vertebrae happened occasionally. It was suggested that the operation be standardized to avoid the leakage of bone cement and the damage to the transverse process and intervertebral joints.

Moreover, nonunion of OVCF (also called Kümmell disease) will cause long-term pain that is difficult to relieve. Ischemic necrosis and exudation formed in the nonunion vertebral body, which are not conducive to adequate fixation of bone cement, made the efficiency uncertain (25). We have excluded all of the Kümmell diseases and chronic fractures, and no osteonecrosis was observed after surgery.

According to the mechanism of vertebral augmentation surgery, the volume of bone cement filling is closely related to pain relief. Some studies have shown that sufficient cement filling helps stabilize the vertebral body and relieve pain (26, 27). However, a classic study showed that 15% of the volume of the vertebral body could be filled to achieve effective safe balance (28). It is noteworthy that multiple factor analysis found that operation type (OR 1.501) was a predictor, indicating that PKP has a higher risk for delayed discharge than PVP. In this study, PVP usually performed on relatively slight compression vertebrae may be a reason. However, we suppose that cement filling in PVP could be more diffuse than a mass usually in PKP that may have a better analgesia effect, although previous studies suggested there was no significant difference in pain relief between PVP and PKP (18, 29).

In general, many issues influence residual pain after surgery, and no consensus has been reached. It should be noted that a comprehensive and accurate diagnosis before surgery plays a crucial role. Assessment of curative effects should be emphasized when accompanying adjacent injury. Furthermore, significant degeneration in the elderly also reminds us to identify the pain source accurately.

Age and cardiopulmonary complications

The mean age of the patients in this study was 71.95 ± 8.79 years, among which the delayed discharge population was 73.58 ± 8.28 (**Table 1**). Elderly patients are often admitted with various chronic diseases, with a risk of acute complications under trauma and surgical stress conditions. We have observed arrhythmias, atrial fibrillation, acute heart failure, acute hypertension, and acute exacerbation of chronic obstructive pulmonary diseases. All 30 patients with complications received in-hospital consultation with treatment suggestions, and serious cases were transferred to a specialized department. It is worth discussing that, although all of these patients were admitted with chronic diseases, the chronic comorbidity indicators were not predictors of delayed discharge after multifactor analysis (**Table 3**). We hypothesized that this was due to the high average age; there was an approximate rate of chronic comorbidities existing between the normal group and the delayed group (**Table 1**). The details of existing chronic comorbidities were yes or no, so it was difficult to distinguish the severity of specific diseases solely by diagnosis information in the medical records. In addition, high-risk patients were excluded from the surgical plan, resulting in selection bias. The occurrence of acute complications may be accidental. For this reason,

clinicians need to strengthen the comprehensive evaluation during the perioperative period to reduce accidents.

Other events

Sixteen patients developed nonspecific symptoms of discomfort and complained of fever, headache, and stomachache, and general treatment was effective. Five patients reported incision pain but denied obvious deep structure pain while moving. We observed slight redness and swelling in the incisions, no fluid exudation, and neither fever nor abnormal laboratory results. As we know, vertebral augmentation has a rare incidence of infection, but it can still be a formidable and life-threatening complication. Surgery should be avoided for patients with infectious tendencies, and preventive antibiotic therapy should be conducted for those with low immune function in the perioperation period (30). Four thromboses might have been associated with bed rest under stress. Patients suffering from OVCF usually seek doctors after days of bed rest. Continuous immobilization and prolonged pressure on the limbs result in venous stasis, posing a risk of thrombosis (10). For the anesthesia methods, we usually choose infiltration anesthesia due to its safety and convenience; a small portion of patients underwent general anesthesia in consideration of pain stimulation. There were fewer cases of prolonged hospitalization due to postanesthesia reactions, which depended on a detailed preanesthesia evaluation.

Limitations

There were several limitations in the present study. First, only a few indicators of medical information were collected in this study. Thus, part of the results in the regression analysis seemed to be nondistinct, such as preoperative stay; it has not been completely explained how the preoperative extension prolonged the length of postoperation. Second, details of cement leakage in all 1,442 patients were not reported, although leakage surrounding the vertebrae can also cause postoperative residual pain. Further research requires improved clinical data for more details.

Conclusion

Overall, 13.2% of patients in this study who underwent vertebral augmentation surgery were not discharged within 3 days after surgery. The most common causes are psychological factors, residual pain, and cardiopulmonary complications. Multifactor analysis revealed that age, number of surgical segments, operation type, and preoperative stay were the main factors related to delayed discharge. Preoperative communication and comprehensive evaluations are calling for more attention, and physicians should adopt an appropriate medical process to enhance rehabilitation in geriatric orthopedics.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Ethics Committee of Honghui Hospital affiliated with Xi'an Jiaotong University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design of the research: HZ and ZZ. Acquisition of data: HZ, BQ, and YL. Analysis and interpretation of data: HZ and YW. Statistical analysis: XC and MY. Funding acquisition: YW and QZ. Writing of the manuscript: HZ and ZZ. Critical revision of the manuscript for intellectual content: QZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European union: medical management, epidemiology and economic burden. A report prepared in collaboration with the international osteoporosis foundation (IOF) and the European federation of pharmaceutical industry associations (EFPIA). *Arch Osteoporos*. (2013) 8(1):136. doi: 10.1007/s11657-013-0136-1.

2. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *J Am Med Assoc*. (2009) 301 (5):513–21. doi: 10.1001/jama.2009.50.

3. Baecker N, Tomic A, Mika C, Gotzmann A, Platen P, Gerzer R, et al. Bone resorption is induced on the second day of bed rest: results of a controlled crossover trial. *J Appl Physiol*. (2003) 95(3):977–82. doi: 10.1152/japplphysiol.00264.2003.

4. Kortebein P, Symons TB, Ferrando A, Paddon-Jones D, Ronsen O, Protas E, et al. Functional impact of 10 days of bed rest in healthy older adults. *J Gerontol A Biol Sci Med Sci*. (2008) 63(10):1076–81. doi: 10.1093/gerona/63.10.1076.

5. Rittweger J, Felsenberg D. Recovery of muscle atrophy and bone loss from 90 days bed rest: results from a one-year follow-up. *Bone*. (2009) 44(2):214–24. doi: 10.1016/j.bone.2008.10.044

6. Clark W, Bird P, Gonski P, Diamond TH, Smerdely P, McNeil HP, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. (2016) 388(10052):1408–16. doi: 10.1016/S0140-6736(16)31341-1

7. Yang EZ, Xu JG, Huang GZ, Xiao WZ, Liu XK, Zeng BF, et al. Percutaneous vertebroplasty versus conservative treatment in aged patients with acute osteoporotic vertebral compression fractures: a prospective randomized controlled clinical study. *Spine*. (2016) 41(8):653–60. doi: 10.1097/BRS.0000000000001298.

8. Peris P, Blasco J, Carrasco JL, Martinez-Ferrer A, Macho J, San Roman L, et al. Risk factors for the development of chronic back pain after percutaneous vertebroplasty versus conservative treatment. *Calcif Tissue Int*. (2015) 96 (2):89–96. doi: 10.1007/s00223-014-9940-x.

9. Saracen A, Kotwica Z. Complications of percutaneous vertebroplasty: an analysis of 1100 procedures performed in 616 patients. *Medicine*. (2016) 95(24): e3850. doi: 10.1097/MD.0000000000003850.

10. Brower RG. Consequences of bed rest. *Crit Care Med*. (2009) 37(10 Suppl): S422–8. doi: 10.1097/CCM.0b013e3181b6e30a.

11. Yang JS, Liu JJ, Chu L, Li J, Chen C, Chen H, et al. Causes of residual back pain at early stage after percutaneous vertebroplasty: a retrospective analysis of 1,316 cases. *Pain Physician*. (2019) 22(5):E495–503. doi: https://www.painphysicianjournal.com/current/pdf?article=NjUxOQ%3D%3D&journal=122

12. Xu JJ, Tang XT, Yang J, Wang YH, Zhu DC, Wu YS, et al. The effect of medial branch block on postoperative residual pain relieve after percutaneous kyphoplasty: a randomized controlled trial with 12-month follow-up. *Pain Physician*. (2021) 24(7):E1059–E66. doi: https://www.painphysicianjournal.com/current/pdf?article=NzM0OQ%3D%3D&journal=139

13. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*. (1983) 17(1):45–56. doi: 10.1016/0304-3959(83)90126-4

14. Goz V, Koehler SM, Egorova NN, Moskowitz AJ, Guillerme SA, Hecht AC, et al. Kyphoplasty and vertebroplasty: trends in use in ambulatory and inpatient settings. *Spine J*. (2011) 11(8):737–44. doi: 10.1016/j.spinee.2011.07.002

15. Shirakami G, Teratani Y, Namba T, Hirakata H, Tazuke-Nishimura M, Fukuda K. Delayed discharge and acceptability of ambulatory surgery in adult outpatients receiving general anesthesia. *J Anesth*. (2005) 19(2):93–101. doi: 10.1007/s00540-004-0297-6

16. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med*. (2009) 361(6):569–79. doi: 10.1056/NEJMoa0900563

17. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med*. (2009) 361(6):557–68. doi: 10.1056/NEJMoa0900429

18. Marcia S, Muto M, Hirsch JA, Chandra RV, Carter N, Crivelli P, et al. What is the role of vertebral augmentation for osteoporotic fractures? A review of the recent literature. *Neuroradiology*. (2018) 60(8):777–83. doi: 10.1007/s00234-018-2042-0

19. Harvey RE, Kallmes DF. Discharge disposition following vertebroplasty. *Am J Neuroradiol*. (2011) 32(9):1614–6. doi: 10.3174/ajnr.A2580.

20. Cao J, Liu B, Li X, Leng J, Meng X, Pan Y, et al. Analysis of delayed discharge after day-surgery laparoscopic cholecystectomy. *Int J Surg*. (2017) 40:33–7. doi: 10.1016/j.ijsu.2017.02.055

21. Berg K, Arestedt K, Kjellgren K. Postoperative recovery from the perspective of day surgery patients: a phenomenographic study. *Int J Nurs Stud*. (2013) 50 (12):1630–8. doi: 10.1016/j.ijnurstu.2013.05.002

22. Yan Y, Xu R, Zou T. Is thoracolumbar fascia injury the cause of residual back pain after percutaneous vertebroplasty? A prospective cohort study. *Osteoporos Int*. (2015) 26(3):1119–24. doi: 10.1007/s00198-014-2972-2

23. Gibson JE, Pilgram TK, Gilula LA. Response of nonmidline pain to percutaneous vertebroplasty. *Am J Roentgenol*. (2006) 187(4):869–72. doi: 10.2214/AJR.05.0084.

24. Wang CH, Ma JZ, Zhang CC, Nie L. Comparison of high-viscosity cement vertebroplasty and balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures. *Pain Physician*. (2015) 18(2):E187–94. https://www.painphysicianjournal.com/current/pdf?article=MjI3OA%3D%3D&journal=87

25. Peh WC, Gelbart MS, Gilula LA, Peck DD. Percutaneous vertebroplasty: treatment of painful vertebral compression fractures with intraosseous vacuum phenomena. *Am J Roentgenol*. (2003) 180(5):1411–7. doi: 10.2214/ajr.180.5.1801411.

26. Fu Z, Hu X, Wu Y, Zhou Z. Is there a dose–response relationship of cement volume with cement leakage and pain relief after vertebroplasty? *Dose Response*. (2016) 14(4):1559325816682867. doi: 10.1177/1559325816682867

27. He SC, Teng GJ, Deng G, Fang W, Guo JH, Zhu GY, et al. Repeat vertebroplasty for unrelieved pain at previously treated vertebral levels with osteoporotic vertebral compression fractures. *Spine*. (2008) 33(6):640–7. doi: 10.1097/BRS.0b013e318166955f.

28. Liebschner MA, Rosenberg WS, Keaveny TM. Effects of bone cement volume and distribution on vertebral stiffness after vertebroplasty. *Spine*. (2001) 26(14):1547–54. doi: 10.1097/00007632-200107150-00009.

29. Zhao S, Xu CY, Zhu AR, Ye L, Lv LL, Chen L, et al. Comparison of the efficacy and safety of 3 treatments for patients with osteoporotic vertebral compression fractures: a network meta-analysis. *Medicine*. (2017) 96(26):e7328. doi: 10.1097/MD.0000000000007328.

30. Abdelrahman H, Siam AE, Shawky A, Ezzati A, Boehm H. Infection after vertebroplasty or kyphoplasty. A series of nine cases and review of literature. *Spine J*. (2013) 13(12):1809–17. doi: 10.1016/j.spinee.2013.05.053

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The clinical efficacy of biportal endoscopy is comparable to that of uniportal endoscopy *via* the interlaminar approach for the treatment of L5/S1 lumbar disc herniation

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Objective: To compare the clinical outcomes of unilateral biportal endoscopy/biportal endoscopic spinal surgery (UBE/BESS) *via* the posterior approach with those of interlaminar endoscopic lumbar discectomy (IELD) for the treatment of L5/S1 lumbar disc herniation.

Methods: We collected the clinical data of patients with L5/S1 lumbar disc herniation who had undergone endoscopic surgery at our center from January 2020 to July 2021, and 92 patients were included. They were divided into UBE/BESS ($n = 42$) and IELD ($n = 50$) groups. The incision length, operative time (overall operative, extracanal operative, and intracanal decompression times), intraoperative radiation exposure dose, changes in hemoglobin before and after surgery, postoperative hospital stay, visual analog scale (VAS) score for low back pain and leg, and Oswestry disability index (ODI) were statistically analyzed.

Results: One case incurred dural tear in the UBE/BESS group, and one case developed recurrence in the IELD group. Postoperatively, the VAS score and ODI index decreased significantly in both groups ($P < 0.01$). VAS and ODI scores (preoperative as well as 3 days, 3 months, 6 months, and 12 months after surgery), the overall operative time, and postoperative hospital stay were not significantly different between the two groups ($P > 0.05$). No statistical difference in intraoperative radiation exposure dose was noted between the two groups ($P > 0.05$). The surgical incision length was greater in the UBE/BESS group ($P < 0.01$), and pre- and postoperative hemoglobin changes were more pronounced in the UBE/BESS group ($P < 0.01$). The UBE/BESS group had a longer extracanal operative time and shorter intracanal decompression time ($P < 0.01$).

Conclusions: The clinical efficacy of UBE/BESS for L5/S1 lumbar disc herniation is comparable to that of IELD. Intraoperative radiation exposure doses were similar in both techniques. UBE/BESS required more time to identify tissue structures and a larger working space when operating outside the spinal

Abbreviations
Hb, hemoglobin; IELD, interlaminar endoscopic lumbar discectomy; ODI, oswestry disability index; UBE/BESS, unilateral biportal endoscopy/biportal endoscopic spinal surgery; VAS, visual analog scale

canal; however, the efficiency of nucleus pulposus removal and nerve root release inside the spinal canal superseded that in IELD. Furthermore, the surgical incision in the UBE/BESS technique was longer, with greater actual blood loss during surgery, thus rendering UBE/BESS inferior to the IELD technique in terms of surgical trauma. Nonetheless, no significant difference was noted between the two techniques in the postoperative recovery time of patients.

KEYWORDS

spinal endoscopy, minimally invasive, biportal endoscopic spine surgery, lumbar disc herniation operative time, operative blood loss

Introduction

Lumbar disc herniation is a disease that is commonly encountered in spine surgery, and it is the main cause of low back pain and lower-limb radiating pain, with a prevalence of 11%–13% in China (1, 2). Although most lumbar disc herniations can be relieved using conservative treatment (3, 4), 25% of affected patients still require surgery for recurrent symptoms (5). With the continuous advancement of medical technology, minimally invasive surgical techniques have gradually become an important part of the stepwise treatment process for lumbar disc herniation (6). In recent years, percutaneous uniportal endoscopic surgery has been widely used, achieving favorable clinical results (7–11). Interlaminar endoscopic lumbar discectomy (IELD) has exhibited immense technical advantages for L5/S1 lumbar disc herniation (12–17). However, the equipment **involved** is expensive and difficult to master (18, 19). In recent years, unilateral biportal endoscopy/biportal endoscopic spinal surgery (UBE/BESS) has emerged, providing a novel option for the minimally invasive endoscopic treatment of lumbar disc herniation (20, 21). Its use has rapidly proliferated owing to widely available equipment and the vast similarity of its surgical concept to that of conventional surgery. Few studies have compared the two techniques for the treatment of lumbar disc herniation. Therefore, to explore the differences between the two surgical techniques, this study examined and compared the clinical efficacy of UBE/BESS with that of IELD in the treatment of L5/S1 lumbar disc herniation *via* the interlaminar approach.

Materials and methods

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) a clear diagnosis of L5/S1 lumbar disc herniation with significant lower extremity radiating pain, low back pain, and lower extremity motor and/or sensory dysfunction; (2) computed tomography scan and magnetic resonance image (MRI) of the lumbar spine consistent with clinical symptoms and signs; and (3) treatment with systematic conservative treatment for a duration >3 months. The exclusion criteria were as follows: (1) history of lumbar spine surgery at the L5/S1 segment; (2) lumbar spine infection, tumor, or trauma; (3) presence of lumbar instability and/or lumbar isthmic fracture; (4) concomitant severe psychiatric disorders; and (5) inability to tolerate general anesthesia.

Patients

This was a retrospective cohort study wherein the data of 92 patients with L5/S1 lumbar disc herniation treated at our center from January 2020 to July 2021 using spinal endoscopic surgery *via* the interlaminar approach were collected. The patients were recruited based on the inclusion and exclusion criteria, and they were all followed up for ≥12 months, mean 13.26 months. The preoperative clinical manifestations were low back pain, lower extremity radiating pain, and lower extremity motor and/or sensory dysfunction, and all patients had preoperative MRIs confirming the diagnosis of lumbar disc herniation (L5/S1).

UBE/BESS group: 23men, 19women, mean age was 45.57 ± 11.15 years (25–66 years), mean body mass index (BMI) was 24.53 ± 2.96. IELD group: 31men, 19women, mean age was 46.68 ± 12.09 years (22–67 years), mean BMI was 24.57 ± 3.71.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and patients or their families provided written informed consent for the procedure.

Surgical technique

All surgical procedures were performed by the same experienced surgeon. Patients in both groups were placed in the prone position and underwent surgery under general anesthesia, and no postoperative drains were utilized in either group.

UBE/BESS

The inferior border of the affected L5 pedicle and superior border of the S1 pedicle were located using a C-arm and marked

on the body surface. A longitudinal skin incision of approximately 5 mm was made at the proximal marker point, and an endoscopic puncture sheath was placed. A transverse skin incision of approximately 10 mm was made at the distal marker point, and a progressive dilator was placed. The puncture sheath and the dilator met together at the L5 spinous process and plate migration, and C-arm fluoroscopy was used to confirm the position. The dilator was subsequently removed and a periosteum detacher placed. After placement of the endoscope, the inferior margin of the L5 lamina was identified using radiofrequency hemostasis, followed by exposure of the interlaminar window. If necessary, the lamina was partially shaped using a grinding drill. The ligamentum flavum was incised at the medial edge of the articular eminence under endoscopic surveillance, and the canal was entered. After entering the spinal canal, the lateral margin of the S1 nerve root was revealed and the S1 nerve root can be retracted in the midline using a nerve puller to reveal the herniated disc. The herniated disc was removed, and the procedure was completed with adequate neurological decompression and hemostasis (**Figure 1**).

IELD

Using a 6.9-mm endoscopic system, the center of the L5/S1 interlaminar window on the affected side was positioned under the C-arm and marked on the body surface. A longitudinal skin incision of approximately 7 mm was made at the marking point, a stepwise dilator and working tube were placed directly on the surface of the L5/S1 interlaminar window, and the position of the working tube was confirmed using C-arm fluoroscopy. After placement of the endoscope, the interlaminar window and ligamentum flavum were exposed. The superficial ligamentum flavum was removed using nucleus pulposus forceps. Subsequently, the deep ligamentum flavum was bluntly separated using a nerve stripper, and the ligamentum flavum was split using a working tube to facilitate entry into the spinal canal. The ligamentum flavum was removed to the medial edge of the facet joint using punches, and the dural sac and nerve root were exposed. Based on the location of the herniated disc, the disk fragment was removed in the axilla of the nerve root or shoulder (**Figure 2**).

Postoperative management

Postoperative analgesic treatment was routinely administered. If no dural tear occurred, the patient could walk after 4 h post surgery; however, if a dural tear occurred, no special treatment was administered to asymptomatic patients, and bed rest for 5–7 days was prescribed for symptomatic patients. The patient's lumbar spine MRI was reviewed before discharge from the hospital. The patient was advised to wear a lumbar brace for 1 month and avoid strenuous activities for 3 months after surgery. Routine blood tests were performed 3 days after surgery, and the hemoglobin (Hb) level was recorded.

Observation indicators

The operative time was recorded for all patients and categorized as follows: (1) overall operative time, (2) extracanal operative time (time from skin incision to entry into the spinal canal), (3) intracanal decompression time (time from entry into the spinal canal to the end of the operation), (4) intraoperative radiation exposure dose, (5) operative incision length (measured as the sum of the two proximal and distal incision lengths in the UBE/BESS group), (6) operative related complications, (7) postoperative hospital stay, and (8) preoperative and postoperative day 3 Hb levels. The visual analog scale (VAS) scores of back/leg pain before and 3 days, 3 months, 6 months, and 12 months after surgery as well as the Oswestry disability index (ODI) before and 3 months, 6 months, and 12 months after surgery were recorded.

Statistical analysis

SPSS (version 26.0; IBM SPSS Inc., Chicago, IL, USA) software was used for statistical analyses. Normally distributed measures are expressed as the mean ± standard deviation (± s). Patient age, operative time, incision length, Hb, and postoperative hospital stay were compared between groups using the independent-samples *t-test* or independent-samples nonparametric test. Hb levels, as well as VAS and ODI scores at different time points, were compared within groups using the paired-samples *t-test* or paired-samples nonparametric test. The χ^2 test was used to compare results between sexes among the patients in the two groups. Statistical significance was set at $P < 0.05$.

Results

Baseline information

Baseline information, such as age, sex, preoperative low back/leg VAS score, and ODI were not statistically significantly different between the two groups ($P > 0.05$), as shown in **Table 1**.

Perioperative outcomes of UBE/BESS and IELD

Patients in both groups underwent surgery successfully. On comparing the two groups, the surgical incision length in the UBE/BESS group was significantly longer than that in the IELD group ($P < 0.01$). A significant difference in Hb level

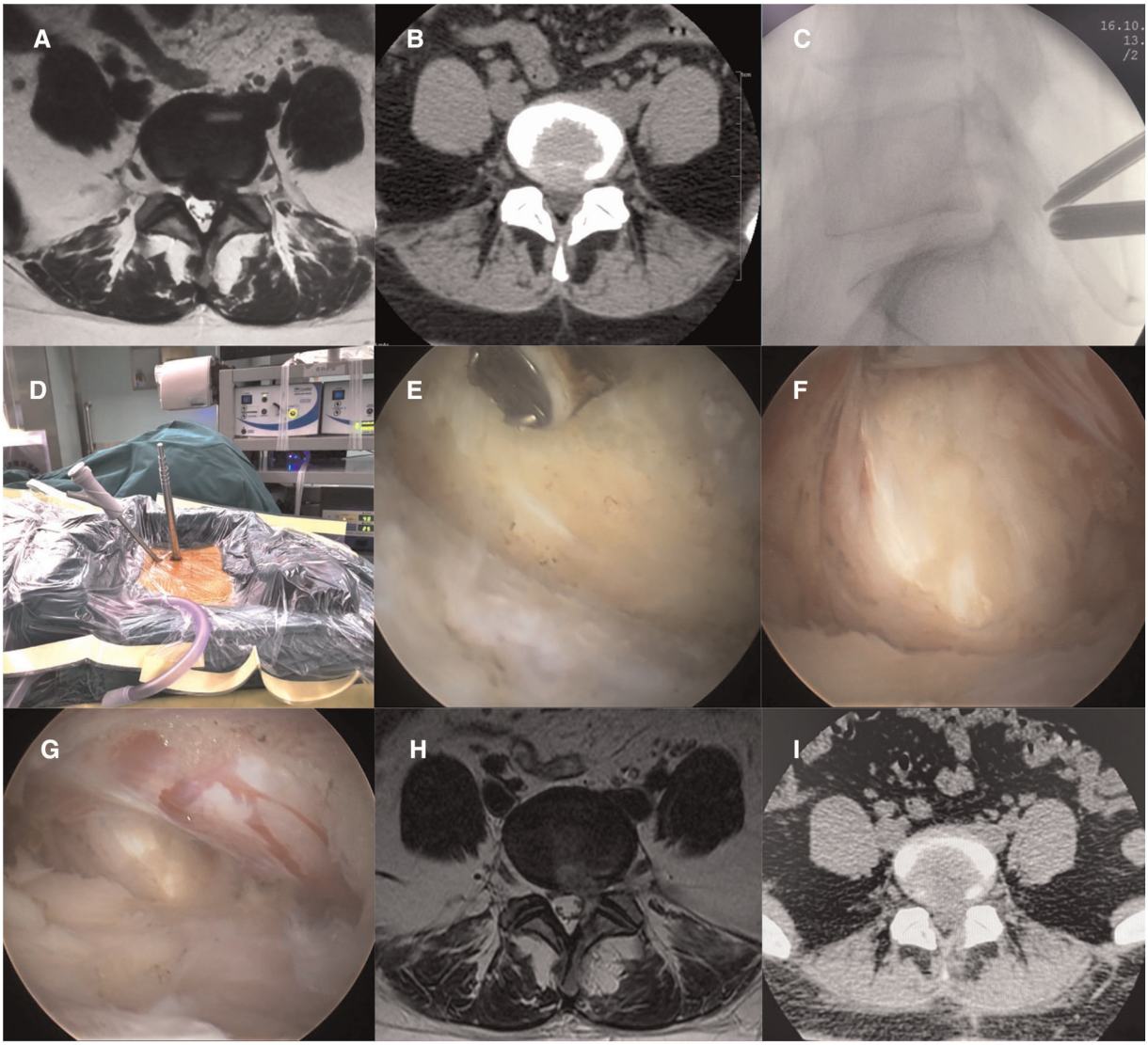

FIGURE 1
(A,B) Preoperative patient MRI and CT revealing L5/S1 disc herniation. (C,D) Intraoperative localization of UBE/BESS and establishment of proximal and distal access. (E) Establishment of a working space to expose the interlaminar window. (F) Medial retraction of the nerve root and exposure of the herniated disc. (G) Loosened nerve roots after disc removal. (H, I) Postoperative patient MRI and CT showed that the L5/S1 herniated disc had been removed.

before and after surgery was noted in the UBE/BESS group compared with that in the IELD group ($P < 0.01$), suggesting that the actual blood loss in the UBE/BESS group was greater than that in the IELD group. No statistical difference in the total operative time was observed between the two groups ($P > 0.05$); however, the extracanal operative time was significantly longer in the UBE/BESS group than in the IELD group ($P < 0.01$), and the operative time for intracanal decompression was significantly shorter in the UBE/BESS group than in the IELD group ($P < 0.01$). The Hb level on postoperative day 3 was significantly different from the preoperative Hb level ($P < 0.01$) in both groups, as shown in Table 2.

Clinical outcomes

Postoperative VAS and ODI scores decreased significantly in the two groups compared with their preoperative scores ($P < 0.01$). No statistically significant differences in VAS and ODI scores at 3 days, 3 months, 6 months, and 12 months after surgery were noted upon comparing the two groups ($P > 0.05$) (Table 3).

The distribution and comparison of the VAS scores for low back/leg pain in the UBE/BESS group at each postoperative time point are shown in Figure 3, and those in the IELD group at each postoperative time point are shown in Figure 4. The

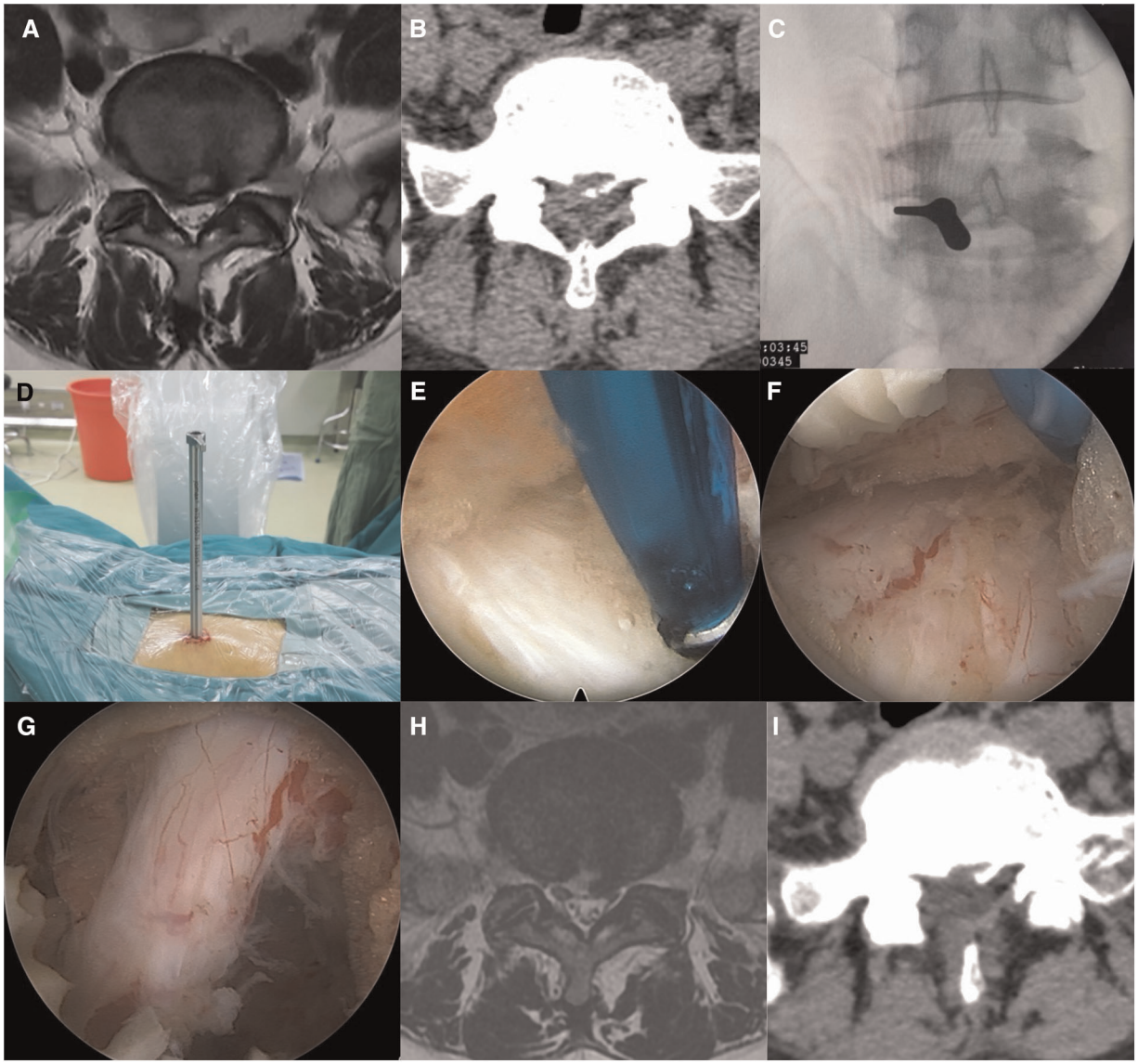

FIGURE 2
(A,B) Preoperative patient MRI and CT revealing L5/S1 disc herniation. (C,D) Intraoperative positioning and access establishment. (E) Exposure of the interlaminar window. (F) Exposure of the prolapsed disc using a working tube in the axilla of the nerve root. (G) Loosened nerve roots after disc removal. (H,I) Postoperative patient MRI and CT showed that the L5/S1 herniated disc had been removed.

distribution and comparison of the ODI at each postoperative time point between the UBE/BESS and IELD groups is shown in Figure 5.

Complications and recurrence

One case incurred a dural tear in the UBE/BESS group. The patient had no postoperative symptoms and did not complain of discomfort upon wearing a lumbar brace to enable mobility on the second day after surgery. Moreover, no special treatment was administered. In the IELD group, one case developed recurrence 7 months after surgery, with symptoms similar to those before surgery, and the diagnosis was confirmed by MRI. The patient recovered well after the revised endoscopic surgery.

Discussion

Lumbar disc herniation is a common disease in spine surgery, and it predominantly affects the L5/S1 segment (22, 23).

TABLE 1 Baseline information of UBE/BESS and IELD.

Group	UBE/BESS ($n = 42$)	IELD ($n = 50$)	Statistical values	P
Age (years)	45.57 ± 11.15	46.68 ± 12.09	$t = -0.454$	>0.05
Male	23	31	$\chi^2 = 0.493$	>0.05
Female	19	19		
Preoperative low back pain VAS	3.95 ± 3.00	3.22 ± 2.88	Z = −1.204	>0.05
Preoperative leg pain VAS	8.14 ± 1.26	7.82 ± 1.7	Z = −0.497	>0.05
Preoperative ODI (%)	66.07 ± 13.48	71.48 ± 15.94	t = −1.74	>0.05

TABLE 2 Comparison of perioperative date of UBE/BESS and IELD.

	UBE/BESS	IELD	Statistical values	P
Total operation time (min)	68.57 ± 10.87	65.6 ± 15.24	t = 1.057	>0.05
Extracorporeal operation time (min)	31.12 ± 4.48	15.84 ± 2.88	t = 19.028	<0.01
Intradural decompression time (min)	37.45 ± 12.32	49.76 ± 14.73	t = −4.295	<0.01
Length of surgical incision (mm)	14.93 ± 1.30	7.46 ± 1.11	Z = −8.293	<0.01
Intraoperative radiation exposure dose (mGy)	0.72 ± 0.11	0.77 ± 0.14	Z = −1.508	>0.05
Preoperative Hb (g/L)	144.79 ± 13.76	138.48 ± 14.33	Z = −1.435	>0.05
Hb (g/L) on the third postoperative day	134.52 ± 13.45*	136.60 ± 14.17**	t = −0.716	>0.05
Hb change (g/L)	10.26 ± 3.21	1.88 ± 1.573	Z = −8.045	< 0.01
Post-operative hospital stay (days)	6.88 ± 1.85	7.36 ± 4.62	Z = −0.812	>0.05

Note: In the intra-group comparison of the two groups, the difference in Hb on the third postoperative day in the UBE/BESS group compared with the preoperative Hb was significant,*$P < 0.01$; the difference in Hb on the third postoperative day in the IELD group compared with the preoperative Hb was significant, **$P < 0.01$.

TABLE 3 Comparison of clinical outcomes of UBE/BESS and IELD.

	UBE/BESS	IELD	Statistical values	P
VAS back				
Preoperative	3.95 ± 3.00	3.22 ± 2.88	Z = −1.204	>0.05
3 days after surgery	1.05 ± 0.85*	0.82 ± 0.75*	Z = −1.282	>0.05
3 months postoperatively	0.57 ± 0.77*	0.58 ± 0.67*	Z = −0.329	>0.05
6 months postoperatively	0.38 ± 0.54*	0.40 ± 0.61*	Z = −0.038	>0.05
12 months postoperatively	0.29 ± 0.46*	0.38 ± 0.49*	Z = −0.948	>0.05
VAS leg				
Preoperative	8.14 ± 1.26	7.82 ± 1.7	Z = −0.497	>0.05
3 days after surgery	0.90 ± 0.79*	1.04 ± 0.83*	Z = −0.740	>0.05
3 months postoperatively	0.79 ± 0.78*	0.94 ± 0.68*	Z = −1.104	>0.05
6 months postoperatively	0.74 ± 0.73*	0.78 ± 0.74*	Z = −0.280	>0.05
12 months postoperatively	0.43 ± 0.59*	0.38 ± 0.53*	Z = −0.297	>0.05
ODI				
Preoperative	66.07 ± 13.48	71.48 ± 15.94	t = −1.74	>0.05
3 months postoperatively	14.57 ± 6.66*	16.82 ± 6.17*	Z = −1.268	>0.05
6 months postoperatively	8.81 ± 5.84*	10.70 ± 6.21*	Z = −1.022	>0.05
12 months postoperatively	4.98 ± 3.11*	5.86 ± 3.73*	Z = −1.156	>0.05

Notes: (1) Within-group comparison of patients; the differences in VAS and ODI scores at each postoperative time point compared with preoperative scores were significant,*$P < 0.01$. (2) There was no significant difference in the VAS and ODI scores of waists and legs at each time point between the two groups of patients, $P > 0.05$.

The L5/S1 interlaminar window is large and located at approximately the same level as the L5/S1 intervertebral space (24); therefore, posterior endoscopic spinal surgery through the interlaminar window is more advantageous for the treatment of L5/S1 disc herniation. Therefore, IELD has been used to treat L5/S1 lumbar disc herniation in several previous studies (12–17). IELD was initially proposed by Professor Rutten in 2006 (25). In the same year, Gun Choi (26) reported the treatment of L5/S1 disc herniation *via* the interlaminar approach, achieving favorable clinical results. Since then, IELD has rapidly developed and emerged as a reliable technique for minimally invasive spine surgery.

Because the operating channel of uniportal endoscopy is integrated with the endoscope, the surgical instruments involved are more slender than traditional surgical instruments, and the surgical procedure differs significantly from traditional surgery. Studies have increasingly shown that uniportal endoscopy is more difficult to master (18, 19). The biportal endoscopy technique was initially proposed in 1996 by De Antoni (27). By 2013, Soliman (28) had introduced the pump irrigation system to biportal endoscopic spinal surgery and proposed "irrigation endoscopic discectomy." In 2017, Heo (29), for the first time, named the unilateral access biportal spinal endoscopy technique "Unilateral Biportal Endoscopy." However, some scholars also called it "Biportal Endoscopy Spine Surgery (BESS)" (30–32). At present, both UBE and BESS represent biportal endoscopic spinal surgery (33). Since then, this technique has been rapidly developed by spine surgeons worldwide through continuous research and

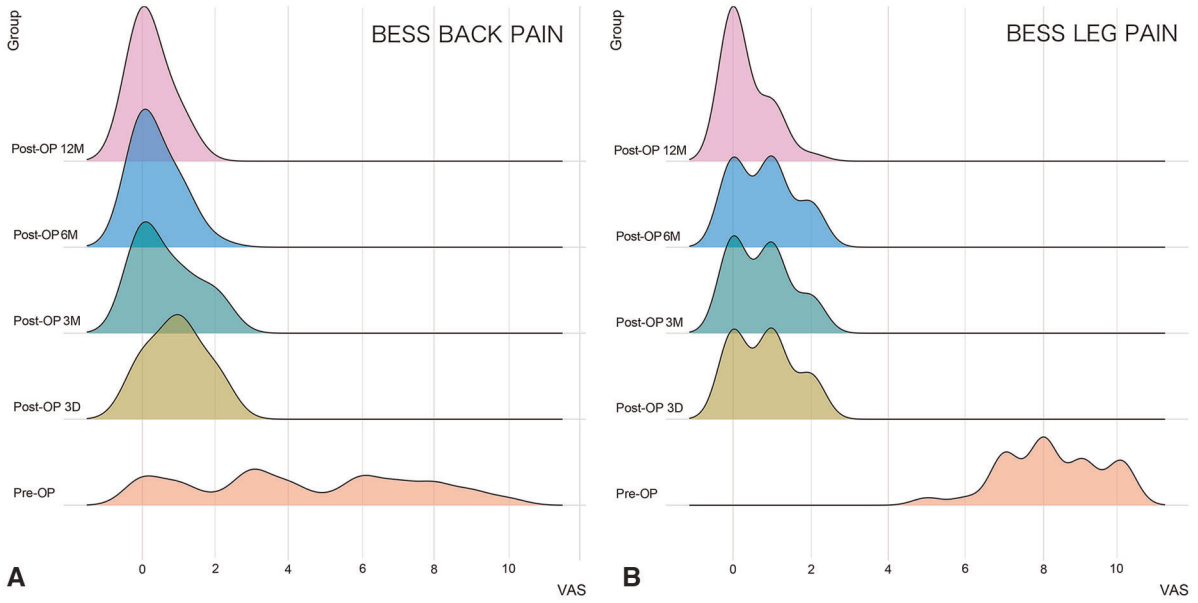

FIGURE 3
(**A**) Comparison of VAS scores for postoperative low back pain in the UBE/BESS group at each time point; no significant decrease was noted at 3 months postoperatively compared with that at 3 days postoperatively, and no significant decrease was noted at 12 months postoperatively compared with that at 6 months postoperatively ($P > 0.05$). Further significant decreases at 6 and 12 months postoperatively compared with that at 3 days and 3 months postoperatively were observed ($P < 0.05$). (**B**) On comparing the VAS scores for postoperative leg pain in the UBE/BESS group at each time point, no significant differences were noted at 3 days, 3 months, and 6 months postoperatively ($P > 0.05$), and a significant decrease at 12 months postoperatively compared with that at 3 days, 3 months, and 6 months postoperatively was observed ($P < 0.05$).

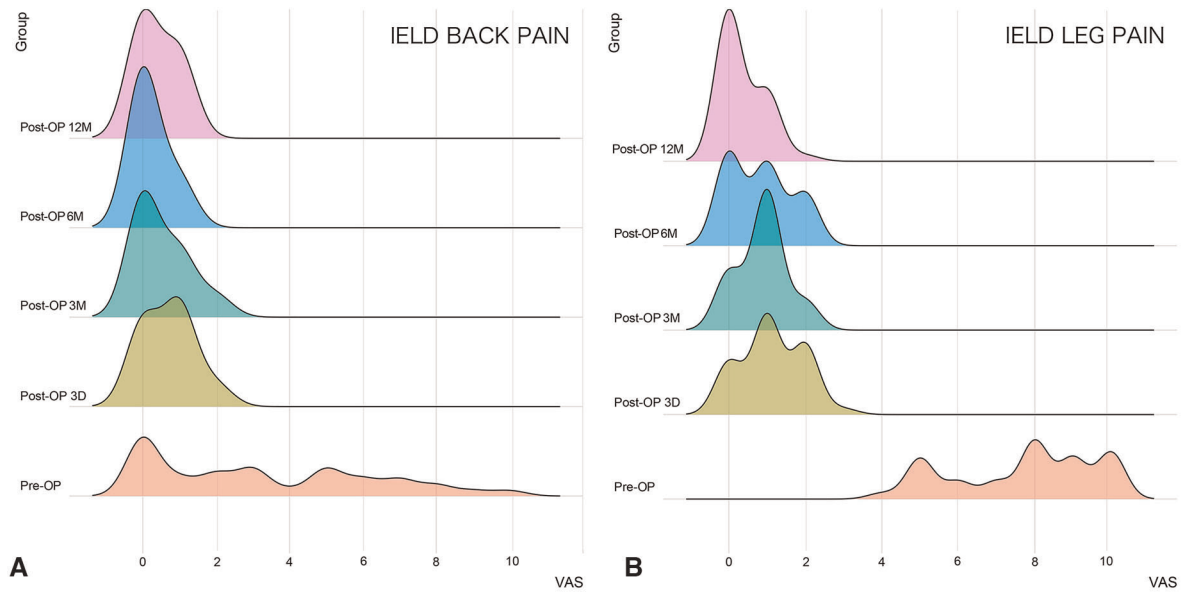

FIGURE 4
(**A**) Comparison of VAS scores for postoperative low back pain in the IELD group at each time point; no significant differences were noted at 3 days and 3 months postoperatively ($P > 0.05$). A significant decrease occurred at 6 months postoperatively compared with that at 3 days and 3 months postoperatively ($P < 0.01$). No significant difference was noted between 12 months postoperatively and 3 days, 3 months, and 6 months postoperatively ($P > 0.05$). (**B**) Comparison of VAS scores for postoperative leg pain in the IELD group at each time point; significant decreases in VAS scores for postoperative leg pain were noted at 12 months postoperatively compared with that at 3 days, 3 months, and 6 months postoperatively ($P < 0.01$). No difference was observed between 6 months postoperatively and 3 months postoperatively ($P > 0.05$); however, a significant decrease occurred in both groups compared with that at 3 days postoperatively ($P < 0.05$).

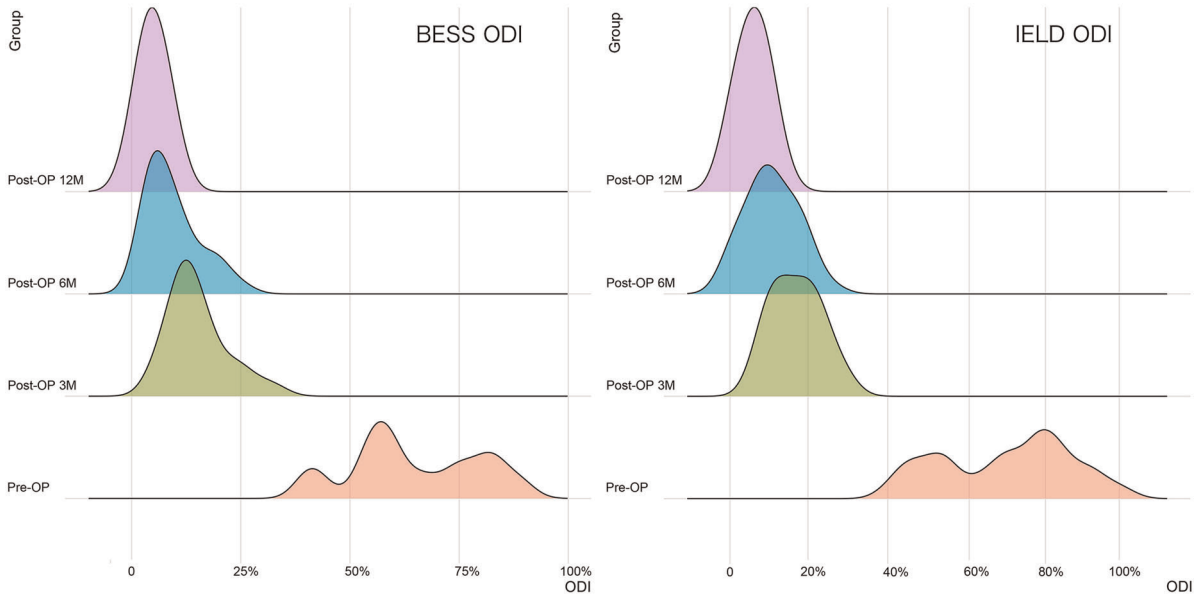

FIGURE 5
In the two groups, significant differences in postoperative ODI were noted at each time point ($P < 0.01$), and the ODI decreased significantly with time.

improvement. Many studies have demonstrated favorable clinical results from UBE/BESS and IELD in the treatment of lumbar disc herniation; nevertheless, research on the possible differences between the two techniques remains limited.

UBE/BESS has unique features compared with IELD: (1) In UBE/BESS, conventional arthroscopes and surgical instruments can be utilized to complete the surgical procedure without purchasing a special uniportal endoscopic system or supporting surgical instruments. (2) UBE/BESS involves two channels. The endoscope and operating instruments are in different channels, which can move independently and freely. This significantly increases the observation range of the endoscope and working area of the surgical instruments. (3) The surgical path and decompression process of UBE/BESS are similar to those of conventional microscopic lumbar discectomy, and studies have demonstrated that the learning curve of the UBE/BESS technique for lumbar disc herniation is 14 cases (31). (4) The distal operating channel of UBE/BESS is not restricted by a rigid working cannula, thus allowing the use of conventional, large-sized surgical instruments, such as an osteotome, rongeur, nucleus pulposus forceps, and nerve retractor, among others, and greatly improving the working efficiency.

Due to the lack of a rigid cannula to dilate the soft tissue in the UBE/BESS technique, blunt dissection of the muscle is required to create a working space before decompression of the spinal canal. Therefore, theoretically, UBE/BESS should result in greater blood loss and worse postoperative back pain than IELD. Certain studies have attempted to address these issues. Hao (34) retrospectively analyzed 40 patients with simple L4/5 disc herniation treated with endoscopy between 2018 and 2021, including 20 cases of UBE/BESS and 20 cases of uniportal endoscopic spinal surgery. In terms of intraoperative blood loss, operative time, postoperative hospital stay, and postoperative pain, uniportal endoscopic spinal surgery was superior to UBE/BESS. Jiang (35) retrospectively analyzed 54 cases of single-segment lumbar disc herniation treated with spinal endoscopy, including four, 33, and 17 cases of the L3/4, L4/5, and L5/S1 segments, respectively. All patients were divided into two groups: 24 and 30 patients in the UBE/BESS and uniportal endoscopy groups, respectively. One dura tear occurred in the UBE/BESS group, and no statistically significant differences were noted in terms of clinical outcome, pain control, and patient satisfaction among the patients in both groups. In this study, the researchers calculated the total surgical blood loss of patients based on hematocrit change before and after surgery and found the total blood loss in the UBE/BESS group to be significantly greater than that in the uniportal endoscopy group. In addition, the UBE/BESS group had a larger surgical incision, longer operative time and hospital stay, and higher total medical costs.

To the best of our knowledge, these are the only two studies to have compared the clinical efficacy of UBE/BESS with that of uniportal endoscopy in the treatment of lumbar disc herniation. However, the above two studies had certain shortcomings in terms of trial design. For example, patients in the control group were operated *via* the lateral foramen, which differed

from the surgical path of the UBE/BESS technique; the control group was operated on under local anesthesia, whereas the trial group was operated on under general anesthesia; the trial group was operated on in the prone position in one study, whereas the control group was operated on in the lateral position; and the surgical segments in one of the studies were not similar in both groups. In the present study, we limited the surgical segment to the L5/S1 segment, and patients in both groups were operated on in the prone position under general anesthesia; moreover, both groups used a posterior trans-interlaminar approach to increase homogeneity, reduce trial bias, and improve the accuracy of the study.

According to our data, both the UBE/BESS and IELD groups achieved favorable clinical results, and postoperative low back pain, leg pain, and ODI scores significantly improved. No significant differences were noted between the two groups, exhibiting consistency with the two studies mentioned above (34, 35). We also found no difference between the two groups in postoperative low back pain, thus conflicting with Hao's results (34) but exhibiting consistency with Jiang's findings (35). This may be related to the fact that we performed blunt stripping of the spinous process lamina migrans when creating the working space in UBE/BESS and used this gap for anatomical identification after placement of the endoscope to rapidly enter the interlaminar window with minimal damage to the multifidus muscle. No significant difference in intraoperative radiation exposure was noted between UBE/BESS and IELD. In terms of operative time, no statistical difference in the overall operative time was observed between the two groups; nonetheless, we categorized the overall operative time based on our decision to enter the spinal canal as a marker and recorded the extracanal operative and intracanal decompression times as well. We found the extracanal time in the UBE/BESS group to be significantly longer than that in the IELD group, while the intracanal decompression time was significantly shorter than that in the IELD group, a phenomenon that reflects the difference between the two techniques during implementation. UBE/BESS required more time to identify the tissue structure and enlarge the working space when operating outside the spinal canal; however, nucleus pulposus removal and nerve root release proved more efficient after entering the spinal canal due to the operating habits and equipment. While IELD required significantly less time to operate outside the spinal canal because of the role of the rigid cannula, the inefficiency of the instruments and difference in operating habits prolonged the removal of the nucleus pulposus and fibrous ring after entering the spinal canal.

In terms of surgical trauma, the difference in postoperative hospitalization time between the two was not significant. The surgical incision length in the UBE/BESS group was significantly longer than that in the IELD group, and the pre- and postoperative Hb change was significantly greater in the UBE/BESS group than in the IELD group, indicating that the actual blood loss in the UBE/BESS group was greater than that in the IELD group. Because both endoscopic surgical techniques require intraoperative saline irrigation, the intraoperative blood loss could not be accurately estimated. Furthermore, the postoperative "hidden" blood loss could not be estimated because no drainage tube was used after surgery. Therefore, in this study, we selected the method of dynamic Hb monitoring to evaluate the actual postoperative blood loss. Certain studies have shown that dynamic monitoring of hematocrit and Hb can effectively and accurately reflect blood loss in surgical patients. Both are potentially useful in calculating the actual blood loss after surgery (36, 37). To reduce the influence of iatrogenic causes, such as preoperative, intraoperative, and postoperative transfusion effects on Hb, strict fluid and medication management were performed on all patients to render the two groups as homogeneous as possible and improve the accuracy of the study. Considering the length of the surgical incision and postoperative Hb level changes, we concluded that the UBE/BESS technique was more invasive than the IELD technique; nevertheless, it did not significantly affect the postoperative recovery time of patients.

This study has certain limitations. First, it is a retrospective study with a short follow-up time and a small sample size. Second, only L5 and S1 segments were compared in this study. In addition, IELD was the exclusive control procedure in this study, whereas microscopic discectomy is also an effective, minimally invasive method for the treatment of lumbar disc herniation. Therefore, these minimally invasive surgical techniques should be discussed together in future studies.

In conclusion, the UBE/BESS and IELD techniques are both safe and effective in the treatment of lumbar disc herniation. The introduction of dynamic Hb in this study revealed that IELD involves less actual blood loss and trauma for the patient than UBE/BESS, suggesting that UBE/BESS requires optimization in the future to further reduce trauma. The rigid cannula used in IELD potentially reduces the extracanal operative time. The surgical equipment used in UBE/BESS is more efficient in removing the nucleus pulposus and releasing the nerve roots.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Beijing Haidian Hospital Medical Ethics

Committee. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

These authors contributed equally to this work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Wang G, Wang G, Peng J, Cai K, Zhang J, Song W, et al. Epidemiology study on pathogenic of lumbar disc herniation. *Mod Prev Med*. (2009) 36(13):2401–3.

2. Zeng Z, Quan H, Zhao J, He L, Su H. A report on the epidemiological survey of lumbar disc herniation in Zhuzhou City, Hunan Province. *Hunan J Tradit Chin Med*. (2015) 31(12):141–3. doi: 10.16808/j.cnki.issn1003-7705.2015.12.075

3. Deyo RA, Diehl AK, Rosenthal M. How many days of bed rest for acute low back pain? A randomized clinical trial. *N Engl J Med*. (1986) 315(17):1064–70. doi: 10.1056/NEJM198610233151705

4. Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, et al. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. *BMJ*. (2012) 344:e497. doi: 10.1136/bmj.e497

5. Deyo RA, Mirza SK. Clinical practice. Herniated lumbar intervertebral disk. *N Engl J Med*. (2016) 374(18):1763–72. doi: 10.1056/NEJMcp1512658

6. Basic R, Transformation Society PCoS, Spinal Cord CAoRM. Guideline for diagnosis, treatment, and rehabilitation of lumbar disc herniation. *Zhonghua Wai Ke Za Zhi*. (2022) 60(5):401–8. doi: 10.3760/cma.j.cn112139-20211122-00548

7. Cong L, Zhu Y, Tu G. A meta-analysis of endoscopic discectomy versus open discectomy for symptomatic lumbar disk herniation. *Eur Spine J*. (2016) 25 (1):134–43. doi: 10.1007/s00586-015-3776-6

8. Ruan W, Feng F, Liu Z, Xie J, Cai L, Ping A. Comparison of percutaneous endoscopic lumbar discectomy versus open lumbar microdiscectomy for lumbar disc herniation: a meta-analysis. *Int J Surg*. (2016) 31:86–92. doi: 10.1016/j.ijsu.2016.05.061

9. Li X, Han Y, Di Z, Cui J, Pan J, Yang M, et al. Percutaneous endoscopic lumbar discectomy for lumbar disc herniation. *J Clin Neurosci*. (2016) 33:19–27. doi: 10.1016/j.jocn.2016.01.043

10. Phan K, Xu J, Schultz K, Alvi MA, Lu VM, Kerezoudis P, et al. Full-endoscopic versus micro-endoscopic and open discectomy: a systematic review and meta-analysis of outcomes and complications. *Clin Neurol Neurosurg*. (2017) 154:1–12. doi: 10.1016/j.clineuro.2017.01.003

11. Kanno H, Aizawa T, Hahimoto K, Itoi E. Minimally invasive discectomy for lumbar disc herniation: current concepts, surgical techniques, and outcomes. *Int Orthop*. (2019) 43(4):917–22. doi: 10.1007/s00264-018-4256-5

12. Chen J, Jing X, Li C, Jiang Y, Cheng S, Ma J. Percutaneous endoscopic lumbar discectomy for L5S1 lumbar disc herniation using a transforaminal approach versus an interlaminar approach: a systematic review and meta-analysis. *World Neurosurg*. (2018) 116:412–20 e412. doi: 10.1016/j.wneu.2018.05.075

13. Eun SS, Chachan S, Lee SH. Interlaminar percutaneous endoscopic lumbar discectomy: rotate and retract technique. *World Neurosurg*. (2018) 118:188–92. doi: 10.1016/j.wneu.2018.07.083

14. Yan TZ, Lyu CL, Wei YC, Niu SZ, Sun GQ. Comparision of surgical outcomes between percuteneous endoscopic interlaminar discectomy and fenestration discectomy for L_5S_1 lumbar disc herniation. *Zhongguo Gu Shang*. (2019) 32(10):933–6. doi: 10.3969/j.issn.1003-0034.2019.10.012

15. Wu TL, Yuan JH, Jia JY, He DW, Miao XX, Deng JJ, et al. Percutaneous endoscopic interlaminar discectomy via laminoplasty technique for L(5) -S(1) lumbar disc herniation with a narrow interlaminar window. *Orthop Surg*. (2021) 13(3):825–32. doi: 10.1111/os.12978

16. Zhou Z, Ni HJ, Zhao W, Gu GF, Chen J, Zhu YJ, et al. Percutaneous endoscopic lumbar discectomy via transforaminal approach combined with interlaminar approach for L4/5 and L5/S1 two-level disc herniation. *Orthop Surg*. (2021) 13(3):979–88. doi: 10.1111/os.12862

17. Song SK, Son S, Choi SW, Kim HK. Comparison of the outcomes of percutaneous endoscopic interlaminar lumbar discectomy and open lumbar microdiscectomy at the L5-S1 level. *Pain Physician*. (2021) 24(4):E467–75. doi: 10.36076/ppj.2021.24.e467

18. Zhou C, Zhang G, Panchal RR, Ren X, Xiang H, Xuexiao M, et al. Unique complications of percutaneous endoscopic lumbar discectomy and percutaneous endoscopic interlaminar discectomy. *Pain Physician*. (2018) 21(2):E105–12. doi: 10.36076/ppj.2018.2.e105

19. Son S, Ahn Y, Lee SG, Kim WK, Yoo BR, Jung JM, et al. Learning curve of percutaneous endoscopic transforaminal lumbar discectomy by a single surgeon. *Medicine*. (2021) 100(4):e24346. doi: 10.1097/MD.0000000000024346

20. Kim SK, Kang SS, Hong YH, Park SW, Lee SC. Clinical comparison of unilateral biportal endoscopic technique versus open microdiscectomy for single-level lumbar discectomy: a multicenter, retrospective analysis. *J Orthop Surg Res*. (2018) 13(1):22. doi: 10.1186/s13018-018-0725-1

21. Lin GX, Huang P, Kotheeranurak V, Park CW, Heo DH, Park CK, et al. A systematic review of unilateral biportal endoscopic spinal surgery: preliminary clinical results and complications. *World Neurosurg*. (2019) 125:425–32. doi: 10.1016/j.wneu.2019.02.038

22. Ong A, Anderson J, Roche J. A pilot study of the prevalence of lumbar disc degeneration in elite athletes with lower back pain at the Sydney 2000 olympic games. *Br J Sports Med*. (2003) 37(3):263–6. doi: 10.1136/bjsm.37.3.263

23. Jordan J, Konstantinou K, O'Dowd J. Herniated lumbar disc. *BMJ Clin Evid*. (2009) 2009:1118. PMID: 19445754; PMCID: PMC2907819

24. Sakci Z, Onen MR, Fidan E, Yasar Y, Ulug H, Naderi S. Radiologic anatomy of the lumbar interlaminar window and surgical considerations for lumbar interlaminar endoscopic and microsurgical disc surgery. *World Neurosurg*. (2018) 115:e22–6. doi: 10.1016/j.wneu.2018.03.049

25. Ruetten S. *The full-endoscopic interlaminar approach for lumbar disc herniations*. Berlin Heidelberg: Springer (2006).

26. Choi G, Lee SH, Raiturker PP, Lee S, Chae YS. Percutaneous endoscopic interlaminar discectomy for intracanalicular disc herniations at L5-S1 using a rigid working channel endoscope. *Neurosurgery*. (2006) 58(1 Suppl):ONS59–68; discussion ONS59-68. doi: 10.1227/01.neu.0000192713.95921.4a

27. De Antoni DJ, Claro ML, Poehling GG, Hughes SS. Translaminar lumbar epidural endoscopy: anatomy, technique, and indications. *Arthroscopy*. (1996) 12(3):330–4. doi: 10.1016/S0749-8063(96)90069-9

28. Soliman HM. Irrigation endoscopic discectomy: a novel percutaneous approach for lumbar disc prolapse. *Eur Spine J*. (2013) 22(5):1037–44. doi: 10.1007/s00586-013-2701-0

29. Heo DH, Son SK, Eum JH, Park CK. Fully endoscopic lumbar interbody fusion using a percutaneous unilateral biportal endoscopic technique: technical note and preliminary clinical results. *Neurosurg Focus*. (2017) 43(2):E8. doi: 10.3171/2017.5.FOCUS17146

30. Choi CM. Biportal endoscopic spine surgery (BESS): considering merits and pitfalls. *J Spine Surg*. (2020) 6(2):457–65. doi: 10.21037/jss.2019.09.29

31. Choi DJ, Choi CM, Jung JT, Lee SJ, Kim YS. Learning curve associated with complications in biportal endoscopic spinal surgery: challenges and strategies. *Asian Spine J*. (2016) 10(4):624–9. doi: 10.4184/asj.2016.10.4.624

32. Choi DJ, Jung JT, Lee SJ, Kim YS, Jang HJ, Yoo B. Biportal endoscopic spinal surgery for recurrent lumbar disc herniations. *Clin Orthop Surg*. (2016) 8 (3):325–9. doi: 10.4055/cios.2016.8.3.325

33. Chu PL, Wang T, Zheng JL, Xu CQ, Yan YJ, Ma QS, et al. Global and current research trends of unilateral biportal endoscopy/biportal endoscopic spinal surgery in the treatment of lumbar degenerative diseases: a bibliometric and visualization study. *Orthop Surg*. (2022) 14(4):635–43. doi: 10.1111/os.13216

34. Hao J, Cheng J, Xue H, Zhang F. Clinical comparison of unilateral biportal endoscopic discectomy with percutaneous endoscopic lumbar discectomy for single l4/5-level lumbar disk herniation. *Pain Pract*. (2021) 22(2):191–9. doi: 10.1111/papr.13078

35. Jiang HW, Chen CD, Zhan BS, Wang YL, Tang P, Jiang XS. Unilateral biportal endoscopic discectomy versus percutaneous endoscopic lumbar discectomy in the treatment of lumbar disc herniation: a retrospective study. *J Orthop Surg Res*. (2022) 17(1):30. doi: 10.1186/s13018-022-02929-5

36. Gross JB. Estimating allowable blood loss: corrected for dilution. *Anesthesiology*. (1983) 58(3):277–80. doi: 10.1097/00000542-198303000-00016

37. Budny PG, Regan PJ, Roberts AH. The estimation of blood loss during burns surgery. *Burns*. (1993) 19(2):134–7. doi: 10.1016/0305-4179(93)90036-8

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The outcome of enhanced recovery after surgery vs. a traditional pathway in adolescent idiopathic scoliosis surgery: A retrospective comparative study

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Objectives: The optimized enhanced recovery after surgery (ERAS) pathway for adolescent idiopathic scoliosis (AIS) patients has not been comprehensively described. The purpose of the study was to explore the feasibility and efficacy of an integral process of ERAS protocol in posterior spinal fusion (PSF) surgery for AIS patients without three-column osteotomy.
Methods: Based on the inclusion and exclusion criteria, a total of 90 AIS patients who underwent PSF were enrolled in the study. Forty-five patients followed a traditional pathway (TP) perioperative care and 45 were treated with an ERAS protocol designed and implemented by a multidisciplinary team. Patient demographic, clinical information, surgical data, and radiographic parameters were collected and analyzed retrospectively.
Results: There is no significant difference in age, gender, body mass index, preoperative hemoglobin level, Cobb angle, curve type, average correction rate, fusion segments, and screw number between ERAS group and TP group. Regarding the estimated blood loss (EBL), surgical duration, pain intensity, drainage duration, drainage volume, first ambulation time, postoperative length of stay (LOS), and the incidence of blood transfusion, they were significantly less in ERAS group than those of TP group.
Conclusions: Based on our findings, we found that the implementation of a standard ERAS protocol in AIS correction surgery could result in less EBL, lower pain intensity, early ambulation, shorter LOS, and rapid rehabilitation. We recommend the widespread adoption of ERAS protocols in AIS surgery.

KEYWORDS

enhanced recovery after surgery, adolescent idiopathic scoliosis, posterior spinal fusion, length of hospital stay, multimodal analgesia

Introduction

Adolescent idiopathic scoliosis (AIS) accounts for the largest population of all types of spinal deformity, most of which need a correction surgery to prevent deformity from deterioration, especially in one's teenage (1–3). In China, it is reported the prevalence of scoliosis is as high as 1.02% in the pre-high school population, with more than 10,000 surgeries performed per annum (4). Posterior spinal fusion (PSF) has been proven to

be an effective method and the standard procedure for AIS correction according to the current study (5, 6). Despite the advantages in radiological parameters improvement, PSF also brings massive pain, great physical trauma, and psychological stress to such patients (5, 7). The concerning challenges for postoperative care of PSF remain adequate pain control, effective management of opioid-related side effects, and delayed mobilization. Besides, postoperative hemorrhage, infection, or procedure-related complications may postpone recovery after surgery, with overall complication rates averaging approximately 9%–15% (8, 9).

First introduced by Kehlet in 1997 (10), an enhanced recovery after surgery (ERAS) pathway has been implemented in various surgical settings and shown to safely decrease the postoperative length of hospital stay (LOS) by 2–3 days and in the complication rate by 30%–50% while improving the satisfaction and outcomes following surgery (11). ERAS protocols consist of a series of evidence-based approaches to perioperative care, with the aim of reducing surgical-stress responses, early mobilization, early oral nutrition, early removal of urinary catheters, and prevention of nausea and vomiting (12, 13).

However, the optimized enhanced recovery after surgery pathway for AIS patients has not been comprehensively described. The efficacy of the protocol should be verified. We are going to report the comparison of the outcomes between the ERAS pathway and the traditional method for AIS postoperative care.

Methods

Ahead of the study, we received the approval of the ethics committee of BJCY hospital, CCMU (Approval number: ke2019–4-5), and it was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria were as follows: patients with AIS who underwent PSF without three-column osteotomy according to operation indications; aged 10–18 years; good physical and psychological status; no history of primary spinal surgery; and at least 1-year follow-up; curve correction achieved by pedicle screws and no procedure exposing the dura mater or performing three-column osteotomy. The PSF indications in AIS were spinal curvature >50° in those with a mature skeleton; or spinal curvature >45° in patients with an immature skeleton and orthotic management that did not prevent the curve from worsening (Cobb angle development >5° within 6 months). The exclusion criteria were: non-idiopathic scoliosis; history of spinal surgery; patients with hematologic diseases or preoperative hemoglobin (HB) level <100 g/L; those with missing data, and patients and families with poor compliance; other conditions that prevent compliance of the ERAS pathway.

We explored and started the ERAS protocol from 2018 to 2019, patients before this point underwent a traditional perioperative care method (traditional pathway group, TP), and those after received rapid recovery care (ERAS group). What should be noted, all patients in both groups underwent similar surgical procedures by the same surgical team. The PSF was achieved using the same pedicle screw-rod system. The surgical procedures were described as exposure of the spine from the skin to the periost, pedicle screws were placed using a standard technique. Facetectomy was performed to increase the spinal flexibility, improve the curve correction as well as facilitate spine fusion, rather than three-column osteotomy. Fusion was augmented using both autogenous and allogeneic bone grafts. Besides, complications were managed similarly and hospital discharge criteria were the same.

A standard ERAS protocol was designed and implemented by a multidisciplinary team comprising spine surgeons, anesthesiologists, nurses, a psychiatrist, and a nutritionist (the psychiatrist and nutritionist help to give a nutritional status evaluation and mental health assessment to optimize the status of patients) based on evidence-based elements and an understanding of rapid recovery principles. Before the protocol was developed, the traditional pathway of PSF perioperative care was executed by the same team, the comparison of procedures between the two groups is listed in **Table 1** (14, 15). The ERAS protocol consisted of three components according to protocol order. The discharge guideline for the two groups is the same, namely, stable vital signs and good mental status, afebrile with no staining on the dressing, tolerable and reduced pain, a routine diet, independent of bowel movement, ambulating independently over 100 m without rest, and mastering the rehabilitation exercises independently.

Outcome measures

Patient demographic, clinical information, surgical data, and radiographic parameters were collected retrospectively. The demographic information included the age, gender, and body mass index (BMI) of the patients. Clinical data, including preoperative and postoperative HB levels, postoperative pain intensity score (visual analog score, VAS), analgesic medicine use duration, drainage duration, first ambulation time, and LOS were documented. Radiological parameters in our study were preoperative and postoperative Cobb angle of the main curve, correction rate of the main curve, and curve type (Lenke classification for AIS). Surgical information including duration, estimated blood loss (EBL), instrumented levels, and screw numbers were extracted from the medical records. Postoperative complications and hospitalization of surgery were also analyzed.

TABLE 1 The protocol of ERAS method and traditional pathway.

Procedure	ERAS group	TP group
Preoperative preparation		
Communication and education	1. Tell the patients about the process, risks, and complications of anesthesia and surgery, to relieve the stress and anxiety from the unknown. 2. Tell the patients about the scheme and principle of ERAS protocol, including the diet, rehabilitation, pain management, and skin cleaning during the perioperative period, to increase compliance with program implementation. 3. Tell the patients about the discharge criteria and general information. 4. Tell the patients about the follow-up scheme, the approach, and the situation of readmissions.	General information about surgery, risks, complications, and rehabilitation.
Special exercise regarding surgery	Start from admission. 1. Start pulmonary function exercise through balloon blowing. 2. Start aerobic exercise by climbing the stairs. 3. Start flexibility exercise by spine extension strengthening and traction.	Not applicable.
Evaluation	1. General evaluation, including demographic characteristics, like weight, height, age, etc., vital signs, like heart rate, blood pressure, blood oxygen, etc. 2. Cardiopulmonary function evaluation. 3. Blood evaluation: coagulation function, electrolyte balance. 4. Nutritional status evaluation. 5. Pain intensity evaluation. 6. Self-function evaluation. 7. Mental health assessment.	1. General evaluation, including demographic characteristics, like weight, height, age, etc., vital signs, like heart rate, blood pressure, blood oxygen, etc. 2. Cardiopulmonary function evaluation. 3. Blood evaluation: coagulation function, electrolyte balance.
Intestinal preparation	1. Clear fluids up to 2 h and solids up to 6 h before induction of anesthesia. 2. Use of preoperative concentrated carbohydrate contained beverage routinely (or drink a 10% glucose 5 ml/kg). 3. Gastrointestinal motility drugs are used to treat abdominal distension after surgery.	No food or drink intake for 8 h before induction of anesthesia.
Intraoperative procedures		
Positioning	1. Pay attention to the chest and abdomen when placing, and reduce the abdominal pressure. 2. Apply elastic compress to skin contact area (shoulders, elbows, chest and lower ribs, anterior superior iliac spine, knees, ankle) to avoid skin damage, protect ulnar nerve, and common peroneal nerve.	General position.
Antibiotic prophylaxis	Antibiotic within 0.5 h of incision, additional antibiotic when the surgery duration exceeds every 3 h.	Same as ERAS.
Anesthesia	General anesthesia. 1. Induction stage based on propofol (2.5 mg/kg, i.v.), midazolam (1–2 mg, i.v.), sufentanil (0.1–0.5 mg/kg, i.v.), and rocuronium (0.6 mg/kg, i.v.). Avoid using inhalation agents and neuromuscular blockade. 2. Maintain stage, propofol (9–15 mg/kg, iv), remifentanil (0.2 μg/kg/min, i.v.).	General anesthesia. Medications rely on individual preference.
Pain management	Multimodal analgesia 1. COX-2 inhibitor (e.g., parecoxib, 40 mg, i.v.) and opioid (e.g., oxycodone, 0.1–0.2 mg/kg, i.v.), within 0.5 h of induction. 2. Maintenance, remifentanil (0.1–0.3 mg/kg/min, i.v. v.p.), dexmedetomidine (0.4 mg/kg/h, i.v. v.p.), and propofol (target-controlled infusion, 4–12 mg/kg/h). 3. Avoid neuromuscular blockade during surgery	Medications rely on individual preference.

(*continued*)

TABLE 1 Continued

Procedure	ERAS group	TP group
Fluid management	Restricted target-oriental fluid therapy.	Medications rely on individual preference.
Temperature management	To maintain a core temperature of 36 °C 1. Fluid warming. 2. Airway humidification. 3. Underbody warm air blower. 4. Warming blanket. 5. Increasing OR temperature.	No precaution for hypothermia
Blood management	1. Controlled hypotensive anesthesia (mean arterial pressure 70–75 mm Hg). 2. Intraoperative cell salvage. 3. TXA (impaction dose 20 mg/kg before skin incision + infusion 10 mg/kg/h + 3 g TXA topical application). 4. Transfusion of blood products when hemoglobin <70 g/L.	Transfusion of blood products when hemoglobin <70 g/L.
Drainage	Subfascial drainage	Subfascial drainage
Surgical techniques	PSF, pedicle screw-rod system, MEPs and SEPs, ultrasonic osteotome.	PSF, pedicle screw-rod system, ultrasonic osteotome.
Postoperative care		
Pain management	Multimodal analgesia 1. Local subcutaneous was applied before skin closure with 0.75% ropivacaine (10 ml) + 0.9% saline (10 ml). 2. Patient-controlled analgesia pump: sufentanil (100 mg) + butorphanol (8 mg) + 0.9% saline, 100 ml totally. 3. COX inhibitor-2 (parecoxib, 40 mg, b.i.d., i.v.) from POD 1, until a favorable pain intensity but no more than 5 days. 4. Oral analgesics began on POD 2, celecoxib capsule (200 mg, b.i.d.) or etoricoxib tablets (120 mg, q.d.), or loxoprofen sodium tablets (60 mg, b.i.d.).	Medications rely on individual preference.
Intake management	1. Clear liquid allowed as requested and tolerated from 2 h postoperatively. 2. Soft diet was commenced 4–6 h as tolerated. 3. Normal diet was allowed on POD 1 if the patient has no PONV. 4. High-quality protein diet was advised from POD 1. 5. Folic acid tablets, iron ions, nourishing blood drink (Chinese medicine), etc., to improve hemoglobin levels.	1. No oral intake until 6 h postoperatively. 2. Liquid and soft diet started on 24–48 h as tolerated. 3. Normal diet started at least 48 h.
Anti-PONV therapy	1. Dual antiemetic prophylactic therapy (ondansetron, 4 mg + dexamethasone, 10 mg, i.v.). 2. Metoclopramide (10 mg, intramuscularly) if nausea and vomiting.	Metoclopramide (10 mg, intramuscularly) if nausea and vomiting.
Rehabilitation plan	1. Encourage mobilization and ambulation independence. 2. Removal of the catheter after anesthesia recovery. 3. Removal of subcutaneous drainage within 24 h (drainage <100 ml daily). 4. Wear customized brace as soon as ambulation within POD 30 days.	1. Early ambulation after removal of drainage. 2. Removal of the catheter after ambulation. 3. Maintain the subfascial drainage when the drainage <100 ml (at least 48 h postoperatively). 4. Ambulation on POD 3.

i.v., intravenous injection; COX-2, cyclooxygenase 2; i.v. v.p., intravenous pumping; OR, operative room; TXA, tranexamic acid; PSF, posterior spinal fusion; MEP, electric motor evoked potential; SEP, somatosensory evoked potential; b.i.d., twice daily; POD, postoperative day; PONV, postoperative nausea, and vomiting; ERAS, enhanced recovery after surgery; TP, traditional pathway.

Statistical analysis

The SPSS version 18 software (IBM Corp., Armonk, NY, United States) was used to perform statistical analyses. Two-sample independent *t*-test was conducted to assess the differences of continuous variables with parametric data between the two cohorts. $\bar{\chi}$ and Fisher's exact test was used to analyze differences of categorical variables in outcome variables, where a p value of ≤ 0.05 was considered statistically significant.

Result

Demographic characteristics

A total of 90 AIS patients who underwent PSF were reviewed, with 45 in the ERAS group and 45 in the traditional group. There are four and five male patients in ERAS group and TP group, respectively, with a total average age of 15.36 ± 1.33 and 15.35 ± 1.53 years, respectively. The demographic characteristics of the patients are shown in Table 2. There is no significant difference in age, gender, and BMI between ERAS group and TP group. Regarding preoperative hemoglobin level, Cobb angle, and Lenke classification for AIS of curve type, the difference is not statistically significant.

Surgical characteristics of two groups

Both groups achieved outstanding deformity correction, with an average correction rate of more than 75%. The Cobb angle of the main curve was corrected from 89.20° ± 11.70° to 20.38° ± 7.16° in the ERAS group and from 85.27° ± 10.16° to 19.96° ± 4.68° in the TP group. Similar fusion segments and screws were employed in both ERAS and TP groups. However, the EBL and surgical duration in ERAS group were significantly less than those of TP group ($p = 0.000$ and 0.000). The detailed information was listed in Table 3.

Postoperative recovery characteristics

The postoperative hemoglobin in ERAS group (114.76 ± 6.74) was significantly higher ($p < 0.001$) than that of TP group (107.56 ± 6.46). The VAS for pain intensity of postoperative day (POD) 1 and POD 3 in the ERAS group was 3.89 ± 0.91 and 2.04 ± 0.64, both of which were significantly lower than those of the TP group (4.80 ± 0.84 for POD 1 and 3.04 ± 0.74 for POD 3). In terms of analgesic medicine applied duration, it was 2.36 ± 0.77 days in ERAS group and 4.51 ± 0.87 days in TP group, which exhibited statistical difference. Drainage duration and volume in the ERAS group were 1.38 ± 0.49 days and 61.13 ± 11.05 ml, both were less than those of the TP group ($p < 0.001$). The first ambulation time for patients in ERAS group is 2.27 ± 0.58 days, which was shorter than 4.96 ± 0.74 days for patients in TP group. The postoperative LOS in the ERAS group was significantly less than in the TP group (4.64 ± 0.86 vs. 6.22 ± 0.97). The allogeneic blood transfusion happened in 3 cases (6.67%) in ERAS group and 12 cases (26.67%) in TP group, which was significantly higher in TP group.

Of the 45 patients in ERAS group, 24 patients returned home on POD 4 (53.33%), 16 returned home on POD 5 (35.56%), 2 returned home on POD 6 (4.44%), and 3 returned home on POD 7 (6.67%). Of the latter 5 patients, 2 had a postoperative fever, 1 for wound infection, and 2 for nausea and vomiting, which were all postoperative complications in the ERAS group. In TP group, 10 patients returned home on POD 5 (22.22%), 21 returned home on POD 6 (46.67%), 9 returned home on POD 7 (20.00%), 4 returned home on POD 8 (8.89%), 9 returned home on POD 9 (2.22%). The complications in the TP group consisted of 4 cases of fever, 4 cases of wound infection, and 5 cases of nausea and vomiting. The overall postoperative recovery characteristics were shown in Table 4.

TABLE 2 Demographic characteristics.

	ERAS group	TP group	*P* value
Sample size	45	45	—
Gender (M: F)	4:41	5:40	1.000
Age (y)	15.36 ± 1.33	15.35 ± 1.53	0.933
BMI (kg/m^2)	21.04 ± 1.43	21.12 ± 1.26	0.772
Preoperative hemoglobin level (g/L)	115.29 ± 7.03	114.89 ± 6.14	0.774
Curve type (Lenke classification): (1:2:3:4:5:6)	2:17:18:5:2:1	1:16:16:6:5:1	0.868

BMI, body mass index; ERAS, enhanced recovery after surgery; TP, traditional pathway.

Discussion

The method of enhanced recovery after surgery was introduced 25 years ago by Kehlet (10). The components of the optimal idea were a series of evidence-based protocols of perioperative care to reduce surgical-stress responses and provide rapid rehabilitation for patients after operation. It has been reported and validated to be effective in various surgical procedures to accelerate postoperative recovery, which is an

TABLE 3 Surgical information of two groups.

	ERAS group	TP group	*P* value
Preoperative cobb of main curve (°)	89.20 ± 11.70	85.27 ± 10.16	0.092
Postoperative Cobb of main curve (°)	20.38 ± 7.16	19.96 ± 4.68	0.741
Correction rate (%)	77.46 ± 6.24	76.71 ± 4.25	0.507
Fusion segment	11.38 ± 1.80	11.16 ± 1.78	0.558
Screw number	22.62 ± 3.45	22.22 ± 3.44	0.583
Estimate blood loss (ml)	313.22 ± 39.73	402.89 ± 37.58	0.000
Surgical duration (min)	244.11 ± 26.46	264.33 ± 23.76	0.000

ERAS, enhanced recovery after surgery; TP, traditional pathway.

TABLE 4 Postoperative recovery characteristics and early complications of two groups.

	ERAS group	TP group	*P* value
Postoperative recovery characteristics			
POD 1 hemoglobin level (g/l)	114.76 ± 6.74	107.56 ± 6.46	0.000
VAS of POD 1	3.89 ± 0.91	4.80 ± 0.84	0.000
VAS of POD 3	2.04 ± 0.64	3.04 ± 0.74	0.000
Analgesic medicine (day)	2.36 ± 0.77	4.51 ± 0.87	0.000
Drainage duration (day)	1.38 ± 0.49	3.80 ± 0.73	0.000
Drainage volume (ml)	61.13 ± 11.05	433.33 ± 107.66	0.000
First ambulation time (day)	2.27 ± 0.58	4.96 ± 0.74	0.000
Postoperative LOS (day)	4.64 ± 0.86	6.22 ± 0.97	0.000
Early complications			
Fever	2	4	0.677
Wound infection	1	4	0.361
Nausea and vomiting	2	5	0.434
Allogeneic blood transfusion	3	12	0.007

POD, postoperative day; VAS, visual analog score; LOS, length of stay; ERAS, enhanced recovery after surgery; TP, traditional pathway.

ideal concept for postoperative rehabilitation of posterior spinal fusion (11, 12, 16).

PSF for scoliosis is known as long duration, traumatic, heavy bleeding, and high risk of neurologic complications. The adoption of ERAS in scoliosis surgery has been explored before. Fletcher et al. reported a novel pathway for patients with AIS undergoing PSF that shortened the LOS without increasing the incidence of complications in 2014 (17). In 2021, Fletcher et al. found patients managed with both an ERAS pathway and a traditional pathway could have a rapid return to normalcy through a prospective dual-center study with 280 patients, but it was shown a 55% less LOS and a significantly less length of surgery and EBL in the ERAS group (18). Rather than a comprehensive and overall protocol for ERAS method, previous studies focus mainly on individual components of ERAS. An optimized ERAS pathway has been lacking in this setting. Thus, we seek to explore the feasibility and efficacy of an integral process of ERAS in PSF for AIS patients.

Based on the advanced experience of previous studies and the characteristics of young patients, we set a multidepartment protocol for AIS surgery including spine surgeon, nurse, anesthetist, psychiatrist, and nutritionist (19, 20). For preoperative preparation, the main goals are performing comprehensive assessment, optimizing the nutritional, psychological, and cardiopulmonary function status, alleviating the tension between patients and their families, and making good communication between doctors and patients. Besides scoliosis correction, it is of great importance to minimize surgical trauma, reduce blood loss, and maintain optimal blood pressure and temperature during operation. Postoperatively, performing satisfied pain management, accelerating rehabilitation, and preventing complications rank first. Nevertheless, spine deformity in adolescents affects the psychological status adversely. It is reported that 40% of AIS patients suffered from solitude and depression during and after treatment (21, 22). Deformity correction was reported to improve the physical and mental health of patients with AIS (23). Spine surgeons should keep aware that preoperative education could contribute to increasing self-confidence and reducing stress to improve patients' psychosocial status (24).

Intraoperative procedure to reduce the EBL

Some measures taken during operation to minimize the surgical trauma and reduce the blood loss were controlling the lowering of blood pressure and tranexamic acid (TXA). The efficacy of TXA to minimize blood loss in AIS surgery has been explored and verified without increasing the risk of deep vein thrombosis (25, 26). The comprehensive studies illustrated that the application of TXA could reduce total blood loss perioperatively and result in a higher hemoglobin level in patients undergoing spinal surgery (27, 28). In our study, the combination of TXA and controlled hypotension result in significantly less EBL and drainage volume, a higher postoperative hemoglobin level, and a lower incidence of blood transfusion in the ERAS group compared to the TP group.

Pain management

Postoperative pain management posed great challenges for AIS surgery. In addition to improving the quality of recovery, effective pain management reduces the patient's stress response, facilitates ambulation, and accelerates postoperative rehabilitation (29). Therefore, the significant role of multimodal analgesia is emphasized in all ERAS society guidelines (30). In the present study, the VAS of POD 1 and POD 3 in the ERAS group were significantly lower and the duration of analgesic medicine in the ERAS group was notably shorter than those of the TP group, which should be attributed to the effects of multimodal analgesia. The pain management for patients in ERAS group consisted of an incision infiltration of 0.375% ropivacaine, application of a patient-controlled analgesia pump (sufentanil + butorphanol), and COX-2 inhibitors medicine, which lead to both analgesia maintenance and reduced consumption of opioids (31).

Reduction of length of stay

Length of stay (LOS) is the indicator of better care, reducing potential medical complications, and rapid rehabilitation. The

postoperative LOS in our study for patients in ERAS group is significantly shorter than TP group. The reduction in LOS of 1–2 days is similar to the previous studies (20). The improvement could attribute to the following reasons: optimization of the nutritional status, reduction in EBL during operation, successful postoperative pain management, and acceleration of rehabilitation.

Early ambulation, less complication, and length of stay are the goals of ERAS concept. In ERAS group, the average time of the first ambulation was 2.27 ± 0.58 days, significantly shorter than 4.96 ± 0.74 days in TP group. Satisfied pain management by multimodal analgesia helped to reduce the bedtime before getting to walk, which also contributed to starting a chain reaction to reduce nausea and vomiting and rapid recovery (32). However, the difference in complication incidence between ERAS and TP groups showed no statistical significance.

Limitations

Our study has limitations. Above all, it is a retrospective study with a small sample size within a single institution, which discounts the persuasive power of the conclusions. In addition, the surgeries were performed by a single surgeon, and as time goes by, the technique of surgery and skills proficiency might be a confounding factor to the outstanding results in the ERAS group. Therefore, a prospective randomized controlled study in multicenter is needed to verify the efficacy of the proposed comprehensive ERAS protocol.

Conclusions

Based on our findings, we found that the implementation of a standard ERAS protocol in AIS correction surgery could result in less EBL, lower pain intensity, early ambulation, shorter LOS, and rapid rehabilitation. We recommend the widespread adoption of ERAS protocols in AIS surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of Beijing Chaoyang Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors contributed to the research conception and design. The first draft of the paper was written by HD. Data collection was performed by BH. Data calculation and analysis were performed by HD and AP. The work was critically revised by YH, LG, and YL. All authors commented on previous versions of the paper, as well as read and approved the final version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Faldini C, Manzetti M, Neri S, Barile F, Viroli G, Geraci G, et al. Epigenetic and genetic factors related to curve progression in adolescent idiopathic scoliosis: a systematic scoping review of the current literature. *Int J Mol Sci*. (2022) 23 (11):5914. doi: 10.3390/ijms23115914

2. Horne JP, Flannery R, Usman S. Adolescent idiopathic scoliosis: diagnosis and management. *Am Fam Physician*. (2014) 89(3):193–8. Available at: https://www.aafp.org/pubs/afp/issues/2014/0201/p193.html

3. Latalski M, Danielewicz-Bromberek A, Fatyga M, Latalska M, Krober M, Zwolak P. Current insights into the aetiology of adolescent idiopathic scoliosis. *Arch Orthop Trauma Surg*. (2017) 137(10):1327–33. doi: 10.1007/s00402-017-2756-1

4. Zhang H, Guo C, Tang M, Liu S, Li J, Guo Q, et al. Prevalence of scoliosis among primary and middle school students in Mainland China: a systematic review and meta-analysis. *Spine (Phila Pa 1976)*. (2015) 40(1):41–9. doi: 10.1097/BRS.0000000000000664

5. Yang H, Jia X, Hai Y. Posterior minimally invasive scoliosis surgery versus the standard posterior approach for the management of adolescent idiopathic scoliosis: an updated meta-analysis. *J Orthop Surg Res*. (2022) 17(1):58. doi: 10.1186/s13018-022-02954-4

6. Sarwahi V, Galina JM, Hasan S, Atlas A, Ansorge A, De Bodman C, et al. Minimally invasive versus standard surgery in idiopathic scoliosis patients: a comparative study. *Spine (Phila Pa 1976)*. (2021) 46(19):1326–35. doi: 10.1097/BRS.0000000000004011

7. Alhammoud A, Alborno Y, Baco AM, Othman YA, Ogura Y, Steinhaus M, et al. Minimally invasive scoliosis surgery is a feasible option for management of idiopathic scoliosis and has equivalent outcomes to open surgery: a meta-analysis. *Global Spine J*. (2022) 12(3):483–92. doi: 10.1177/2192568220988267

8. Patil CG, Santarelli J, Lad SP, Ho C, Tian W, Boakye M. Inpatient complications, mortality, and discharge disposition after surgical correction of idiopathic scoliosis: a national perspective. *Spine J*. (2008) 8(6):904–10. doi: 10.1016/j.spinee.2008.02.002

9. Shan LQ, Skaggs DL, Lee C, Kissinger C, Myung KS. Intensive care unit versus hospital floor: a comparative study of postoperative management of patients with adolescent idiopathic scoliosis. *J Bone Joint Surg Am*. (2013) 95(7):e40. doi: 10.2106/JBJS.L.00467

10. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth*. (1997) 78(5):606–17. doi: 10.1093/bja/78.5.606

11. Zhuang CL, Ye XZ, Zhang XD, Chen BC, Yu Z. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: a meta-analysis of randomized controlled trials. *Dis Colon Rectum*. (2013) 56(5):667–78. doi: 10.1097/DCR.0b013e3182812842

12. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surg*. (2017) 152(3):292–8. doi: 10.1001/jamasurg.2016.4952

13. Ljungqvist O. ERAS—Enhanced recovery after surgery: moving evidence-based perioperative care to practice. *JPEN J Parenter Enteral Nutr*. (2014) 38(5):559–66. doi: 10.1177/0148607114523451

14. Powers J. Guidelines for preoperative fasting for hospitalized patients. *Crit Care Nurse*. (2017) 37(5):90–2. doi: 10.4037/ccn2017778

15. Sarin A, Chen LL, Wick EC. Enhanced recovery after surgery-preoperative fasting and glucose loading-A review. *J Surg Oncol*. (2017) 116(5):578–82. doi: 10.1002/jso.24810

16. Steenhagen E. Enhanced recovery after surgery: it's time to change practice!. *Nutr Clin Pract*. (2016) 31(1):18–29. doi: 10.1177/0884533615622640

17. Fletcher ND, Andras LM, Lazarus DE, Owen RJ, Geddes BJ, Cao J, et al. Use of a novel pathway for early discharge was associated with a 48% shorter length of stay after posterior spinal fusion for adolescent idiopathic scoliosis. *J Pediatr Orthop*. (2017) 37(2):92–7. doi: 10.1097/BPO.0000000000000601

18. Fletcher ND, Murphy JS, Austin TM, Bruce Jr. RW, Harris H, Bush P, et al. Short term outcomes of an enhanced recovery after surgery (ERAS) pathway versus a traditional discharge pathway after posterior spinal fusion for adolescent idiopathic scoliosis. *Spine Deform*. (2021) 9(4):1013–9. doi: 10.1007/s43390-020-00282-3

19. Gadiya AD, Koch JEJ, Patel MS, Shafafy M, Grevitt MP, Quraishi NA. Enhanced recovery after surgery (ERAS) in adolescent idiopathic scoliosis (AIS): a meta-analysis and systematic review. *Spine Deform*. (2021) 9(4):893–904. doi: 10.1007/s43390-021-00310-w

20. Koucheki R, Koyle M, Ibrahim GM, Nallet J, Lebel DE. Comparison of interventions and outcomes of enhanced recovery after surgery: a systematic review and meta-analysis of 2456 adolescent idiopathic scoliosis cases. *Eur Spine J*. (2021) 30(12):3457–72. doi: 10.1007/s00586-021-06984-0

21. Matsunaga S, Hayashi K, Naruo T, Nozoe S, Komiya S. Psychologic management of brace therapy for patients with idiopathic scoliosis. *Spine (Phila Pa 1976)*. (2005) 30(5):547–50. doi: 10.1097/01.brs.0000154648.53535.52

22. Talic G, Ostojic L, Bursac SN, Nozica-Radulovic T, Stevanovic-Papic D. Idiopathic scoliosis from psychopathological and mind-body medicine perspectives. *Psychiatr Danub*. (2016) 28(4):357–62. Available at: https://www.psychiatria-danubina.com/UserDocsImages/pdf/dnb_vol28_no4/dnb_vol28_no4_357.pdf

23. Duramaz A, Yilmaz S, Ziroglu N, Bursal Duramaz B, Kara T. The effect of deformity correction on psychiatric condition of the adolescent with adolescent idiopathic scoliosis. *Eur Spine J*. (2018) 27(9):2233–40. doi: 10.1007/s00586-018-5639-4

24. Rhodes L, Nash C, Moisan A, Scott DC, Barkoh K, Warner Jr. WC, et al. Does preoperative orientation and education alleviate anxiety in posterior spinal fusion patients? A prospective, randomized study. *J Pediatr Orthop*. (2015) 35(3):276–9. doi: 10.1097/BPO.0000000000000260

25. Lin JD, Lenke LG, Shillingford JN, Laratta JL, Tan LA, Fischer CR, et al. Safety of a high-dose tranexamic acid protocol in complex adult spinal deformity: analysis of 100 consecutive cases. *Spine Deform*. (2018) 6(2):189–94. doi: 10.1016/j.jspd.2017.08.007

26. Xie J, Lenke LG, Li T, Si Y, Zhao Z, Wang Y, et al. Preliminary investigation of high-dose tranexamic acid for controlling intraoperative blood loss in patients undergoing spine correction surgery. *Spine J*. (2015) 15(4):647–54. doi: 10.1016/j.spinee.2014.11.023

27. Luo W, Sun RX, Jiang H, Ma XL. The efficacy and safety of topical administration of tranexamic acid in spine surgery: a meta-analysis. *J Orthop Surg Res*. (2018) 13(1):96. doi: 10.1186/s13018-018-0815-0

28. Yerneni K, Burke JF, Tuchman A, Li XJ, Metz LN, Lehman Jr. RA, et al. Topical tranexamic acid in spinal surgery: a systematic review and meta-analysis. *J Clin Neurosci*. (2019) 61:114–9. doi: 10.1016/j.jocn.2018.10.121

29. Gelman D, Gelmanas A, Urbanaite D, Tamosiunas R, Sadauskas S, Bilskiene D, et al. Role of multimodal analgesia in the evolving enhanced recovery after surgery pathways. *Medicina (B Aires)*. (2018) 54(2):20. doi: 10.3390/medicina54020020

30. Beverly A, Kaye AD, Ljungqvist O, Urman RD. Essential elements of multimodal analgesia in enhanced recovery after surgery (ERAS) guidelines. *Anesthesiol Clin*. (2017) 35(2):e115–43. doi: 10.1016/j.anclin.2017.01.018

31. Yang YJ, Huang X, Gao XN, Xia B, Gao JB, Wang C, et al. An optimized enhanced recovery after surgery (ERAS) pathway improved patient care in adolescent idiopathic scoliosis surgery: a retrospective cohort study. *World Neurosurg*. (2021) 145:e224–32. doi: 10.1016/j.wneu.2020.10.009

32. Chiu C, Aleshi P, Esserman LJ, Inglis-Arkell C, Yap E, Whitlock EL, et al. Improved analgesia and reduced post-operative nausea and vomiting after implementation of an enhanced recovery after surgery (ERAS) pathway for total mastectomy. *BMC Anesthesiol*. (2018) 18(1):41. doi: 10.1186/s12871-018-0505-9

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Analysis of the surgical strategy and postoperative clinical effect of thoracic ossification of ligament flavum with dural ossification

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Purpose: Our research was designed to analyse the postoperative clinical results of patients suffering from single-segment thoracic ossification of the ligamentum flavum (TOLF) combined with dural ossification (DO) who underwent posterior laminar decompression and internal fixation.
Methods: This retrospective research included thirty-two patients who underwent surgery for ossifying the ligamentum flavum in the thoracic spine between January 2016 and January 2020. Patients were fallen into one group included patients with evidence of DO during surgery, and the other group included patients without evidence of DO. We assessed and compared general clinical characteristics and health-related outcomes before surgery and during follow-up.
Results: The DO group had a longer operation duration, more blood loss, and longer hospital stay (operation time: 94.75 ± 6.78 min vs. 80.00 ± 10.13 min, $p < 0.001$; blood loss: 331.67 ± 50.06 ml vs. 253.00 ± 48.24 ml, $p < 0.001$; length of hospital stay: 13.83 ± 2.76 days vs. 10.05 ± 2.33 days, $p < 0.001$).
Complications: There were 12 cases of cerebrospinal fluid leakage and 1 case of superficial wound infection in the DO group. However, the neurological recovery and health-associated quality of life (HRQOL) scores showed no statistically significant changes between the DO and non-DO groups ($p > 0.05$).
Conclusions: Posterior laminectomy and internal fixation combined with intraoperative resection of the ossified ligamentum flavum and dura is an efficient and relatively safe method for treating TOLF with DO, which can provide satisfactory results. Moreover, DO had no significant effect on postoperative neurological recovery and health-related quality of life scores.

KEYWORDS

single-Segment, ligamentum flavum ossification, dural ossification, posterior laminar decompression and internal fixation, postoperative clinical efficacy

Introduction

As a chronic degenerative disease of the thoracic spine, ossification of thoracic ligamentum flavum (TOLF) is characterized by heterotropic thoracic OLF (1). In thoracic myelopathy, the incidence is often lower than ossification of the posterior longitudinal ligament (OPLL) and higher than herniation of the nucleus pulposus

(HNP) (2). Patients with ossification of the thoracic ligament flavum are more common among East Asian populations, and the onset stage is mainly T9-T12. The prevalence of TOLF varies from 12.0% to 37.7% in different studies (3–5). To date, the pathogenesis of TOLF is not fully understood, and its main factors may be due to osteogenic cytokines (e.g., BMP) and mechanical stress (6–9).

For asymptomatic TOLF patients, surgery is rarely performed; however, thoracic spinal stenosis and spinal cord compression brought by TOLF are usually progressive and difficult to treat conservatively, requiring surgical treatment as soon as possible (10–14). When pressed, the ossified ligamentum flavum is in close contact with the dura mater, which may also ossify. The ossified ligamentum flavum and the dura fuse to form a hard-to-separate bone mass (9), which will undoubtedly enhance the difficulty of operation and the risk of complications such as spinal cord injury, CSF leakage and infection (15–17). Dural tearing of OLF is often considered to be caused by dural adhesion (DA) and dural ossification (DO) (16). Therefore, it is important to choose a more appropriate, safe and effective surgical approach. At the same time, there are relatively few studies on OLF with DO, and often the subjects with OLF are often multisegmental and the number of focal segments is not uniform (15, 16, 18, 19). In order to avoid the selective bias and reduce the error. So this paper includes patients with single-segment thoracic OLF with DO to further add to the analysis of the correlation between the surgical approach to TOLF with DO and postoperative clinical outcomes.

Materials and methods

Patient population

The institutional review board of our institution approved the current retrospective research, and a waiver of consent was acquired. The study evaluated patients receiving posterior lamina decompression and internal fixation for single-segment TOLF at our hospital between January 2016 and January 2020. Inclusion criteria: (1) TOLF diagnosed by CT or MRI with a single segmental lesion; (2) complete imaging and clinical data; and (3) patients followed up ≥24 months after surgery. Exclusion criteria: (1) history of thoracic or lumbar surgery; (2) previous history of infection, trauma, tumour, or congenital malformation; and (3) incomplete clinical records. Thirty-two patients (15 women and 17 men) were enrolled in the study. Patients were divided into two groups: the first group included 12 patients (9 females and 3 males) with intraoperative evidence of DO; the second group included 20 patients (6 females and 14 males) without evidence of DO.

Radiography

Preoperative radiology included general x-rays, computed tomography (CT), and magnetic resonance imaging (MRI). Preoperative plain x-ray exerted a significant effect on deciding the intraoperative site of TOLF. The location and extent of ossified spinal lesions were confirmed by performing CT scans. The location and number of segments influenced by TOLF, spinal cord engagement and any coexisting spinal disorders were determined by performing MRI.

Surgical procedure

All 32 patients were operated on by the same surgeon. Both groups underwent posterior laminar decompression and internal fixation. The related segment was preliminarily determined based on clinical manifestations and imaging examinations. Under general anaesthesia with endotracheal intubation, the patient was put in the prone position, and the surgical segment was positioned by fluoroscopy before the operation. The median incision on the posterior side was made with the lesion in the centre; the skin, subcutaneous tissue, and thoracolumbar dorsal fascia were incised in sequence; dissection of the paraspinal muscles occurred along the bilateral subperiosteal of the spinous process of the focal segment, stripped to the bilateral articular processes. Then, the spinous process and lamina were spread on both sides with a single hook to expose the intervertebral space of the focal segment. After the surgical incision was exposed and the decompression range was confirmed to be correct, the pedicle of the lesion segment was expanded to make a screw canal, the rongeur bit the spinous process of the corresponding vertebral body, the lamina and ligamentum flavum were removed with a drill, and the OLF in the lesion segment compressed the dura mater. A nerve peeler was used to assess the degree of adhesion of the OLF to the dura. In case of no adhesion, the OLF and lamina were pulled apart with forceps until the head and tail of the ossified tissue opened. One-third of the facet joints were opened outwards bilaterally, exposing the bilateral dura, which could be fully expanded. If there was dural ossification adhesion, the ossified dura mater was excised with a sharp knife, and the dural defect was repaired. Small dural tears were repaired with 4–0 silk sutures, and large dural defects were generally repaired with muscle flaps or adipose tissue. The dura mater was routinely covered with 1–2 layers of gelatine sponge. After thorough decompression, pedicle screws were placed on both sides of the lesion segment, connecting rods were placed on both sides, and nuts were fixed. The decompressed area was reflush with normal saline. A drainage tube was placed next to the median incision; instruments were counted; and the wound was sutured. According to the intraoperative exploration, there were 12 cases in the DO group and 20 in the non-DO group.

All patients were given routine antibiotic therapy within 3 days after surgery. Seven days after the surgery, the patients wore the brace to walk, and brace protection was kept for about 3 months.

Clinical evaluation

The following data of each patient were recorded: age, sex, BMI, smoking history, alcohol consumption history, history of hypertension, history of diabetes, duration of preoperative symptoms, estimated intraoperative blood loss (EBL), duration of surgery, length of hospital stay (LOH), compression segment of OLF, postoperative complications, the 36-item Short-Form Health Survey (SF-36) (20) and the modified Japanese Orthopaedic Association (mJOA) scoring system were adopted to assess the neurological improvement at preoperative and the last postoperative follow-up, with the highest mark of 11 indicating normal function, a total mark ≤3 indicating severe neurological impairment, 4–6 indicating moderate function, and ≥7 indicating mild function (12). The recovery rate (RR) was calculated as follows: (postoperative JOA score−preoperative JOA score)/(11− preoperative JOA score)× 100 (%), with excellent (RR ≥ 75%), good (75% > RR ≥ 50%), fair (50% > RR ≥ 25%), or poor (RR < 25%) (21).

Statistical analysis

The measurement data is shown as the mean ± standard deviation, and the counting data are totals and percentages. SPSS software (version 26.0; SPSS, Chicago, Illinois) was adopted to perform all analyses. The comparison of independent variables between the two groups was made by paired sample T test, independent sample T test, χ^2 test or Fisher's exact test, and Mann–Whitney U test. Multivariate logistic regression was used to analyse the factors associated with dural ossification in patients with single-segment thoracic OLF. Modified odds ratios (aORs) and 95% confidence intervals (CIs) were used. A p value of <0.05 was of statistical significance.

Results

Patient population

Thirty-two patients with single-level TOLF who underwent posterior lamina decompression and fusion and internal fixation were selected for the current study. Based on the intraoperative exploration, the patients were fallen into the DO group ($n = 12$) and the non-DO group ($n = 20$). Table 1 summarizes the features of these patients. There was no great diversity between the two groups in age, sex, BMI, number of smokers, number of drinkers, incidence of hypertension or diabetes. A typical case is shown in Figure 1.

TABLE 1 Patient Backgrounds.

	OLF with DO	OLF without DO	p-Value
No. of patients	12 (37.5%)	20 (62.5%)	
Age (year)	59.25 ± 9.97	57.20 ± 8.19	0.532
Sex			0.055
Male	3	12	
Female	9	8	
BMI (Kg/m^2)	26.42 ± 3.06	26.85 ± 3.72	0.736
Smoker (n)	1 (3.1%)	4 (12.5%)	0.626
Drinking (n)	1 (3.1%)	4 (12.5%)	0.626
Hypertension (n)	7 (21.9%)	6 (18.8%)	0.150
DM (n)	2 (6.2%)	1 (3.1%)	0.540

OLF, ossification of the ligament flavum; DO, dural ossification; BMI, body mass index; DM, diabetes mellitus.

Clinical characteristics

The mean preoperative symptom duration was 14.92 months in the DO group and 12.10 months in the non-DO group ($p = 0.527$). Compared with the non-DO group, the DO group had a longer operation duration, more blood loss, and longer hospital stay (operation time: 94.75 ± 6.78 min vs. 80.00 ± 10.13 min, $p < 0.001$; estimated blood loss: 331.67 ± 50.06 ml vs. 253.00 ± 48.24 ml, $p < 0.001$; length of stay: 13.83 ± 2.76 days vs. 10.05 ± 2.33 days, $p < 0.001$). Complications included cerebrospinal fluid leakage (DO group: 12, non-DO group: 0), spinal cord injury (DO group: 0, non-DO group: 0), superficial infection (DO group: 1, non-DO group: 0), and screw loosening/failure (DO group: 0, non-DO group: 0) (Table 2).

Distribution

Figure 2 shows the distribution of TOLF with DO. TOLF is more common in the lower thoracic vertebrae, with more than half (75%) of DO located in T9–T12.

Postoperative neurological recovery and health-related quality of life scores

Both the DO and non-DO groups showed significant improvements in most health-related outcomes (Table 3). The mean mJOA for all patients gradually improved from

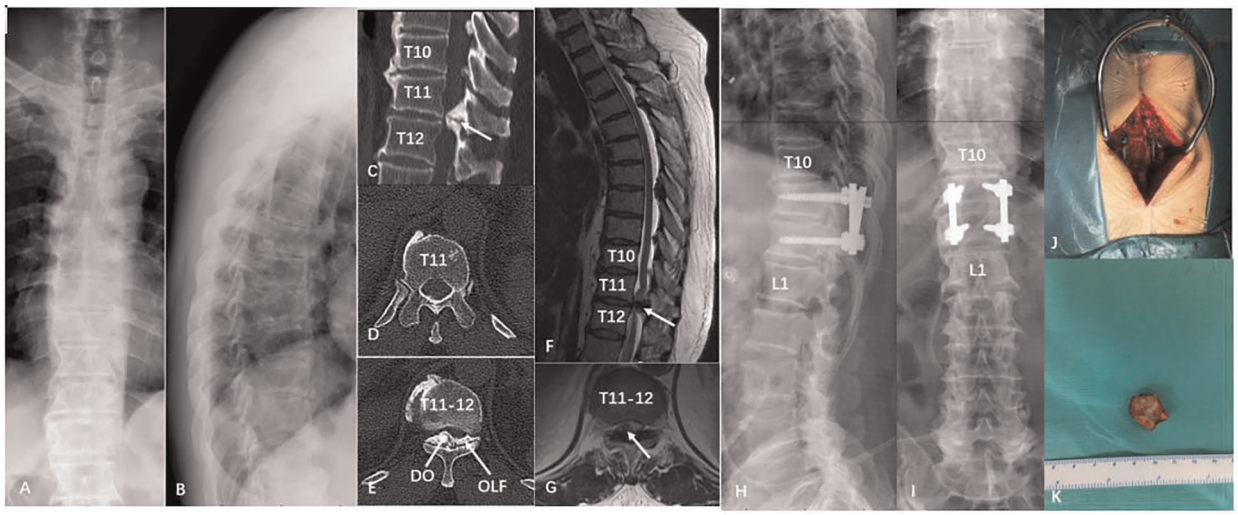

FIGURE 1
A patient with thoracic ossification of ligamentum flavum in T11/12. (A,B) Preoperative x-ray; (C–E) Preoperative coronal and axial section computed tomography scan; (F,G) Preoperative sagittal and axial section magnetic resonance imaging scan; (H,I) Postoperative x-ray; (J,K) Intraoperative photo and postoperative sample of ligamentum flavum ossification.

TABLE 2 Clinical characteristics.

	OLF with DO	OLF without DO	*p*-Value
Preoperative duration of symptoms (months)	14.92 ± 16.05	12.10 ± 13.79	0.527
Operation time (minutes)	89.17 ± 7.33	80.00 ± 10.13	<0.001[a]
LOH (days)	13.83 ± 2.76	10.05 ± 2.33	<0.001[a]
EBL (ml)	331.67 ± 50.06	253.00 ± 48.24	<0.001[a]
No. of complications (*n*)			
Leakage of cerebrospinal fluid	12	0	
Spinal cord injury	0	0	
Superficial infection	1	0	
Screw looseness/failure	0	0	

OLF, ossification of the ligament flavum; DO, dural ossification; IQR, interquartile range; LOH, length of hospitalization at postoperative; EBL, estimate blood loss.
[a]Statistically signifcant.

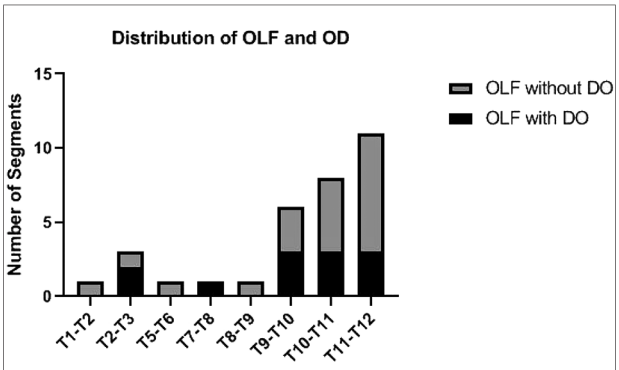

FIGURE 2
Distribution of OLF and DO: OLF was more common in the lower thoracic spine. More than half (75%) of the DO was located in T9-T12. DO, dural ossification; OLF, ossification of ligamentum flavum.

4.67 to 7.75 in the DO group and from 5.75 to 8.40 in the non-DO group. The RR was 50.83 ± 11.09% in the DO group and 53.15 ± 11.29% in the non-DO group. Although the mJOA score of the DO group was lower than that of the non-DO group, no great diversity was observed in neurological function recovery between the group with and without DO ($p > 0.05$). Surgical outcome: The DO group was excellent in 1 (8.3%) patient, good in 6 (50.0%) patients, fair in 5 (41.7%) patients and poor in 0 (0%) patients. The non-DO group was excellent in 1 (5.0%) patient, good in 12 (60.0%) patients, fair in 7 (35.0%) patients and poor in 0 (0%) patients (Table 2). Patients showed no worsened neurological symptoms. No great diversity was found in surgical effect between the two groups ($p = 0.860$). Preoperative spinal cord severity: in the DO group, 1 case was ≥7 (8.3%), 8 cases were 4–6 (66.7%), and 3 cases were ≤3 (25.0%). The non-DO group was divided into 5 patients (18.8%) with ≥7 scores, 14 patients (68.8%) with 4–6 scores, and 1 patient (12.5%) with ≤3 scores. No great diversity was observed in preoperative spinal cord severity between the group with and without DO ($p = 0.211$).

These clinical SF-36 outcomes showed no great diversities between the two groups during follow-up. For the SF-36, most measures, including social functioning, physical functioning, mental health, vitality, and general health, were

significantly enhanced compared to presurgery, with the exception of bodily pain in the DO group ($p > 0.05$) (Table 3).

TABLE 3 Comparison of postoperative neurological recovery and health related quality of life.

	OLF with DO	OLF without DO	*p*-Value
mJOA (score)			
Pre	4.67 ± 1.37	5.75 ± 1.55	0.055
F/U	7.75 ± 1.29	8.40 ± 1.23	0.166
Pre VS. F/U	<0.001[a]	<0.001[a]	
RR%	50.83 ± 11.09%	53.15 ± 11.29%	0.576
RR% classification (*n*)			0.860
Excellent	1	1	
Good	6	12	
Fair	5	7	
Poor	0	0	
Preoperative severity of myelopathy (*n*)			0.211
≥7	1	5	
4–6	8	14	
≤3	3	1	
SF-36			
Physical functioning			
Pre	50.83 ± 16.21	61.25 ± 17.53	0.105
F/U	74.58 ± 11.37	81.50 ± 10.77	0.095
Pre vs. F/U	<0.001[a]	<0.001[a]	
Social functioning			
Pre	46.08 ± 17.20	55.85 ± 18.33	0.146
F/U	69.00 ± 14.72	77.15 ± 12.39	0.103
Pre vs. F/U	<0.001[a]	<0.001[a]	
Bodily pain			
Pre	72.83 ± 7.16	73.50 ± 6.19	0.783
F/U	73.67 ± 7.33	75.10 ± 5.67	0.540
Pre vs. F/U	0.137	0.080	
Vitality			
Pre	45.42 ± 8.65	49.00 ± 8.37	0.256
F/U	60.83 ± 6.34	62.25 ± 5.50	0.510
Pre vs. F/U	<0.001[a]	<0.001[a]	
Mental health			
Pre	59.33 ± 8.32	58.45 ± 7.46	0.758
F/U	75.00 ± 6.12	73.80 ± 7.40	0.640
Pre vs. F/U	<0.001[a]	<0.001[a]	
General health			
Pre	50.83 ± 7.33	53.25 ± 7.83	0.394
F/U	68.33 ± 7.49	71.00 ± 6.61	0.301
Pre vs. F/U	<0.001[a]	<0.001[a]	

OLF, ossification of the ligament flavum; DO, dural ossification; mJOA, the modified Japanese Orthopaedic Association; RR, recovery rate; Pre, preoperative; F/U, follow up; SF-36, Short Form-36.
[a]Statistically signifcant.

Multivariate logistic regression analysis

The variables related to DO in univariate analysis were operation time, length of hospital stay, and estimated blood loss. According to multivariate logistic regression analysis, the length of hospital stay and estimated blood loss were independently correlated with the DO group (length of hospital stay OR = 2.201, $p = 0.024$, 95% CI 1.110–4.365; estimated blood loss: OR = 1.033, $p = 0.048$, 95% CI 1.000–1.067) (Table 4).

Postoperative complications

The ossified dura and ligamentum flavum were directly resected in 12 patients in the DO group, so the dura was torn during the operation, resulting in CSF leakage. Small dural lacerations were repaired with 4-0 silk sutures, while large dural defects were usually repaired with muscle flaps or adipose tissue. CSF leakage was stopped after delayed drainage tube removal and conservative treatment with local pressure was applied for 5∼7 days. One patient developed a superficial wound infection, which was cured after 1∼2 weeks of specific antibiotic treatment.

Discussion

Distribution and incidence of TOLF and DO

Patients with TOLF are more common among East Asian populations, and the onset stage is mainly T9–T12 (3–5). This research describes the surgical experience of 32 Chinese patients who underwent single-segment TOLF with or without DO. TOLF was found to be mostly in the lower thoracic spine, with more than half (75%) of the DO located in T9–T12, consistent with previous studies.

The exact incidence of dural ossification in thoracic ligamentum flavum ossification is unclear because most articles mainly describe multisegmental TOLF, few studies have been conducted to explain the combination of DO in

TABLE 4 Multivariate logistic regression analysis of OLF with DO.

Parameters	aOR	95%CI	*p*-Value
Operation time (minutes)	1.124	0.897–1.048	0.309
LOH (days)	1.033	1.000–1.067	0.048[a]
EBL (ml)	2.201	1.110–4.365	0.024[a]

aOR, adjusted odds ratio; CI, confdence interval; LOH, length of hospitalization at postoperative; EBL, estimate blood loss.
[a]Statistically signifcant.

single-segment TOLF alone, and it has been suggested that the occurrence of DO is rare. In contrast, among the 32 patients with segmental TOLF included in this paper, 12 patients had combined DO, the prevalence of which was 37.5%, which is like the outcomes reported by Muthukumar and Li et al (16, 18). The incidence of TOLF with DO is relatively high. However, studies on the distribution and prevalence of DO are inadequate, and the present study further provides an additional explanation.

Surgical procedure and results

Surgical decompression has been the best treatment option for compressive myelopathy because TOLF-associated myelopathy influences the posterior part of the spinal canal (11–13). However, surgical decompression for TOLF with DO has been treated in different ways. Sun et al (11). reported two surgical approaches for the treatment of TOLF combined with DO: dural opening and removal of ossification and floating of the ossified dura by drilling and thinning. Wang et al (12). compared posterior decompression laminectomy with or without internal fixation and fusion therapy, and both surgical methods are effective methods for the treatment of TOLF and can provide satisfactory clinical improvement. In patients with thoracic spinal myelopathy combined with specific types of TOLF, the use of percutaneous total endoscopic posterior decompression (PEPD) is feasible as the most minimally invasive spinal decompression procedure. However, this surgical approach makes it difficult to treat TOLF patients with DO (13). In combination with the surgical approach of the abovementioned studies, this study adopts posterior laminar decompression and internal fixation, and if DO is found intraoperatively, it is removed together with TOLF. The great advantage of this surgical approach is complete decompression and avoidance of ossification recurrence. Although the thoracic spine has restricted motion and better stability compared to the cervical and lumbar spine, our previous study on the clinical efficacy analysis of laminectomy alone and with instrumentation in treating TOLF showed better clinical outcomes and lower perioperative complication rates after internal fixation laminectomy (LI) compared to postoperative laminectomy alone (LA) (22). For insurance purposes, we performed internal fusion of the operated segments to increase stability and safety and reduce the risk of complications in the thoracic spine.

In this study, no diversity was found in the preoperative duration of symptoms between the two groups compared with those without DO, but the DO group had longer surgery, more bleeding, and longer hospital stays. Multivariate logistic regression analysis showed no great diversity in operative time between the two groups, while intraoperative blood loss and length of hospital stay were related to the DO group. If the OLF adhered to the DO during the operation, it would be difficult to separate, so it would need to be removed together; when removing the DO, the surgeon needs to be careful to avoid spinal cord injury because the removal of the DO will cause CSF leakage, so the amount of blood loss during the operation is greater. Postoperative treatment with local pressure and delayed drainage tube removal is needed, so the length of stay is also longer.

In our study, the postoperative recovery of the two groups was mainly good and fair. This is similar to the results of Wang et al (12)., who reported that 8 (24.2%) patients had excellent recovery, 22 (66.7%) patients recovered well, 2 (6%) patients recovered fairly and 1 (3%) patient recovered poorly. However, compared with the complications in other studies, the complications in this study were relatively simple. The main complication in our study was CSF leakage, which was related to the surgical method adopted in this study. During the operation, we found that patients with DO would be directly excised together with TOLF, so patients with DO would suffer from CSF leakage caused by dural defects. Recovery is usually possible with intraoperative repair of the defective dura and with conservative postoperative treatment.

Postoperative neurological recovery and health-related quality of life scores

There are relatively few reports on the postoperative neurological recovery and quality of life of single segment TOLF combined with DO. Aizawa et al (23). reported that poor recovery after TOLF may be related to inadequate decompression. Sun et al (15). displayed that despite a diversity in JOA scores between the two groups both preoperatively and postoperatively, with the DO group being lower than the non-DO group, there is no statistically significant diversity in neurological recovery between the two groups. In this study, there was no significant difference in postoperative neurological function recovery between the DO and non-DO groups. This may be related to adequate decompression found in both groups. Therefore, under sufficient decompression, DO was not associated with the recovery of neurological function after TOLF. All patients in our research underwent posterior laminar decompression and internal fixation. At the follow-up examination, a significant improvement was found in the preoperative and postoperative JOA scores. However, most of the recovery was incomplete, with a mean value of $50.83 \pm 11.09\%$ for the DO group and $53.15 \pm 11.29\%$ for the non-DO group for RR. Similar to previous reports (14, 24, 25).

No great diversity was found in HRQOL between the two groups during follow-up. Nevertheless, most postoperative indicators of patients, including social function, physical

function, mental health, vitality and overall health, were significantly enhanced, but the improvement in postoperative bodily pain showed no difference between the group with or without DO. This may be because DO mainly compresses the spinal cord centrally rather than the nerve roots, and therefore, the improvement in somatic pain is not significant.

There were some limitations in this study. First, the duration of follow-up was short, and longer follow-up is therefore needed to verify the outcomes of this research. Second, small sample size may affect the statistical results. Third, there may be some inherent biases in the retrospective study design and patient data. However, this article examines patients with single-segment TOLF with DO to add a more nuanced perspective on this type of disease.

Conclusions

Posterior laminectomy and internal fixation combined with intraoperative resection of the ossified ligamentum flavum and dura is an efficient and relatively safe method for treating TOLF with DO, which can provide satisfactory results. Moreover, DO had no significant effect on postoperative neurological recovery and health-related quality of life scores.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Third Afliated Hospital of Hebei Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

TL, SY and ST performed all the experiments and wrote the manuscript. TL, ZW and ZL participated in the collection of experimental data. WD and DY are responsible for document collection. DY and ZW conceived and designed the study. All the authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Li H, Jiang L, Dai L. Hormones and growth factors in the pathogenesis of spinal ligament ossification. *Eur Spine J*. (2007) 16:1075–84. doi: 10.1007/s00586-007-0356-4

2. Fong SY, Wong HK. Thoracic myelopathy secondary to ligamentum flavum ossification. *Ann Acad Med Singap*. (2004) 33:340–6.

3. Liang H, Liu G, Lu S, Chen S, Jiang D, Shi H, et al. Epidemiology of ossification of the spinal ligaments and associated factors in the Chinese population: a cross-sectional study of 2000 consecutive individuals. *BMC Musculoskelet Disord*. (2019) 20:253. doi: 10.1186/s12891-019-2569-1

4. Kim SI, Ha KY, Lee JW, Kim YH. Prevalence and related clinical factors of thoracic ossification of the ligamentum flavum-a computed tomography-based cross-sectional study. *Spine J*. (2018) 18:551–7. doi: 10.1016/j.spinee.2017.08.240

5. Fujimori T, Watabe T, Iwamoto Y, Hamada S, Iwasaki M, Oda T. Prevalence, concomitance, and distribution of ossification of the spinal ligaments. *Spine*. (2016) 41:1668–76. doi: 10.1097/BRS.0000000000001643

6. Ahn DK, Lee S, Moon SH, Boo KH, Chang BK, Lee JI. Ossification of the ligamentum flavum. *Asian Spine J*. (2014) 8:89. doi: 10.4184/asj.2014.8.1.89

7. Ha K, Seo J, Son I, Kim Y, Kim K. Thoracic myelopathy caused by ossification of the yellow ligament in patients with posterior instrumented lumbar fusion. *Eur Spine J*. (2012) 21:2443–9. doi: 10.1007/s00586-012-2413-x

8. Xu P, Wang C, He H, Xu G, Ye X. Spinal balance failure: a potential cause of spinal ligament ossification. *Med Hypotheses*. (2011) 76:908–10. doi: 10.1016/j.mehy.2011.03.006

9. Li B, Guo S, Qiu G, Li W, Liu Y, Zhao Y. A potential mechanism of dural ossification in ossification of ligamentum flavum. *Med Hypotheses*. (2016) 92:1–2. doi: 10.1016/j.mehy.2016.03.011

10. Inamasu J, Guiot BH. A review of factors predictive of surgical outcome for ossification of the ligamentum flavum of the thoracic spine. *J Neurosurg Spine*. (2006) 5:133–9. doi: 10.3171/spi.2006.5.2.133

11. Sun J, Zhang C, Ning G, Li Y, Li Y, Wang P, et al. Surgical strategies for ossified ligamentum flavum associated with dural ossification in thoracic spinal stenosis. *J Clin Neurosci*. (2014) 21:2102–6. doi: 10.1016/j.jocn.2014.02.027

12. Wang H, Wei F, Long H, Han G, Sribastav SS, Li Z, et al. Surgical outcome of thoracic myelopathy caused by ossification of ligamentum flavum. *J Clin Neurosci*. (2017) 45:83–8. doi: 10.1016/j.jocn.2017.07.008

13. Li X, An B, Gao H, Zhou C, Zhao X, Ma H, et al. Surgical results and prognostic factors following percutaneous full endoscopic posterior decompression for thoracic myelopathy caused by ossification of the ligamentum flavum. *Sci Rep*. (2020) 10:1305. doi: 10.1038/s41598-020-58198-x

14. Li M, Wang Z, Du J, Luo Z, Wang Z. Thoracic myelopathy caused by ossification of the ligamentum flavum: a retrospective study in Chinese patients. *J Spinal Disord Tech*. (2013) 26:E35–40. doi: 10.1097/BSD.0b013e31827ada68

15. Sun XZ, Chen ZQ, Qi Q, Guo ZQ, Sun CG, Li WS, et al. Diagnosis and treatment of ossification of the ligamentum flavum associated with dural ossification: clinical article. *J Neurosurg Spine*. (2011) 15:386–92. doi: 10.3171/2011.5.SPINE10748

16. Muthukumar N. Dural ossification in ossification of the ligamentum flavum: a preliminary report. *Spine (Phila Pa 1976)*. (2009) 34:2654–61. doi: 10.1097/BRS.0b013e3181b541c9

17. Sun X, Sun C, Liu X, Liu Z, Qi Q, Guo Z, et al. The frequency and treatment of dural tears and cerebrospinal fluid leakage in 266 patients with thoracic myelopathy caused by ossification of the ligamentum flavum. *Spine*. (2012) 37:E702–7. doi: 10.1097/BRS.0b013e31824586a8

18. Li B, Qiu G, Guo S, Li W, Li Y, Peng H, et al. Dural ossification associated with ossification of ligamentum flavum in the thoracic spine: a retrospective analysis. *Bmj Open*. (2016) 6:e13887. doi: 10.1136/bmjopen-2016-013887

19. Ju JH, Kim SJ, Kim KH, Ryu DS, Park JY, Chin DK, et al. Clinical relation among dural adhesion, dural ossification, and dural laceration in the removal of ossification of the ligamentum flavum. *Spine J*. (2018) 18:747–54. doi: 10.1016/j.spinee.2017.09.006

20. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 health survey for use in Japan. *J Clin Epidemiol*. (1998) 51:1037–44. doi: https://doi.org/10.1016/S0895-4356(98)00095-X

21. Li M, Meng H, Du J, Tao H, Luo Z, Wang Z. Management of thoracic myelopathy caused by ossification of the posterior longitudinal ligament combined with ossification of the ligamentum flavum—a retrospective study. *Spine J*. (2012) 12:1093–102. doi: 10.1016/j.spinee.2012.10.022

22. Wang Z, Wang Z, Zhou Y, Sun J, Ding W, Yang D. Clinical effect analysis of laminectomy alone and laminectomy with instrumentation in the treatment of TOLF. *Bmc Musculoskel Dis*. (2021) 22:667. doi: 10.1186/s12891-021-04564-3

23. Aizawa T, Sato T, Sasaki H, Matsumoto F, Morozumi N, Kusakabe T, et al. Results of surgical treatment for thoracic myelopathy: minimum 2-year follow-up study in 132 patients. *J Neurosurg Spine*. (2007) 7:13–20. doi: 10.3171/SPI-07/07/013

24. Yu S, Wu D, Li F, Hou T. Surgical results and prognostic factors for thoracic myelopathy caused by ossification of ligamentum flavum: posterior surgery by laminectomy. *Acta Neurochir*. (2013) 155:1169–77. doi: 10.1007/s00701-013-1694-0

25. Li Z, Ren D, Zhao Y, Hou S, Li L, Yu S, et al. Clinical characteristics and surgical outcome of thoracic myelopathy caused by ossification of the ligamentum flavum: a retrospective analysis of 85 cases. *Spinal Cord*. (2016) 54:188–96. doi: 10.1038/sc.2015.139

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Evaluating bone quality and asymmetrical aplasia of the thoracic vertebral body in Lenke 1A adolescent idiopathic scoliosis using hounsfield units

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Study Design: Retrospective analysis.
Objective: To evaluate bone quality and investigate asymmetrical development of the thoracic vertebral body in adolescent idiopathic scoliosis (AIS) based on Hounsfield unit (HU) measurements obtained from computed-tomography (CT) scans.
Summary of Background Data: HU value demonstrated higher reliability and accuracy than the traditional method, indicating that they could be used to individually evaluate and effectively assess the bone quality of every vertebra in the CT films.
Methods: Total 30 AIS patients classified as Lenke Type 1A and 30 paired controls were included in this study. Regions of interest for HU value were measured on three horizontal images of the thoracic vertebrae. HU measurements of the whole vertebral body in each vertebra were obtained. Using HU value, we separately measured the concave and convex sides of each vertebral body in patients' group, as well as within the left and right sides in controls.
Results: In controls, the mean HU value of T1–T12 thoracic vertebral bodies was 240.03 ± 39.77, with no statistical differences among different levels. As for AIS patients, in the structural curve, the apical region had a significantly lower HU compared with the other regions, and asymmetrical change was found between the concave and convex sides, most significantly in the apical region. In the non-structural curve, the average HU value was 254.99 ± 44.48, and no significant difference was found either among the different levels of vertebrae or between the concave and convex sides.
Conclusions: Abnormal and asymmetrical changes in bone quality of the thoracic vertebral body in patients with Lenke 1A AIS were indicated. Low bone quality in the convex side of the structural curve indicated stronger internal fixation in surgery to correct the deformity.

Abbreviations
AIS, adolescent idiopathic scoliosis; HU, hounsfield units; CT, computed-tomography; UEV, upper end vertebra; LEV, lower end vertebra; AV, apex vertebra; CSVL, central sacral vertical line.

KEYWORDS

adolescent idiopathic scoliosis, bone quality, Hounsfield units, bone mineral density, spine

Background

Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional deformity of the spine, characterized by lateral spinal curvature with a Cobb angle exceeding 10 degrees (1–4). The incidence of AIS is currently about 2%–3%, making it the most common spinal deformity in children (5). When untreated, progressive AIS is associated with restrictive lung disease, pain, severe deformity, and even mental health problems, posing a serious burden to the family and society (6, 7).

The causes of AIS are complex, including genetics, abnormal nervous-system function, endocrine abnormalities, biomechanical changes, and abnormal vertebral development (8, 9). Low bone quality had been found in AIS patients compared with healthy controls (10–17). AIS patients were reported to have poorer bone mineral density in bilateral femoral neck and central skeleton compared with controls (13, 14). Asymmetrical development of the vertebrae was also considered to be an important factor in the pathogenesis of AIS. Previous studies had established that longitudinal growth of the vertebral body in AIS patients was disproportionate (1, 9, 18). Asymmetrical changes in the width of thoracic pedicle in AIS patients vs. controls had also been found (19). However, only a few studies have evaluated the bone quality of the vertebral body in AIS patients.

The Hounsfield unit (HU) is a dimensionless unit generated from computed-tomography(CT) scans, which is obtained by linear transformation of the measured attenuation coefficient. HU value is considered an effective benchmark of bone quality (20–22). Compared with traditional methods, HU value permits more effective evaluation of the bone quality of every vertebral body, but it does not register the abdominal calcification that dual-energy x-ray absorptiometry scans cannot distinguish from attenuation (23–26). The purpose of our study is to evaluate bone quality and investigate asymmetrical development of the thoracic vertebral bodies based on HU measurements obtained from CT scans.

Material and methods

Subjects

Inclusion criteria for AIS patients were as follows: (1) careful screening to ensure that their scoliosis was idiopathic and classified as Lenke 1A (27); and (2) preoperative radiographs and CT images were available on file. Exclusion criteria for AIS patients were as follows: (1) proven or even suspected congenital, muscular, neurological, or hormonal cause of scoliosis; (2) receipt of spinal surgery or brace treatment; and (3) spinal infection or metabolic disease that could affect the accuracy of HU measurement. Inclusion criteria for controls were as follows: (1) gender, age, weight and height matched with patients; (2) clinical indications for CT (such as pneumonia) but no abnormal skeletal system findings assessed by a radiologist; and (3) no spinal bone infection or metabolic disease. Ultimately, 30 Lenke 1A AIS patients and 30 paired controls were included in our study. Therefore, total 30 structural curves (main thoracic curves) and 30 non-structural curves (proximal thoracic curves) were measured. Their demographic data were shown in **Table 1**.

Data collection and assessment

Demographic data, including age (year), height (cm), weight (kg) and body mass index (BMI; kg/m^2) were collected. Standard whole-spine x-ray in the anteroposterior (AP), lateral and bending-position views were used. As shown in **Figure 1**, measurement of radiographic data mainly relied on the patient's whole-spine AP x-ray. We measured the Cobb angle and differentiated structural from non-structural curves by Lenke classification (27). A total 30 structural curves (main thoracic curves) and 30 non-structural curves (proximal thoracic curves) were measured. The apex vertebra (AV) was defined as the vertebral body farthest from the center sacral vertical line (CSVL). If the intervertebral disc was located at the farthest position, we collected data from the upper and lower vertebrae at the same time, bringing two apical vertebrae into one apical region. AV-1 was defined as the upper vertebra adjacent to AV; AV-2 was defined as the upper vertebra adjacent to AV-1; AV + 1 was defined as the lower vertebra adjacent to AV; AV + 2 was defined as the lower vertebra adjacent to AV + 1. The upper-end and lower-end vertebrae (UEV, LEV) were defined as the vertebrae with the largest inclinations at the head and at the tail of the curve respectively.

TABLE 1 Demographic data of AIS patients and controls.

Demographic	Patients	Control subjects	*P*-value
Number	30	30	–
Gender	Female	Female	–
Age (years)	17.6 ± 3.40	17.8 ± 3.50	0.82
Height (cm)	156.3 ± 4.60	157.9 ± 2.90	0.13
Weight (kg)	44.8 ± 4.60	46.5 ± 3.40	0.08
BMI (kg/m^2)	18.3 ± 1.40	18.4 ± 1.40	0.71
Cobb angle (°)	56.70 ± 20.20	–	–

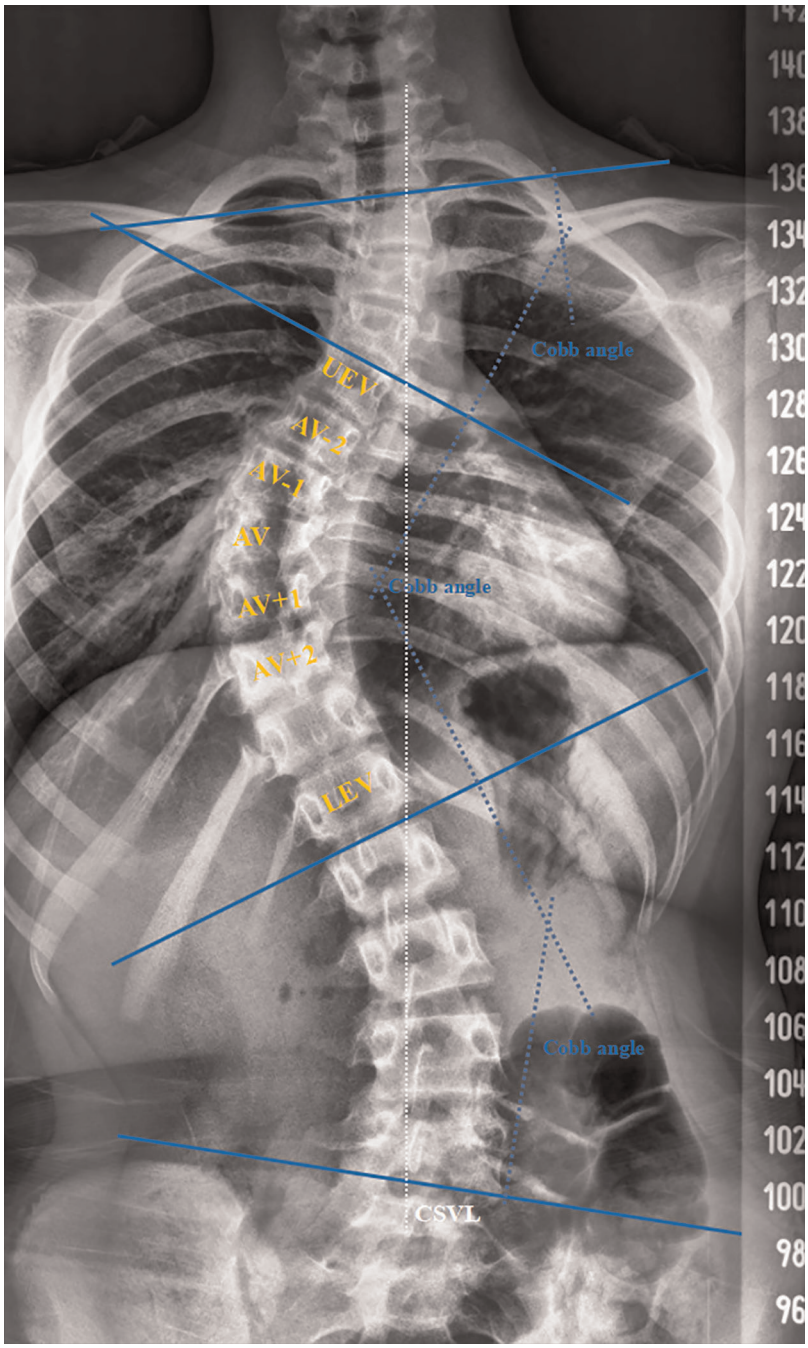

FIGURE 1
Measurement diagram of the AP x-ray of the whole spine. Three Cobb angles, including the structural and non-structural curves, was shown. The AV was defined as the vertebral body farthest from the CSVL. If the intervertebral disc was located at the farthest position, we collected data from the upper and lower vertebrae at the same time, bringing two apical vertebrae into one apical region. AV-1 was defined as the upper vertebra adjacent to AV; AV-2 was defined as the upper vertebra adjacent to AV-1; AV + 1 was defined as the lower vertebra adjacent to AV; AV + 2 was defined as the lower vertebra adjacent to AV + 1. The UEV and LEV were defined as the vertebrae with the largest inclinations at the head and at the tail of the curve respectively.

CT scans were performed on a 64-slice scanner (Toshiba Aquilion1 64-slice; Toshiba Medical Systems Corporation, Otawara-shi, Japan) at 120 kV and less than 200 mA, with a slice thickness of 0.5 mm and a resultant average radiation burden less than 10 mGy to reduce radiation exposure. During the scans, protections of sensitive glands were performed. Before taking measurements, 3D reconstruction of the CT film was performed and three suitable slices were

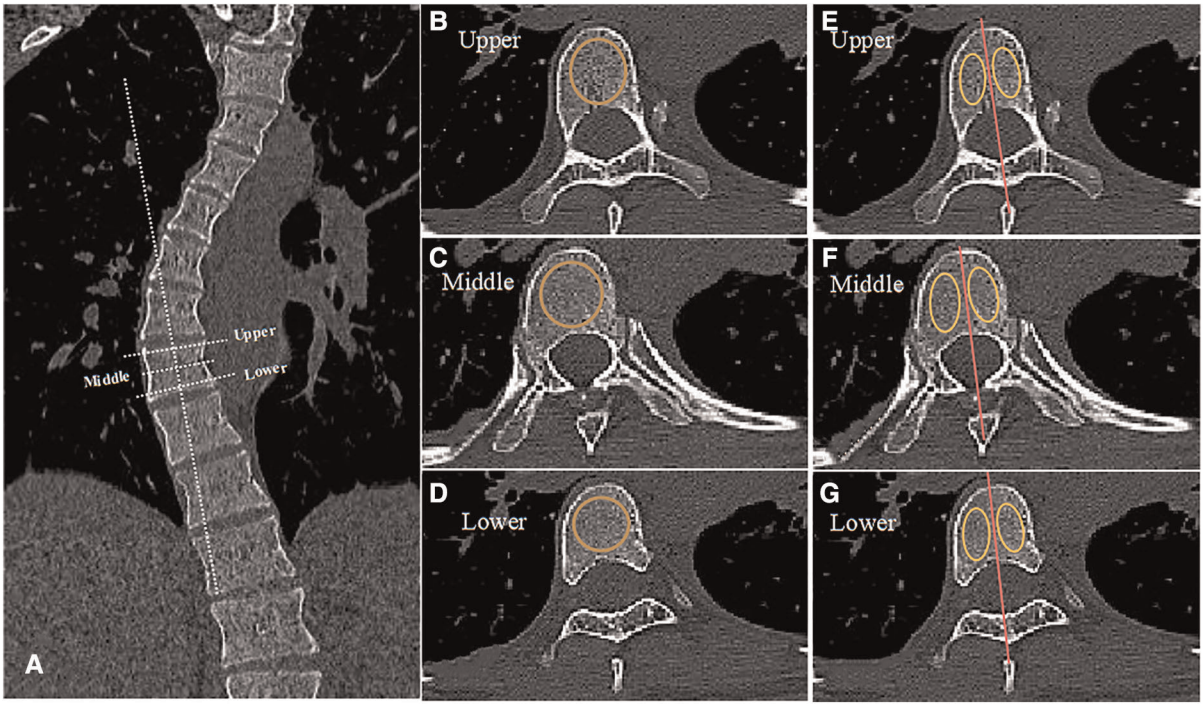

FIGURE 2
Measurement diagram of HU value. (A) The dashed white line represents the appropriate angulation on a reformatted workstation for obtaining the transverse CT image for each vertebra, displaying different planes. (B–D) The dotted orange circle represents the area we focused on in three different planes of the same vertebra: below the upper endplate of the vertebra, in the middle of the vertebra, and above the lower endplate of the vertebra. (E–G) We drew the red line to divide the vertebra into concave and convex sides through the spinous process as shown. The solid yellow circle represents the area we focused on for HU value measurement.

obtained, as shown in Figure 2. The dashed white line represented the appropriate angulation on a reformatted workstation for obtaining the transverse CT image for each vertebra. HU value of the whole vertebral bodies, the concave and convex sides were separately measured at three locations of the vertebra on three horizontal planes: below the upper endplate of the vertebra, in the middle of the vertebra, and above the lower endplate of the vertebra. The solid yellow circle represented the areas that we focused on, which were used for HU measurement. The HU value of each vertebra was defined as the average HU value for all three planes. For each measurement, we drew the largest possible elliptical region of interest, excluding the cortical margins to prevent volume averaging.

Statistical analysis

We analyzed all data using GraphPad Prism version 8.0.1 (GraphPad Software, San Diego, CA, USA) and SPSS version 20.0 (IBM Corp., Armonk, NY, USA). HU value among different vertebrae and degrees of variation in different regions were compared *via* one-way analysis of variance (ANOVA) followed by Bonferroni's *post hoc* test. We compared HU value between the concave and convex sides of each vertebra using the paired *t* test. The results were considered to be significant when two-way $P < 0.05$, and the range of agreement was defined as mean ± standard deviations (SDs).

Results

Vertebral-body bone quality in the apical region of the structural curve was decreased in AIS patients

A total of 30 patients with Lenke 1A AIS and 30 paired controls were included in our study. The HU value of T1-T12 thoracic vertebral bodies in controls were shown in Table 2. There was no significant difference among the different levels (Figure 3A). As for AIS patients, the HU value in the apical region of the structural curve was significantly lower than that in other regions (Table 3 and Figure 3B), but in the non-structural curve we found no significant difference among HU value in different regions (Table 3 and Figure 3B). Besides, we found that the average HU value of structural curve in

Lenke 1A AIS patients was lower when compared to controls (Supplementary Figure S1). Meanwhile, we compared the average HU value between the structural and non-structural curves in AIS patients, and found that there was a statistically significant decrease in the regions of structural curves (Supplementary Figure S2).

Asymmetrical changes in vertebral-body bone quality in AIS patients

HU values were measured within the left and right sides of thoracic vertebral bodies in controls and within the concave and convex sides of thoracic vertebral bodies in AIS patients. As shown in Figure 4A, no significant difference in HU value was found between the left and right sides in controls (Figure 4A). As for AIS patients, the structural curve showed significant asymmetrical changes in HU values between the concave and convex sides in the AV-2, AV-1, AV, AV + 1, and AV + 2 regions but not in the UEV or LEV region. In the non-structural curve, no significant difference was found between the concave and convex sides in the UEV, AV-1, AV, AV + 1, or LEV region (Figure 4B). Besides, HU values in convex were lower than that in concave in AIS patient, and this difference could be more obvious in the apical region (Figure 4C).

In AIS patients, asymmetrical changes in vertebral-body bone quality were most significant in the apical region

To compare the degree of asymmetrical change between the concave and convex sides in different regions of AIS patients, we calculated the variation degree of bone quality (VDBQ) as follows:

$$\text{VDBQ}\ (\%) = \Sigma[(\text{HU value of concave side} - \text{convex side})\ \text{convex side}]\text{number of vertebrae involved in the region}$$

As shown in Table 4 and Figure 5, we found that the VDBQ (%) in AV (26.82 ± 12.73) was higher than that in AV ± 2 (15.71 ± 12.24), UEV (7.28 ± 12.06) and LEV (3.30 ± 13.70), but we found no significant difference between AV (26.82 ± 12.73) and AV ± 1 (24.69 ± 12.73). The VDBQ in AV

TABLE 2 Hu value in controls.

Level	HU value
T-1	268.38 ± 49.56
T-2	251.26 ± 39.42
T-3	230.34 ± 30.90
T-4	231.22 ± 34.25
T-5	236.75 ± 36.98
T-6	229.96 ± 38.66
T-7	237.41 ± 41.41
T-8	235.27 ± 35.56
T-9	243.38 ± 46.11
T-10	241.31 ± 39.01
T-11	237.59 ± 36.24
T-12	237.50 ± 36.36
Average	240.03 ± 39.77

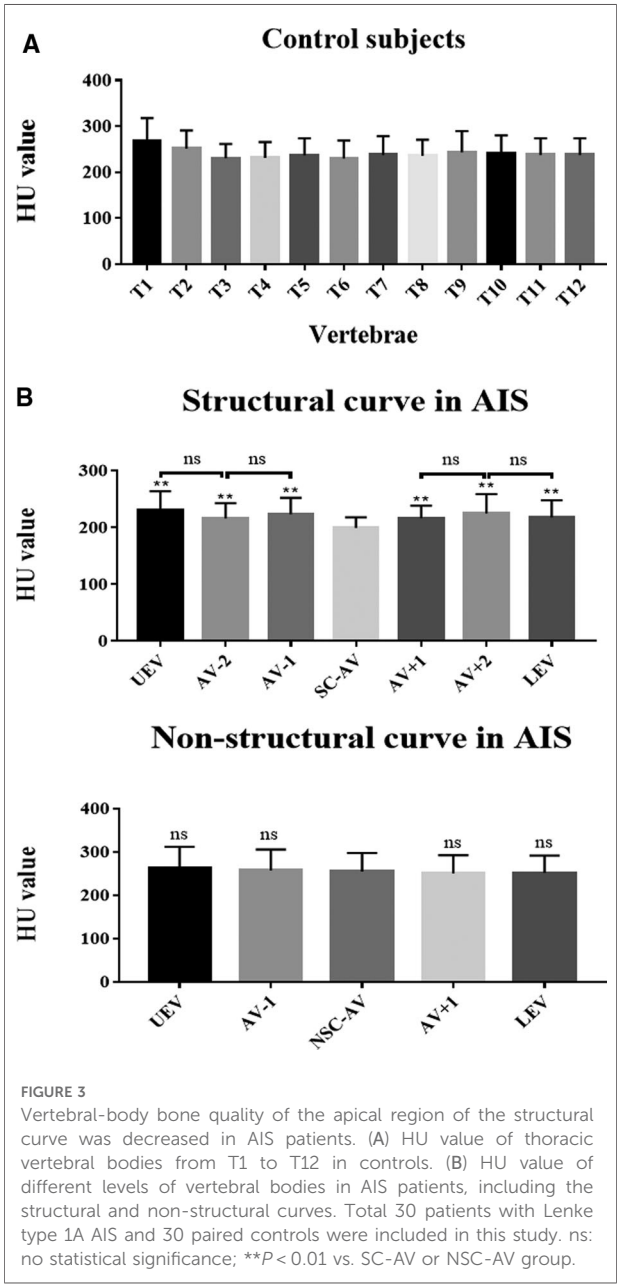

FIGURE 3
Vertebral-body bone quality of the apical region of the structural curve was decreased in AIS patients. (A) HU value of thoracic vertebral bodies from T1 to T12 in controls. (B) HU value of different levels of vertebral bodies in AIS patients, including the structural and non-structural curves. Total 30 patients with Lenke type 1A AIS and 30 paired controls were included in this study. ns: no statistical significance; $^{**}P < 0.01$ vs. SC-AV or NSC-AV group.

TABLE 3 Hu value in AIS patients. .

Structural curve		Non-structural curve	
Level	HU value	Level	HU value
UEV	229.60 ± 34.28**	UEV	261.41 ± 50.36
AV-2	215.75 ± 26.99**	AV-1	256.73 ± 48.92
AV-1	223.23 ± 29.03**	AV	254.85 ± 42.35
AV	199.40 ± 18.26	AV + 1	250.57 ± 41.93
AV + 1	216.38 ± 22.11**	LEV	251.42 ± 40.05
AV + 2	224.86 ± 33.92**	Average	254.99 ± 44.48
LEV	217.75 ± 30.09**		

UEV means upper-end vertebra; AV-2 means upper vertebra adjacent to AV-1; AV-1 means upper vertebra adjacent to AV; AV means apex vertebra; AV + 1 means lower vertebra adjacent to AV; AV + 2 means lower vertebra adjacent to AV + 1; LEV means lower-end vertebra. **$P < 0.01$ vs. AV group.

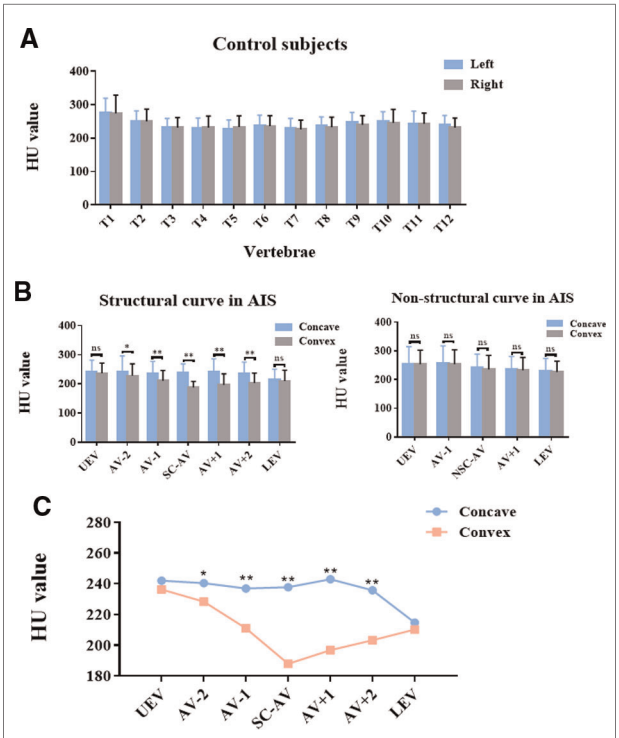

FIGURE 4
Asymmetrical changes in vertebral-body bone quality in AIS patients. (A) HU value on the left and right sides of thoracic vertebral bodies in controls. (B) HU value on the concave and convex sides of thoracic vertebral bodies in different regions of the structural and non-structural curves in AIS patients. (C) Comparison of HU values within the concave and convex sides of thoracic vertebral bodies in different regions of the structural curve in AIS patients. Total 30 patients with Lenke type 1A AIS and 30 paired controls were included in this study. ns: no statistical significance; *$P < 0.05$ vs. convex group, **$P < 0.01$ vs. convex group.

± 1 (24.69 ± 12.73) was higher than that in AV ± 2 (15.71 ± 12.24), but no statistical difference among AV ± 2 (15.71 ± 12.24), UEV (7.28 ± 12.06) and LEV (3.30 ± 13.70) was found.

TABLE 4 Variation degree of bone quality in different regions of the structural curve in AIS patients.

Region	Variation degree (%)
AV	26.82 ± 12.73
AV ± 1	24.69 ± 12.73
AV ± 2	15.71 ± 12.24*,***
UEV	7.28 ± 12.06**
LEV	3.30 ± 13.70**

AV, apex vertebra; AV + 1, vertebra adjacent to AV; AV + 2, vertebra adjacent to AV + 1; UEV, upper-end vertebra; LEV, lower-end vertebra. *$P < 0.05$ vs. AV group; **$P < 0.01$ vs. AV group; ***$P < 0.05$ vs. AV ± 1 group.

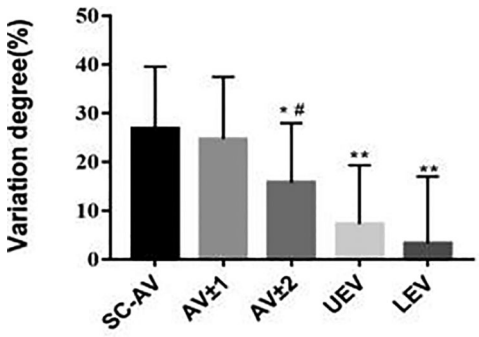

FIGURE 5
In AIS patients, asymmetrical changes in vertebral-body bone quality were most significant in the apical region. Comparison of variation degree of bone quality in different regions of the structural curve in AIS patients. Total 30 patients with Lenke type 1A AIS and 30 paired controls were included in this study. *$P < 0.05$ vs. SC-AV group, **$P < 0.01$ vs. AV group, $^{\#}P < 0.05$ vs. AV ± 1 group.

Discussion

HU value was considered to be a effective method to evaluate bone quality in many studies. Correlations of HU value with *T*-score have been reported, and it has been proposed as the primary criterion in the diagnosis of osteoporosis when the HU value at the L1 vertebral body was less than 110 (28, 29). Christensen et al. found that HU value at the proximal femur could be used to predict the risk of fracture, and a decline in HU value was closely related to the occurrence of fracture (30). HU value shows higher reliability and accuracy than traditional methods and can be used to evaluate the bone quality effectively and individually of every vertebra included in CT films (23–25).

In our study, we found that vertebral-body bone quality in the apical region of the structural curve in AIS patients was decreased when compared to the controls. Abnormal bone metabolism was considered to be an important factor in the pathogenesis of AIS (1, 9, 31). In a previous study, a significant difference in the bone mineral density between patients with AIS and non-affected paired controls was

proven (32). Li et al. reported that AIS patients had poorer bone mineral density of the bilateral femoral neck than controls (13), and lower bone volume from the histological sections of the spinous process taken from AIS patients was found (33). Besides, Almomen et al. reported that female AIS patients with greater higher Cobb angles exhibited a significantly higher risk of low bone density (34). Our study is the first to use the HU value obtained from CT scans to evaluate the bone quality of vertebral bodies in AIS patients.

The asymmetric bony growth of vertebral bodies in AIS patients had been previously reported (19, 35–39). In our study, we evaluated bone quality using HU value and found the asymmetrical bone quality changes between the concave and convex sides of thoracic vertebral bodies in the AV-2, AV-1, AV, AV + 1, and AV + 2 regions of the structural curve in AIS patients. Besides, the bone quality of the convex side of vertebral bodies was significantly lower than that in the concave side. In addition, asymmetrical change in vertebral-body bone quality was most significant in the apical region. Although the mechanism was still unclear, it suggested that there was an asymmetrical change during the development of the skeleton system in AIS patients. In a previous study, the average width of pedicle was smaller in the non-structural curve than that in the structural curve in AIS patients (19). In our study, asymmetric change between the concave and convex sides was found in the region of structural curve but no significant difference in non-structural curve with a *p*-value larger than 0.05. The non-structural curve referred to the temporary and compensable curve without structural changes, which indicated that the change existed primarily in the structural curve. Moreover, it remains elusive whether a significant difference between concave and convex sides would be shown with a larger Cobb angle of the non-structural curve in AIS patients, and further studies are needed.

In surgery to correct AIS deformities, choosing the suitable screw could be important (40, 41). As known, the length and width of pedicle were generally considered to be the major factors in the choice of pedicle screw fixation during a deformity correction surgery (42, 43). Meanwhile, in previous studies, the thickness of cortical bone of pedicle had been reported to be an important factor for enhancing holding force of pedicle screw, and the screw stability depends on the structural characteristics of the pedicle (44–46). Besides, the quality of cancellous bone was also considered to be an influencing factor on the holding force of pedicle screws. Lower bone mass was considered as an affected factor of pedicle screw loosening, and regional HU value of the screw trajectory could be a strong predictor of long-term screw fixation (47, 48). Zou et al. reported that HU value measured on CT was an independent predictor for pedicle screw loosening, and lower HU value was significantly correlated with higher risk of screw loosening (49, 50). Another study showed that anti-osteoporosis treatment could achieve strong pedicle screw fixation effectively with an increase in bone mineral density around the screw assessed by QCT (51).Our results found lower bone quality in the convex vs. the concave side in the AV, AV ± 1, and AV ± 2 regions of the structural curve in AIS patients, suggesting that surgeons should exercise increased vigilance when selecting pedicle screw dimensions, a thicker and longer pedicle screw should be better to provide stronger holding force for internal fixation on the convex side during surgery when the width and length were suitable.

This study had the following limitations. Our results can not be applied to males because only female subjects were included in our study. Additionally, only Lenke 1A AIS patients were included. It would be ideal if we could repeat the same measurements in AIS patients of all other Lenke types. Furthermore, this is a single-center study and the entire study cohort was recruited from the southern region of China, which limits generalizability to other geographic locations, including the differences of temperature and elevation.

Conclusions

Based on HU value obtained from CT scans of AIS patients, the bone quality of vertebral bodies in the apical region of the structural curve was significantly decreased compared with other regions, and asymmetrical changes were found between the concave and convex sides of vertebral bodies. Further, we found that the asymmetry was most significant in the apical region. In terms of application, thicker and longer pedicle screws should be chosen to provide stronger holding force for internal fixation on the convex side during surgery.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

Our study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University (Guangzhou, China). All methods were carried out in accordance with relevant guidelines and regulations, and informed consent was obtained from all subjects and/or their legal guardians.

Author contributions

WJG and DSH designed the experiments. TQC, WJH, YP, YL, JCQ, XJQ, PFL, SGL, and AJL conducted the experiments. TQC, WJH, and YP acquired the data. TQC, WJH, YP, WJG, and DSH analyzed the data. TQC, WJG, and DSH wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1028873/full#supplementary-material.

References

1. Pérez-Machado G, Berenguer-Pascual E, Bovea-Marco M, Rubio-Belmar PA, García-López E, Garzón MJ, et al. From genetics to epigenetics to unravel the etiology of adolescent idiopathic scoliosis. *Bone*. (2020) 140:115563. doi: 10.1016/j.bone.2020.115563

2. Wise CA, Sepich D, Ushiki A, Khanshour AM, Kidane YH, Makki N, et al. The cartilage matrisome in adolescent idiopathic scoliosis. *Bone Res*. (2020) 8:13. doi: 10.1038/s41413-020-0089-0

3. Cheng JC, Castelein RM, Chu WC, Danielsson AJ, Dobbs MB, Grivas TB, et al. Adolescent idiopathic scoliosis. *Nat Rev Dis Primers*. (2015) 1:15030. doi: 10.1038/nrdp.2015.30

4. Dunn J, Henrikson NB, Morrison CC, Blasi PR, Nguyen M, Lin JS. Screening for adolescent idiopathic scoliosis: evidence report and systematic review for the US preventive services task force. *JAMA*. (2018) 319(2):173–87. doi: 10.1001/jama.2017.11669

5. de Mendonça RGM, Sawyer JR, Kelly DM. Complications after surgical treatment of adolescent idiopathic scoliosis. *Orthop Clin North Am*. (2016) 47 (2):395–403. doi: 10.1016/j.ocl.2015.09.012

6. Glassman SD, Carreon LY, Shaffrey CI, Polly DW, Ondra SL, Berven SH, et al. The costs and benefits of nonoperative management for adult scoliosis. *Spine*. (2010) 35(5):578–82. doi: 10.1097/BRS.0b013e3181b0f2f8

7. Marya S, Tambe AD, Millner PA, Tsirikos AI. Adolescent idiopathic scoliosis: a review of aetiological theories of a multifactorial disease. *Bone Joint J*. (2022) 104-B(8):915–21. doi: 10.1302/0301-620X.104B8.BJJ-2021-1638.R1

8. Weinstein SL, Dolan LA, Cheng JC, Danielsson A, Morcuende JA. "Adolescent idiopathic scoliosis. *Lancet (London, England)*. (2008) 371 (9623):1527–37. doi: 10.1016/S0140-6736(08)60658-3

9. Peng Y, Wang SR, Qiu GX, Zhang JG, Zhuang QY. Research progress on the etiology and pathogenesis of adolescent idiopathic scoliosis. *Chin Med J*. (2020) 133(4):483–93. doi: 10.1097/CM9.0000000000000652

10. Alsiddiky A, Alfadhil R, Al-Aqel M, Ababtain N, Almajed N, Bakarman K, et al. Assessment of serum vitamin D levels in surgical adolescent idiopathic scoliosis patients. *BMC Pediatr*. (2020) 20(1):202. doi: 10.1186/s12887-020-02114-9

11. Cațan L, Cerbu S, Amaricai E, Suciu O, Horhat DI, Popoiu CM, et al. Assessment of static plantar pressure, stabilometry, vitamin D and bone mineral density in female adolescents with moderate idiopathic scoliosis. *Int J Environ Res Public Health*. (2020) 17(6):2167. doi: 10.3390/ijerph17062167

12. Zhang J, Wang Y, Cheng KL, Cheuk K, Lam TP, Hung ALH, et al. Association of higher bone turnover with risk of curve progression in adolescent idiopathic scoliosis. *Bone*. (2021) 143:115655. doi: 10.1016/j.bone.2020.115655

13. Li X, Hung VWY, Yu FWP, Hung ALH, Ng BKW, Cheng JCY, et al. Persistent low-normal bone mineral density in adolescent idiopathic scoliosis with different curve severity: a longitudinal study from presentation to beyond skeletal maturity and peak bone mass. *Bone*. (2020) 133:115217. doi: 10.1016/j.bone.2019.115217

14. Diarbakerli E, Savvides P, Wihlborg A, Abbott A, Bergström I, Gerdhem P. Bone health in adolescents with idiopathic scoliosis. *Bone Joint J*. (2020) 102-B (2):268–72. doi: 10.1302/0301-620X.102B2.BJJ-2019-1016.R1

15. Du Q, Zhou X, Li JA, He XH, Liang JP, Zhao L, et al. Quantitative ultrasound measurements of bone quality in female adolescents with idiopathic scoliosis compared to Normal controls. *J Manipulative Physiol Ther*. (2015) 38 (6):434–41. doi: 10.1016/j.jmpt.2015.06.009

16. Yu WS, Chan KY, Yu FW, Ng BK, Lee KM, Qin L, et al. Bone structural and mechanical indices in Adolescent Idiopathic Scoliosis evaluated by high-resolution peripheral quantitative computed tomography (HR-pQCT). *Bone*. (2014) 61:109–15. doi: 10.1016/j.bone.2013.12.033

17. Cheng JC, Qin L, Cheung CS, Sher AH, Lee KM, Ng SW, et al. Generalized low areal and volumetric bone mineral density in adolescent idiopathic scoliosis. *J Bone Min Res*. (2000) 15(8):1587–95. doi: 10.1359/jbmr.2000.15.8.1587

18. Latalski M, Danielewicz-Bromberek A, Fatyga M, Latalska M, Kröber M, Zwolak P. Current insights into the aetiology of adolescent idiopathic scoliosis.

Arch Orthop Trauma Surg. (2017) 137(10):1327–33. doi: 10.1007/s00402-017-2756-1

19. Gao B, Gao W, Chen C, Wang Q, Lin S, Xu C, et al. What is the difference in morphologic features of the thoracic pedicle between patients with adolescent idiopathic scoliosis and healthy subjects? a CT-based case-control study. *Clin Orthop Relat Res*. (2017) 475(11):2765–74. doi: 10.1007/s11999-017-5448-9

20. Schreiber JJ, Hughes AP, Taher F, Girardi FP. An association can be found between Hounsfield units and success of lumbar spine fusion. *HSS J*. (2014) 10 (1):25–9. doi: 10.1007/s11420-013-9367-3

21. Lee S, Chung CK, Oh SH, Park SB. Correlation between bone mineral density measured by dual-energy x-ray absorptiometry and Hounsfield units measured by diagnostic CT in lumbar spine. *J Korean Neurosurg Soc*. (2013) 54 (5):384–9. doi: 10.3340/jkns.2013.54.5.384

22. Schreiber JJ, Anderson PA, Rosas HG, Buchholz AL, Au AG. Hounsfield units for assessing bone mineral density and strength: a tool for osteoporosis management. *J Bone Joint Surg Am*. (2011) 93(11):1057–63. doi: 10.2106/JBJS.J.00160

23. Mi J, Li K, Zhao X, Zhao CQ, Li H, Zhao J. Vertebral body compressive strength evaluated by dual-energy x-ray absorptiometry and hounsfield units in vitro. *J Clin Densitometry*. (2018) 21(1):148–53. doi: 10.1016/j.jocd.2016.08.011

24. Earp BE, Kallini JR, Collins JE, Benavent KA, Tintle SM, Rozental TD. Correlation of hounsfield unit measurements on computed tomography of the shoulder with dual-energy x-ray absorptiometry scans and fracture risk assessment tool scores: a potential for opportunistic screening. *J Orthop Trauma*. (2021) 35(7):384–90. doi: 10.1097/BOT.0000000000001994

25. Zou D, Jiang S, Zhou S, Sun Z, Zhong W, Du G, et al. Prevalence of osteoporosis in patients undergoing lumbar fusion for lumbar degenerative diseases: a combination of DXA and hounsfield units. *Spine*. (2020) 45(7): E406–10. doi: 10.1097/BRS.0000000000003284

26. Booz C, Noeske J, Albrecht MH, Lenga L, Martin SS, Yel I, et al. Diagnostic accuracy of quantitative dual-energy CT-based bone mineral density assessment in comparison to Hounsfield unit measurements using dual x-ray absorptiometry as standard of reference. *Eur J Radiol*. (2020) 132:109321. doi: 10.1016/j.ejrad.2020.109321

27. Lenke LG, Betz RR, Clements D, Merola A, Haher T, Lowe T, et al. Curve prevalence of a new classification of operative adolescent idiopathic scoliosis: does classification correlate with treatment? *Spine*. (2002) 27(6):604–11. doi: 10.1097/00007632-200203150-00008

28. Zou D, Li W, Deng C, Du G, Xu N. The use of CT Hounsfield unit values to identify the undiagnosed spinal osteoporosis in patients with lumbar degenerative diseases. *Eur Spine J*. (2019) 28(8):1758–66. doi: 10.1007/s00586-018-5776-9

29. Hendrickson NR, Pickhardt PJ, Del Rio AM, Rosas HG, Anderson PA. Bone mineral density T-scores derived from CT attenuation numbers (Hounsfield units): clinical utility and correlation with dual-energy x-ray absorptiometry. *Iowa Orthop J*. (2018) 38:25–31. PMID: 30104921; PMCID: PMC6047377

30. Christensen DL, Nappo KE, Wolfe JA, Tropf JG, Berge MJ, Wheatley BM, et al. Ten-year fracture risk predicted by proximal femur Hounsfield units. *Osteoporosis Int*. (2020) 31(11):2123–30. doi: 10.1007/s00198-020-05477-y

31. Li XF, Li H, Liu ZD, Dai LY. Low bone mineral status in adolescent idiopathic scoliosis. *Eur Spine J*. (2008) 17(11):1431–40. doi: 10.1007/s00586-008-0757-z

32. Ramos O, Razzouk J, Chung JH, Cheng WK, Danisa OA. Opportunistic assessment of bone density in patients with adolescent idiopathic scoliosis using MRI-based vertebral bone quality. *J Clin Neurosci*. (2022) 103:41–3. doi: 10.1016/j.jocn.2022.06.030

33. Tanabe H, Aota Y, Nakamura N, Saito T. A histomorphometric study of the cancellous spinal process bone in adolescent idiopathic scoliosis. *Eur Spine J*. (2017) 26(6):1600–9. doi: 10.1007/s00586-017-4974-1

34. Almomen FA, Altaweel AM, Abunadi AK, Hashem AE, Alqarni RM, Alsiddiky AM. Determining the correlation between Cobb angle severity and bone mineral density in women with adolescent idiopathic scoliosis. *J Taibah Univ Med Sci*. (2021) 16(3):365–8. doi: 10.1016/j.jtumed.2020.12.019

35. Stokes IAF. Analysis and simulation of progressive adolescent scoliosis by biomechanical growth modulation. *Eur Spine J*. (2007) 16(10):1621–8. doi: 10.1007/s00586-007-0442-7

36. Somerville EW. Rotational lordosis; the development of single curve. *J Bone Joint Surg Br*. (1952) 34-B(3):421–7. doi: 10.1302/0301-620X.34B3.421

37. Castelein RM, van Dieën JH, Smit TH. The role of dorsal shear forces in the pathogenesis of adolescent idiopathic scoliosis–a hypothesis. *Med Hypotheses*. (2005) 65(3):501–8. doi: 10.1016/j.mehy.2005.03.025

38. Castelein RM. Pre-existent rotation of the normal spine at different ages and its consequences for the scoliotic mechanism. *Stud Health Technol Inform*. (2012) 176:20–5. PMID: 22744449

39. Makino T, Kaito T, Sakai Y, Kashii M, Yoshikawa H. Asymmetrical ossification in the epiphyseal ring of patients with adolescent idiopathic scoliosis: a retrospective review. *Bone Joint J*. (2016) 98-B(5):666–71. doi: 10.1302/0301-620X.98B5.37133

40. Hu X, Siemionow KB, Lieberman IH. Thoracic and lumbar vertebrae morphology in Lenke type 1 female adolescent idiopathic scoliosis patients. *Int J Spine Surg*. (2014) 8:30. doi: 10.14444/1030

41. Sarwahi V, Sugarman EP, Wollowick AL, Amaral TD, Lo Y, Thornhill B. Prevalence, distribution, and surgical relevance of abnormal pedicles in spines with adolescent idiopathic scoliosis vs. no deformity: a CT-based study. *J Bone Joint Surg Am*. (2014) 96(11):e92. doi: 10.2106/JBJS.M.01058

42. Takeshita K, Maruyama T, Chikuda H, Shoda N, Seichi A, Ono T, et al. Diameter, length, and direction of pedicle screws for scoliotic spine: analysis by multiplanar reconstruction of computed tomography. *Spine*. (2009) 34 (8):798–803. doi: 10.1097/BRS.0b013e3181895c36

43. Puvanesarajah V, Liauw JA, Lo SF, Lina IA, Witham TF. Techniques and accuracy of thoracolumbar pedicle screw placement. *World J Orthop*. (2014) 5 (2):112–23. doi: 10.5312/wjo.v5.i2.112

44. Hirano T, Hasegawa K, Takahashi HE, Uchiyama S, Hara T, Washio T, et al. Structural characteristics of the pedicle and its role in screw stability. *Spine*. (1997) 22(21):2504–9; discussion 2510. doi: 10.1097/00007632-199711010-00007

45. Makino T, Kaito T, Fujiwara H, Yonenobu K. Morphometric analysis using multiplanar reconstructed CT of the lumbar pedicle in patients with degenerative lumbar scoliosis characterized by a Cobb angle of 30° or greater. *J Neurosurg Spine*. (2012) 17(3):256–62. doi: 10.3171/2012.6.SPINE12227

46. Bianco RJ, Arnoux PJ, Mac-Thiong JM, Aubin CE. Thoracic pedicle screw fixation under axial and perpendicular loadings: a comprehensive numerical analysis. *Clin Biomech (Bristol, Avon)*. (2019) 68:190–6. doi: 10.1016/j.clinbiomech.2019.06.010

47. Matsukawa K, Abe Y, Yanai Y, Yato Y. Regional Hounsfield unit measurement of screw trajectory for predicting pedicle screw fixation using cortical bone trajectory: a retrospective cohort study. *Acta Neurochir*. (2018) 160(2):405–11. doi: 10.1007/s00701-017-3424-5

48. Sakai Y, Takenaka S, Matsuo Y, Fujiwara H, Honda H, Makino T, et al. Hounsfield unit of screw trajectory as a predictor of pedicle screw loosening after single level lumbar interbody fusion. *J Orthop Scie*. (2018) 23(5):734–8. doi: 10.1016/j.jos.2018.04.006

49. Zou D, Sun Z, Zhou S, Zhong W, Li W. Hounsfield units value is a better predictor of pedicle screw loosening than the T-score of DXA in patients with lumbar degenerative diseases. *Eur Spine J*. (2020) 29(5):1105–11. doi: 10.1007/s00586-020-06386-8

50. Zou D, Muheremu A, Sun Z, Zhong W, Jiang S, Li W. Computed tomography Hounsfield unit-based prediction of pedicle screw loosening after surgery for degenerative lumbar spine disease. *J Neurosurg Spine*. (2020):1–6. doi: 10.3171/2019.11.SPINE19868

51. Tani S, Ishikawa K, Kudo Y, Tsuchiya K, Matsuoka A, Maruyama H, et al. The effect of denosumab on pedicle screw fixation: a prospective 2-year longitudinal study using finite element analysis. *J Orthop Surg Res*. (2021) 16 (1):219. doi: 10.1186/s13018-021-02360-2

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Comparison of perioperative outcomes in frail patients following multilevel lumbar fusion surgery with and without the implementation of the enhanced recovery after surgery protocol

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Background: Enhanced recovery after surgery (ERAS) is an evidence-based multimodal perioperative management designed to reduce the length of stay (LOS) and complications. The purpose of the present study is to evaluate the recovery of physiological function, LOS, complications, pain score, and clinical efficacy in frail elderly patients undergoing multisegment fusion surgery after the implementation of the ERAS protocol.

Methods: Frail patients older than 75 years undergoing multilevel lumbar fusion surgery for degenerative discogenic conditions, lumbar spinal stenosis, and lumbar spondylolisthesis from January 2017 to December 2018 (non-ERAS frail group) and from January 2020 to December 2021 (ERAS frail group) were enrolled in the present study. Propensity score matching for age, sex, body mass index, and smoking status was performed to keep comparable characteristics between the two groups. Further recovery of physiological function, LOS, complications, pain score, and clinical efficacy were compared between the groups.

Results: There were 64 pairs of well-balanced patients, and the clinical baseline data were comparable between the two groups. There was significant improvement in terms of recovery of physiological function (10.65 ± 3.51 days vs. 8.31 ± 3.98 days, $p = 0.011$) and LOS (12.18 ± 4.69 days vs. 10.44 ± 4.60 days, $p = 0.035$), while no statistical discrepancy was observed with regard to complications between the groups, which indicated favorable outcomes after the implementation of the ERAS protocol. Further analysis indicated that more patients were meeting a minimally clinical important difference for the visual analog score for the legs and the Oswestry Disability Index in the ERAS frail group. With regard to postoperative pain, the score was higher in the ERAS frail group than in the non-ERAS frail group on postoperative day (POD) 1 (4.88 ± 1.90 in the ERAS frail group vs. 4.27 ± 1.42 in the non-ERAS frail group, $p = 0.042$), while there was no significant discrepancy on POD 2 (3.77 ± 0.88 in the ERAS frail group vs. 3.64 ± 1.07 in

the non-ERAS frail group, $p = 0.470$) and POD 3 (3.83 ± 1.89 in the ERAS frail group vs. 3.47 ± 1.75 in the non-ERAS frail group, $p = 0.266$).

Conclusions: In this retrospective cohort study, we found a significant improvement in terms of LOS, recovery of physiological function, and clinical efficacy after the implementation of the ERAS protocol in elderly and frail patients undergoing multilevel lumbar fusion surgery, while there was no significant discrepancy with regard to complications, 90-day readmission, and postoperative pain.

KEYWORDS

enhanced recovery after surgery, frail, multilevel, lumbar fusion surgery, propensity score matching

Introduction

Enhanced recovery after surgery (ERAS) is an evidence-based, multidisciplinary perioperative approach adopted to decrease postoperative adverse events by mitigating stress response in patients following surgical intervention (1–4). First introduced for colon surgery, the ERAS protocol has been implemented successfully in various surgical specialties. Substantial attention has been paid to spine surgery, and several studies have found that patients undergoing lumbar fusion surgery (short-segment or multilevel) can benefit from the implementation of the ERAS protocol (5–10). Studies have demonstrated that ERAS for lumbar fusion could reduce hospitalization costs, postoperative pain, and complications, while facilitating the recovery of physiological function without adversely affecting readmission rates; this is the case irrespective of whether the protocol is implemented preoperatively, intraoperatively, or postoperatively (11, 12).

There is now an increased focus on desirable perioperative outcomes in vulnerable patients due to the increasing incidence of age-related disorders. Frailty is clinically defined as a syndrome characterized by decreased physiological reserve that can predispose patients undergoing surgery to suboptimal outcomes (13, 14). Moreover, previous studies have shown that frail patients are susceptible to an increased risk of complications, a longer length of stay (LOS), and more hospitalization expenditures arising from lumbar surgery (15, 16). Accurate risk stratification and predicting postoperative complications in time are imperative in older patients undergoing lumbar fusion surgery. The Fried frailty phenotype was described by Fried and colleagues (17), which is comprised of five variables, namely unintentional weight loss, self-reported exhaustion, low physical activity, slowness, and weakness. The score assigns one point for any of these factors and is calculated by adding each variable.

Previous studies have demonstrated the clinical efficacy of the ERAS protocol in lumbar fusion surgery; however, there has been a lack of sufficient data pool for evaluating ERAS in frail patients following lumbar fusion surgery, especially multisegment lumbar fusion surgery (8). Furthermore, with increasing age, elderly patients often suffer from comorbidities, making the vulnerable among them more prone to an increased risk of suboptimal outcomes (18). Against this background, this study aims to evaluate the return of physiological function, LOS, complication rates, pain scores, and clinical efficacy in frail elderly patients undergoing multisegment fusion surgery after the implementation of the ERAS protocol.

Methods

Population

This was a retrospective cohort study. This study was approved by the institutional review board in Xuanwu Hospital Capital Medical University (No. 2018086). Informed consent was waived due to the nature of the study design. Consecutive patients who underwent multilevel lumbar fusion surgery, defined as fusion segments greater than or equal to 3 before and after the implementing the ERAS protocol, were reviewed in this study. Inclusion criteria were (1) age >75 years; (2) undergoing multilevel lumbar fusion surgery for degenerative discogenic conditions, lumbar spinal stenosis, and lumbar spondylolisthesis; and (3) completed preoperative data. A multidisciplinary appraisal team was established in 2019 at our institution with the aim of minimizing selection bias, and the Fried phenotype score was evaluated by specially trained nurses. A patient was defined as frail if the score was >2. Exclusion criteria were (1) history of spinal surgery; (2) concomitant cervical surgery or thoracic spine surgery; and (3) lack of clinical data. The ERAS protocol was implemented in July 2019 to increase the reliability and comparability of the data, patients reviewed from January 2017 to December 2018 were classified as non-ERAS frail group, and those reviewed from January 2020 to December 2021 were classified as ERAS frail group. Propensity score matching for age, sex, body mass index (BMI), and smoking status was performed to maintain comparable clinical characteristics.

Enhanced recovery after surgery interventions

The ERAS protocol for multilevel lumbar fusion surgery was fully implemented in our department in July 2019 and a

multidisciplinary assessment team was established. The ERAS program is a patient-specific perioperative management approach, and a tailor-made management regimen is adopted for patients by following ERAS principles. Our ERAS protocol consisted of preoperative, intraoperative, and postoperative interventions. The perioperative measures were (1) perioperative education and counseling: informing the patients about the risk of surgery and describing the ERAS pathway to ensure their understanding; (2) nutritional assessment: patients with malnutrition were provided with personalized and diet guidance and nutritional supplements from an expert nutritionist before surgery; (3) cessation of smoking and alcohol: 2 weeks before surgery; (4) no prolonged fasting: eating was permitted up to 6 h prior to surgery and carbohydrate-containing drinks were allowed up to 2 h before surgery; (5) multimodal analgesia: various analgesics were used according to pain stratifications; (6) antibiotic prophylaxis: within 1 h of the incision. Intraoperative interventions were (1) tranexamic acid: within half an hour of incision; (2) maintenance of normothermia: keeping temperature at 36–37°C; (3) local infiltration analgesia: 10 ml ropivacaine and 10 ml lidocaine; (4) standard anesthetic protocol: total intravenous anesthesia-based anesthetic technique with propofol, lidocaine, ketamine, ketorolac, antiemetics, and with up to 0.5% minimum alveolar concentration–inhaled anesthetics. Postoperative interventions were (1) early oral feeding: oral feeding after recovery from anesthesia; (2) early ambulation: patients with multilevel lumbar fusion surgery were suggested to ambulate out-of-bed with or without assistance within 48 h after surgery; (3) early removal of the bladder catheter: consider removing the catheter after 24 h; (4) multimodal analgesia: similar to the preoperative multimodal analgesia regimen with a patient-controlled analgesia pump.

Collected variables

Patient-specific and procedure-specific variables were reviewed from the medical records. The patient-specific perioperative variables included age, sex, BMI, smoking status, visual analog score (VAS) for the back and legs, Oswestry Disability Index (ODI) score before and after surgery, American Society of Anesthesiologists (ASA) classification, and Charlson comorbidity index (CCI) (19). The procedure-specific variables included operation time, intraoperative blood loss, intraoperative blood transfusion, LOS, fusion segments, 90-day readmission, and postoperative complications (i.e., deep vein thrombosis, pneumonia, surgical site infection, bacteremia, uroschesis, urinary tract infection, myocardial ischemia, neurological deficit, hematoma, delirium, spinal fluid leakage, and nausea and vomiting). We recorded the time to first ambulation, time to first bowel movement, and time to void, and the return of physiological function was defined as the sum of these parameters. Clinical efficacy was compared between the two groups according to the minimal clinically important difference (MCID) with a cutoff of 12.8 points for the ODI, 1.2 points for back pain, and 1.6 points for leg pain (20).

Surgical technique

A standard midline approach was performed to expose the posterior elements. The nerve roots were decompressed by hemilaminectomy or laminectomy according to the preoperative lumbar symptoms, radicular symptoms, and MRI. Spinal instrumentation was performed using a pedicle screw-rod construct, followed by a decompression of responsible segments with transforaminal lumbar interbody fusion. All surgeries were performed by the same team.

Statistical methods

Continuous variables were summarized as mean ± standard deviation when data were normally distributed, while categorical variables were expressed as frequencies and percentages. The continuous variables were analyzed using independent two-sample *t*-tests and categorical variables were compared using a chi-square test or the Fisher's exact test. All statistical analyses were performed using SPSS software version 25.0 (SPSS, Inc., Armonk, NY, USA). *P*-values < 0.05 were considered statistically significant.

Results

Demographics

The detailed demographic patient data are presented in **Table 1**. After propensity score matching for age, sex, BMI, and smoking status, there were 64 pairs of well-balanced patients. The mean age was 79.94 ± 3.23 years and BMI was 25.24 ± 2.98 kg/m^2 with 73.44% of women in the ERAS frail group. Analogously, the mean age was 79.32 ± 3.21 years and BMI was 25.69 ± 2.56 kg/m^2 with 75.00% of women in the non-ERAS frail group. Patient-specific and procedure-specific baseline characteristics were comparable in both cohorts. CCI, ASA, pre-ODI, and pre-VAS for the back and legs were similar. In addition, there were no significant differences in terms of fusion segment, operation time, estimated blood loss, or intraoperative blood transfusions.

Perioperative outcomes

Perioperative characteristics are given in **Table 2**. There was no significant difference with regard to complication rates,

TABLE 1 Patients' demographics.

Variable	non-ERAS frail	ERAS frail	*P*
Sample size	64	64	
Age	79.32 ± 3.21	79.94 ± 3.23	0.281
Female	48/64	47/64	0.840
BMI	25.69 ± 2.56	25.24 ± 2.98	0.355
CCI	1.91 ± 1.65	2.05 ± 1.85	0.652
Smoking	4/64	6/64	0.510
Fusion segment			0.829
3	41	40	
4	18	17	
5	5	7	
Pre-ODI	48.15 ± 9.78	48.55 ± 13.98	0.880
Pre-VAS for the back	4.50 ± 2.18	4.31 ± 2.36	0.758
Pre-VAS for the legs	4.96 ± 1.56	4.59 ± 2.01	0.407
ASA			0.529
I	0	1	
II	12	16	
III	51	46	
IV	1	1	
Operation time	279.03 ± 63.35	265.50 ± 62.61	0.225
EBL	597.85 ± 375.32	604.22 ± 333.92	0.919
Intraoperative blood transfusion	569.48 ± 559.74	559.00 ± 456.65	0.908

BMI, body mass index; CCI, Charlson comorbidity index; ODI, Oswestry Disability Index; VAS, visual analog score; ASA, American Society of Anesthesiologists classification; EBL, estimated blood loss.

90-day readmission, post-ODI, post-VAS for the back, and post-VAS for the legs for both cohorts. However, there was a significant reduction in the LOS in the ERAS frail group (12.18 ± 4.69 days vs. 10.44 ± 4.60 days, $p = 0.035$).

Recovery of physiological function

Significant improvements were seen on the first day of ambulation (3.42 ± 1.72 days vs. 2.38 ± 1.72 days, $p = 0.010$) and the first day of bowel movement (4.31 ± 1.32 days vs. 3.44 ± 1.47 days, $p = 0.010$) in the ERAS frail group. On average, the first day of bladder voiding occurred 0.42 days earlier (2.92 ± 1.79 days vs. 2.50 ± 1.84 days, $p = 0.322$) in the ERAS frail group, although no significant difference was observed. There was significant improvement in terms of recovery of physiological function in the ERAS frail group (10.65 ± 3.51 days vs. 8.31 ± 3.98 days, $p = 0.011$). The detailed characteristics are displayed in Figure 1.

Postoperative pain

The mean pain scores on postoperative days (PODs) 1–3 between the cohorts are illustrated in Figure 2. A significant

TABLE 2 Perioperative outcomes between the enhanced recovery after surgery frail group and the non-enhanced recovery after surgery frail group.

Variable	non-ERAS frail ($n = 64$)	ERAS frail ($n = 64$)	*P*
Complications			
Deep vein thrombosis	0 (0)	1 (1.56%)	1
Pneumonia	1 (1.56%)	3 (4.69%)	0.611
Surgical site infection	3 (4.69%)	4 (6.25%)	1
Bacteremia	1 (1.56%)	0 (0)	1
Uroschesis	4 (6.25%)	3 (4.69%)	1
Urinary tract infection	4 (6.25%)	3 (4.69%)	1
Myocardial ischemia	3 (4.69%)	3 (4.69%)	1
Neurological deficit	0 (0)	1 (1.56%)	1
Hematoma	2 (3.13%)	1 (1.56%)	1
Delirium	0 (0)	1 (1.56%)	1
Spinal fluid leakage	1 (1.56%)	0 (0)	1
Nausea and vomiting	6 (9.38%)	3 (4.69%)	0.489
Complication rates	18 (28.13%)	15 (23.44%)	0.544
LOS	12.18 ± 4.69	10.44 ± 4.60	0.035
90-day readmission	7 (10.94%)	5 (7.81%)	0.544
Post-ODI	33.38 ± 23.89	33.09 ± 24.00	0.945
Post-VAS for the back	2.92 ± 1.60	2.91 ± 1.72	0.954
Post-VAS for the legs	2.95 ± 1.81	2.78 ± 1.71	0.588
Return of physiological function			
1st ambulation POD	3.42 ± 1.72	2.38 ± 1.72	0.010
1st void POD	2.92 ± 1.79	2.50 ± 1.84	0.322
1st bowel movement POD	4.31 ± 1.32	3.44 ± 1.47	0.010

LOS, length of stay; ODI, Oswestry Disability Index; VAS, visual analog score; POD, postoperative day.

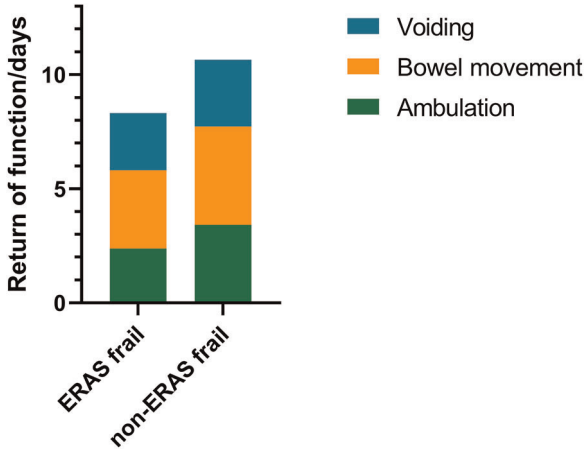

FIGURE 1
Stacked bar graph denoting recovery of physiological function for the ERAS frail group and the non-ERAS frail group. ERAS, enhanced recovery after surgery.

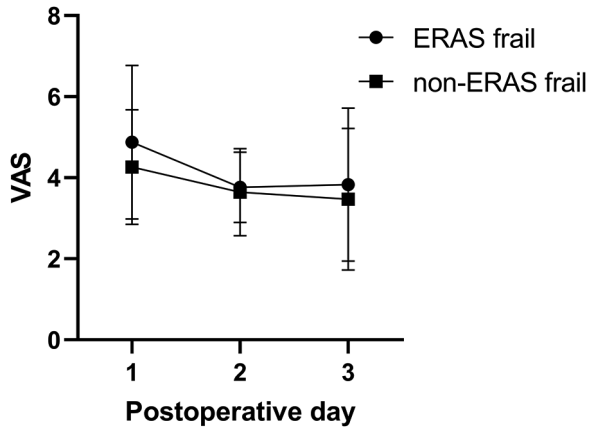

FIGURE 2
Pain scores on POD 1–3 between the ERAS frail group and the non-ERAS group. POD, postoperative day; ERAS, enhanced recovery after surgery.

difference was observed in the pain score on POD 1 (4.88 ± 1.90 in the ERAS frail group vs. 4.27 ± 1.42 in the non-ERAS frail group, $p = 0.042$), while there was no significant difference on POD 2 (3.77 ± 0.88 in the ERAS frail group vs. 3.64 ± 1.07 in the non-ERAS frail group, $p = 0.470$) and POD 3 (3.83 ± 1.89 in the ERAS frail group vs. 3.47 ± 1.75 in the non-ERAS frail group, $p = 0.266$).

Clinical efficacy

There were 51 (79.69%) patients in the ERAS group and 40 (62.50%) patients in the non-ERAS frail group meeting an MCID for the ODI, respectively ($p = 0.032$). In addition, there was substantial improvement in the VAS for the legs in the ERAS frail group compared with that in the non-ERAS frail group (70.31% vs. 53.13%, $p = 0.045$). More patients were meeting an MCID for the VAS for the back in the ERAS frail group, without a significant discrepancy (67.19% vs. 60.94%, $p = 0.461$).

TABLE 3 Clinical efficacy described by recovery for the Oswestry Disability Index and visual analog score according to the minimal clinically important difference between groups.

Achieved MCID for	Non-ERAS frail ($n = 64$)	ERAS frail ($n = 64$)	*P*
ODI	40 (62.5%)	51 (79.69%)	0.032
VAS for the back	39 (60.94%)	43 (67.19%)	0.461
VAS for the legs	34 (53.13%)	45 (70.31%)	0.045

ODI, Oswestry Disability Index; VAS, visual analog score; MCID, minimal clinically important difference.

Discussion

ERAS is an evidence-based multidisciplinary perioperative pathway designed to achieve early convalescence, a reduction of LOS, and postoperative complications (5, 21, 22). Conspicuous perioperative outcomes in previous studies resulted in ERAS gaining in popularity in spine surgery. Although ERAS studies have increased exponentially, there is a dearth of studies investigating the implementation of the ERAS protocol in frail older patients (>75 years) (8). The present study indicated that the implementation of the protocol amplified the recovery of physiological function, improvement of clinical efficacy, and reduction of LOS.

Frailty is clinically defined as a syndrome characterized by a decreased physiological reserve, predisposing patients to undergo surgery to avoid suboptimal outcomes. Further, multilevel lumbar fusion surgery exhibits higher complication rates and a longer LOS than their short-level counterparts (18). Therefore, if there are no external meticulous interventions, frail elderly patients would incur an increased risk of suboptimal postoperative outcomes. In a recently published retrospective study of frail patients following 1- or 2-level transforaminal lumbar interbody fusion, Porche et al. (8) indicated that ERAS significantly improved the LOS compared with their non-frail counterparts. In the present study, we found a significant reduction in the LOS in the ERAS frail group, though there was no significant difference in complications. Based on clinical experience, postoperative wound pain is correlated with patient satisfaction (23). Hence, a multimodal analgesia regimen as a part of an ERAS protocol should help maintain pain in the tolerable range. In this study, there was a significant difference in the pain score on POD 1, while there was no significant discrepancy on POD 2 and POD 3. The pain score appeared to have decreased from POD 1 to POD 3, especially in the non-ERAS frail group. In our previously published study (24), we stated that the patient-controlled multimodal analgesia pump is usually removed on POD 3 in our department, and this practice might account for the pain score being a little higher on POD 3 than on POD 2 in the ERAS frail group.

Early ambulation is the backbone of the ERAS protocol, and ERAS is designed to reduce adverse events based on a theoretical rationale for diminishing surgical-related stress response and insulin resistance (25). Hence, early recovery of physiological function occurs after implementing the ERAS protocol theoretically. Consistent with Proche et al., the total days for recovery of physiological function were significantly lower in the ERAS frail group (pre-ERAS: 6.7 days, post-ERAS: 3.4 days, $p < 0.001$). In this study, the first day of ambulation occurred on average 1.04 days earlier, the first day of bowel movement occurred on average 0.87 days earlier, and the first day of bladder voiding occurred 0.42 days earlier in the ERAS frail group than in the non-ERAS frail group, respectively. Furthermore, the number of days to the recovery

of physiological function was significantly less, with an average of 2.34 days earlier in the ERAS frail group.

Clinical efficacy is evaluated according to patient-reported health-related quality-of-life questionnaires including the ODI and VAS in spinal surgery studies. However, even subtle changes can yield statistically significant differences in sample sizes and measurement accuracy, and these are sufficient. Therefore, the MCID suggests a threshold to assess clinical efficacy, which makes intergroup analysis intuitive and explicit (20). In a retrospective study, Ayling et al. (26) indicated that there was no significant difference in the ODI and numeric rating scale between patients undergoing 1- to 2-level open transforaminal lumbar interbody fusion or minimally invasive transforaminal lumbar interbody fusion. Further analysis suggested that a higher baseline leg pain score predicted achieving the MCID in both cohorts. Jacob et al. (23) conducted a retrospective study suggesting that meeting an MCID for the back and leg pain was associated with patient satisfaction in lumbar decompression patients. Our study showed a significant improvement in the ODI and VAS after the performance of the procedures both in the ERAS frail group and in the non-ERAS frail group. In addition, despite finding the analogous preoperative and postoperative ODI, VAS for the back, and VAS for the legs, we found a significantly increased number of patients who met an MCID for the ODI and VAS for the legs after the implementation of the ERAS protocol. More patients in the ERAS frail group met an MCID in the VAS for the back; however, there was no significant difference because the postoperative patient-reported outcomes included in this study were evaluated before discharge, which provides favorable evidence for immediate recovery for daily activities after implementing the ERAS protocol in clinical practice.

This study was not without limitations. First, the study suffered from inherent limitations associated with retrospective analysis. Second, we did not perform multivariate analysis for patients who did not meet an MCID on the grounds of insufficient statistical power due to the small sample size. Finally, long-term patient-reported outcomes were not included in this study, as this study primarily focused on ERAS exposure with frailty as the variable, whereas ERAS is a multimodal management approach focusing on perioperative outcomes. Further multicenter studies with large cohorts are required to confirm our findings.

Conclusion

In this retrospective cohort study, we found a significant improvement in terms of the LOS, recovery of physiological function, and clinical efficacy after the implementation of the ERAS protocol in elderly and frail patients undergoing multilevel lumbar fusion surgery, while there was no significant discrepancy with regard to complications, 90-day readmission rates, and postoperative pain.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the institutional review board in Xuanwu Hospital Capital Medical University (No.2018086). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

PC and SW were responsible for conceptualization, preparation of the methodology, data curation, and writing of the original draft; PW and LY were responsible for supervision and reviewing of statistical analysis; CK and SL were responsible for project administration, supervision, and evaluation of the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Debono B, Corniola MV, Pietton R, Sabatier P, Hamel O, Tessitore E. Benefits of enhanced recovery after surgery for fusion in degenerative spine surgery: impact on outcome, length of stay, and patient satisfaction. *Neurosurg Focus*. (2019) 4:E6. doi: 10.3171/2019.1.FOCUS18669

2. Elsarrag M, Soldozy S, Patel P, Norat P, Sokolowski JD, Park MS, et al. Enhanced recovery after spine surgery: a systematic review. *Neurosurg Focus*. (2019) 4:E3. doi: 10.3171/2019.1.FOCUS18700

3. Smith J, Probst S, Calandra C, Davis R, Sugimoto K, Nie L, et al. Enhanced recovery after surgery (ERAS) program for lumbar spine fusion. *Perioper Med (Lond)*. (2019) 8:4. doi: 10.1186/s13741-019-0114-2

4. Soffin EM, Vaishnav AS, Wetmore DS, Barber L, Hill P, Gang CH, et al. Design and implementation of an enhanced recovery after surgery (ERAS) program for minimally invasive lumbar decompression spine surgery: initial experience. *Spine*. (2019) 9:E561–70. doi: 10.1097/brs.0000000000002905

5. Brusko GD, Kolcun JPG, Heger JA, Levi AD, Manzano GR, Madhavan K, et al. Reductions in length of stay, narcotics use, and pain following implementation of an enhanced recovery after surgery program for 1- to 3-level lumbar fusion surgery. *Neurosurg Focus*. (2019) 4:E4. doi: 10.3171/2019.1.FOCUS18692

6. Wang P, Wang Q, Kong C, Teng Z, Li Z, Zhang S, et al. Enhanced recovery after surgery (ERAS) program for elderly patients with short-level lumbar fusion. *J Orthop Surg Res*. (2020) 1:299. doi: 10.1186/s13018-020-01814-3

7. Chen J, Li D, Wang R, Wang S, Shang Z, Wang M, et al. Benefits of the enhanced recovery after surgery program (ERAS) in short-segment posterior lumbar interbody fusion surgery. *World Neurosurg*. (2021) 159:e303–10. doi: 10.1016/j.wneu.2021.12.046

8. Porche K, Yan S, Mohamed B, Garvan C, Samra R, Melnick K, et al. Enhanced recovery after surgery (ERAS) improves return of physiological function in frail patients undergoing 1-2 level TLIFs: an observational retrospective cohort study. *Spine J*. (2022) 22(9):1513–22. doi: 10.1016/j.spinee.2022.04.007

9. Dagal A, Bellabarba C, Bransford R, Zhang F, Chesnut RM, O'Keefe GE, et al. Enhanced perioperative care for major spine surgery. *Spine (Phila Pa 1976)*. (2019) 13:959–66. doi: 10.1097/BRS.0000000000002968

10. Angus M, Jackson K, Smurthwaite G, Carrasco R, Mohammad S, Verma R, et al. The implementation of enhanced recovery after surgery (ERAS) in complex spinal surgery. *J Spine Surg*. (2019) 1:116–23. doi: 10.21037/jss.2019.01.07

11. d'Astorg H, Fière V, Dupasquier M, Vieira TD, Szadkowski M. Enhanced recovery after surgery (ERAS) protocol reduces LOS without additional adverse events in spine surgery. *Orthop Traumatol Surg Res*. (2020) 6:1167–73. doi: 10.1016/j.otsr.2020.01.017

12. Sun Z, Qi Y. Application of enhanced recovery after surgery care protocol in the perioperative care of patients undergoing lumbar fusion and internal fixation. *J Orthop Surg Res*. (2022) 1:240. doi: 10.1186/s13018-022-03099-0

13. Shahrestani S, Ton A, Chen XT, Ballatori AM, Wang JC, Buser Z. The influence of frailty on postoperative complications in geriatric patients receiving single-level lumbar fusion surgery. *Eur Spine J*. (2021) 12:3755–62. doi: 10.1007/s00586-021-06960-8

14. Agarwal N, Goldschmidt E, Taylor T, Roy S, Dunn SC, Bilderback A, et al. Impact of frailty on outcomes following spine surgery: a prospective cohort analysis of 668 patients. *Neurosurgery*. (2021) 3:552–7. doi: 10.1093/neuros/nyaa468

15. Sun W, Lu S, Kong C, Li Z, Wang P, Zhang S. Frailty and post-operative outcomes in the older patients undergoing elective posterior thoracolumbar fusion surgery. *Clin Interv Aging*. (2020) 15:1141–50. doi: 10.2147/CIA.S245419

16. Beauchamp-Chalifour P, Flexman AM, Street JT, Fisher CG, Ailon T, Dvorak MF, et al. The impact of frailty on patient-reported outcomes after elective thoracolumbar degenerative spine surgery. *J Neurosurg*. (2021):1–9. doi: 10.3171/2021.2.Spine201879

17. Fried L, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol*. (2001) 3:M146–56. doi: 10.1093/gerona/56.3.m146

18. Li G, Patil CG, Lad SP, Ho C, Tian W, Boakye M. Effects of age and comorbidities on complication rates and adverse outcomes after lumbar laminectomy in elderly patients. *Spine*. (2007) 33:1250–55.

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying pronnostic comorbidity in long itudinal studies: development and validation. *Pergamon J*. (1987) 40:373–83.

20. Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. *Spine J*. (2008) 6:968–74. doi: 10.1016/j.spinee.2007.11.006

21. Porche K, Samra R, Melnick K, Brennan M, Vaziri S, Seubert C, et al. Enhanced recovery after surgery (ERAS) for open transforaminal lumbar interbody fusion: a retrospective propensity-matched cohort study. *Spine J*. (2021) 22(3):399–410. doi: 10.1016/j.spinee.2021.10.007

22. Adeyemo EA, Aoun SG, Barrie U, Nguyen ML, Badejo O, Pernik MN, et al. Enhanced recovery after surgery reduces postoperative opioid use and 90-day readmission rates after open thoracolumbar fusion for adult degenerative deformity. *Neurosurgery*. (2021) 2:295–300. doi: 10.1093/neuros/nyaa399

23. Jacob KC, Patel MR, Collins AP, Park GJ, Vanjani NN, Prabhu MC, et al. Meeting patient expectations and achieving a minimal clinically important difference for back disability, back pain, and leg pain may provide predictive utility for achieving patient satisfaction among lumbar decompression patients. *World Neurosurg*. (2022) 162:e328–35. doi: 10.1016/j.wneu.2022.03.002

24. Cui P, Wang P, Kong C, Li XY, Wang SK, Wang JL, et al. Patients older than 75 years undergoing polysegmental lumbar fusion surgery can also benefit from enhanced recovery after surgery program. *Clin Interv Aging*. (2022) 17:245–52. doi: 10.2147/CIA.S353511

25. Ripolles-Melchor J, Abad-Motos A, Diez-Remesal Y, Aseguinolaza-Pagola M, Padin-Barreiro L, Sanchez-Martin R, et al. Association between use of enhanced recovery after surgery protocol and postoperative complications in total hip and knee arthroplasty in the postoperative outcomes within enhanced recovery after surgery protocol in elective total hip and knee arthroplasty study (POWER2). *JAMA Surg*. (2020) 4:e196024. doi: 10.1001/jamasurg.2019.6024

26. Ayling OG, Rampersaud YR, Dandurand C, Yuan PHS, Ailon T, Dea N, et al. Surgical outcomes of patients who fail to reach minimal clinically important differences: comparison of minimally invasive versus open transforaminal lumbar interbody fusion. *J Neurosurg*. (2022):1–8. doi: 10.3171/2022.2.Spine211210

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Relationship between spinocranial angle and clinical outcomes after laminoplasty in patients with ossification of the posterior longitudinal ligament

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Background: The aims of this study were to identify the relationship between the spinocranial angle (SCA) and clinical outcomes and to explore whether the SCA is a suitable indicator to predict clinical outcomes for patients with ossification of the posterior longitudinal ligament (OPLL).

Methods: Sixty-five patients with cervical OPLL who underwent laminoplasty with at least 24 months of follow-up were selected for the current study and were divided into two groups according to whether the SCA was greater than or less than the mean preoperative SCA. Sagittal alignment changes were compared between the groups. The Pearson correlation coefficient was applied to assess the relationship among sagittal parameters. Univariate and multiple linear regression analyses were applied to identify the relationship between the recovery rate (RR) and radiological parameters.

Results: Patients were classified into two groups based on the mean value of preoperative SCA (85.1°). SCA was negatively correlated with T1 slope (T1s) and cervical lordosis (CL) and positively correlated with the C2–7 sagittal vertical axis (cSVA) ($p < 0.001$). Patients with lower SCA had larger T1s and CL preoperatively and at the follow-up (T1s: $p < 0.001$; CL: $p < 0.001$) and showed greater loss of cervical lordosis after laminoplasty ($p < 0.001$). However, no significant differences in the incidence of kyphosis, Japanese Orthopaedic Association (JOA) or RR were noted between the two groups. Although Pre-SCA, Pre-CL, F/U-CL and Pre-T1sCL were significantly associated with RR, these indicators were not associated with RR in the multivariate regression analysis.

Conclusion: Patients with lower SCA tended to have higher T1s and CL before surgery and greater loss of cervical lordosis at the follow-up visit but still maintained a greater lordosis angle. Although preoperative SCA is significantly related to RR, the relationship is not sufficient to indicate that preoperative SCA can be used to predict clinical outcomes. Therefore, further research is needed to confirm the impact of SCA on clinical outcomes for OPLL.

KEYWORDS

ossification of the posterior longitudinal ligament, spinocranial angle, laminoplasty, clinical outcomes, t1 slope

Introduction

Ossification of the posterior longitudinal ligament (OPLL) refers to a phenomenon of abnormal ossification of the ligament that is slow in the pathological process, and its specific pathogenesis is unclear. For cervical OPLL patients with severe clinical symptoms, anterior or posterior surgical intervention methods are currently used to facilitate decompression to relieve nerve compression and preserve nerve function. The scope of ossification lesions is often large and spans multiple segments. Patients with OPLL typically exhibit severe spinal cord compression accompanied by hypertrophy or ossification of the ligamentum flavum and spinal stenosis, which can easily cause nerve damage during anterior surgery. This notion led to increased interest in the use of laminoplasty in the treatment of cervical spine OPLL (1). Specifically, posterior spinal canal enlargement and laminoplasty achieved good prognostic effects during treatment (2, 3). Currently, cervical sagittal parameters are receiving increasing attention and are widely used to predict quality of life (4–7). Among them, the spinocranial angle (SCA), T1 slope (T1s) and C2–7 sagittal vertical axis (cSVA) are considered to be the three parameters that can better reflect sagittal balance and are also key research objects in the future (8). Regardless of whether it is T1s or cSVA, relevant studies on the evaluation of the sagittal alignment of cervical OPLL have been performed (9–11). However, although SCA, which is defined as the angle between a line from the sella turcica centre and C7 endplate and the C7 plateau line, has been reported to exhibit a significant correlation with many sagittal parameters (12), few studies have attempted to explore and correlate SCA with clinical results. Therefore, exploring the relationship between SCA and clinical outcomes is necessary.

The aim of our study was to explore the relationship between SCA and surgical effects after laminoplasty for cervical OPLL and to identify the significance of SCA as a predictor of clinical outcomes in patients with OPLL.

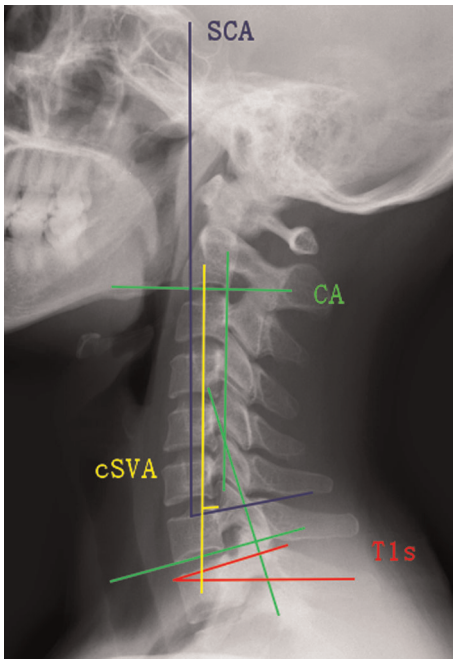

FIGURE 1
Spinocranial angle (SCA): the angle is defined as the angle between the C7 slope and the straight line joining the middle of the C7 end plate and the middle of the sella turcica. T1 slope (T1s): the angle between a horizontal line and the superior endplate of T1 or C7. C2–C7 lordosis (CL): the angle between the lower plate of C2 and the lower plate of C7. C2–C7 SVA (cSVA): the distance from the posterior, superior corner of C7 to the plumbline from the centroid of C2.

Materials and methods

Patient population

We retrospectively reviewed 65 consecutive patients (33 males and 32 females) with cervical OPLL who underwent laminoplasty between January 2010 and December 2016 in the Department of Spinal Surgery, the Third Hospital of Hebei Medical University (**Figure 1**). We included patients with (1) OPLL diagnosed by computed tomography; (2) completed radiographic and clinical data available; and (3) greater than 24 months of follow-up data. We excluded the following patients: (1) previous surgery involving the cervical spine; (2) cervical fractures, tumours, and metabolic disorders; (3) follow-up period less than 2 years; and (4) radiological parameters that were too unclear to measure. Health-related outcomes were evaluated preoperatively and at the follow-up period, including the Japanese Orthopaedic Association (JOA) (score 0–17) and recovery rate (RR) (postoperative score-preoperative score)/(17-preoperative score) × 100%).

Radiographic analysis

Lateral radiographs of the cervical spine were obtained preoperatively and at the 2-year follow-up. Radiological parameters included SCA, T1s, cervical lordosis (CL), cSVA, and T1sCL, which were measured as follows (**Figure 2**): (1) SCA is defined as the angle defined between the C7 slope and the straight line joining the midpoint of the C7 end plate and the midpoint of the sella turcica. (2) T1s is defined as the angle between the upper endplate of T1s and a horizontal line. (3) CL is defined as the angle formed by the inferior end plates of C2 and C7. (4) cSVA is defined as the horizontal distance from the posterior, superior corner of C7 vertebra to the plumbline from the centroid of C2 vertebra. (5) T1sCL is defined as the angle

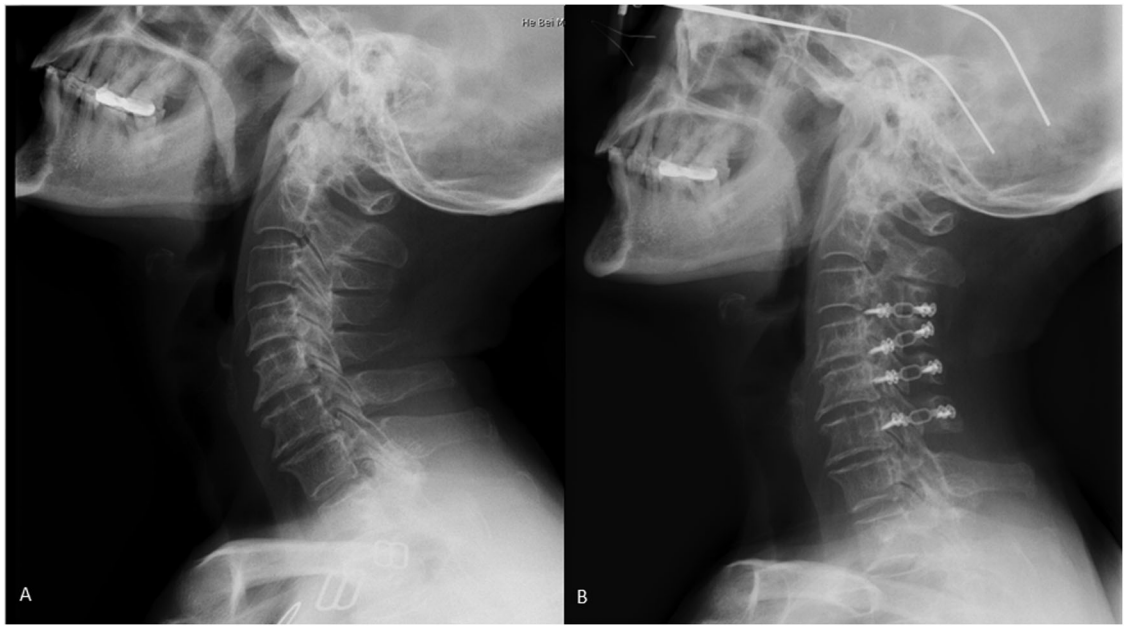

FIGURE 2
Posterior cervical surgery was performed to release the compression. Lateral x-ray of cervical spine was taken in a male patient with OPLL at preoperative and postoperative. A is preoperative, B is postoperative.

that is calculated based on the T1 slope minus C2–C7 lordosis. Here, Δ represents the change of each sagittal parameter.

All of the patients had undergone posterior cervical singledoor laminoplasty. The surgeries were conducted by the same group of surgeons followed by the same procedure. The decompression and fixation surgeries were described briefly as follows: The patients were in the prone position after anesthesia was performed with close monitoring. After the skin, subcutaneous, and fascia were cut, bilateral paraspinal muscles were peeled off to expose the posterior structure of vertebral. The surgery only cut the muscle longitudinally, not horizontally. At the same time, the muscles that did not interfere with the surgery were left intact. The posterior vertebral plates were turned over and then fixed in a position where the spinal canal was enlarged. The decompression range of vertebral lamina is C3–C6.

Statistical analysis

Data are revealed as the number of subjects in each group or the mean ± standard deviation and were calculated by SPSS (version 22.0; SPSS Inc., Chicago, IL, USA). Each independent variable was compared between the two groups using the independent-sample t test or Mann-Whitney U test and the χ^2 test or Fisher's exact test. The Pearson correlation coefficient was applied to assess the relationships among preoperative SCA, preoperative T1s, preoperative CL, preoperative cSVA and preoperative T1sCL. Univariate and multiple linear regression analyses were applied to evaluate the relationship between RR and various sagittal parameters. Significance was noted at the $p < 0.05$ level.

Results

Comparison of patient backgrounds according to preoperative SCA

Sixty-five patients were selected for the current study and were divided into two groups according to the mean preoperative SCA (85.1°). Patient clinical features according to preoperative SCA are summarized in Table 1. The value of SCA varied from 67.9° to 83.9° in low-SCA group and from 85.3° to 105.6° in high-SCA group. No statistically significant differences in age, sex, type of OPLL, number of expanded laminae or incidence of diabetes mellitus were noted between the two groups. The prognostic indicators included F/U-JOA (low-SCA: 14.23 ± 1.09°, high-SCA: 13.94 ± 0.85°; $p = 0.195$) and RR (low-SCA: 59.32 ± 16.63°, high-SCA: 52.92 ± 15.66°; $p = 0.067$). None of the above indicators showed significant differences, except for F/U-JOA (low-SCA, $p < 0.001$; high-SCA, $p < 0.001$).

Comparison of radiologic parameters according to preoperative SCA

The values for and differences in radiological parameters between the two groups are summarized in Table 2. The

TABLE 1 Comparison of patient backgrounds according to preoperative SCA.

	Low-SCA group (lower half)	High-SCA group (upper half)	*p*-value
No. of patients	31	34	
Range of SCA (°)	67.9–83.9	85.3–105.6	
Age (year)	57.61 ± 8.29	59.62 ± 8.58	0.434[a]
Sex (male/female)	18/13	15/19	0.261[b]
Type of OPLL			0.674[b]
Continuous	6	9	
Segmental	10	12	
Mixed	15	13	
No. of expanded laminae	4.68 ± 1.23	4.53 ± 1.11	0.587[a]
incidence of diabetes mellitus	48.4% (15/31)	55.9% (19/34)	0.546[b]
JOA			
Pre	10.33 ± 1.64	10.15 ± 1.91	0.926[a]
F/U 2y	14.23 ± 1.09	13.94 ± 0.85	0.195[a]
Pre vs. F/U	<0.001[c]	<0.001[c]	
RR	59.32% ± 16.63%	52.92% ± 15.66%	0.067[a]

SCA, spino cranial angle; OPLL, ossification of the posterior longitudinal ligament; Pre, preoperative; F/U, follow up; JOA, Japanese Orthopaedic Association; RRJOA, JOA recovery rate.
[a]Mann-Whitney *U* test.
[b]Chi-square test.
[c]Wilcoxon Signed Ranks test.

following radiologic results were observed: Pre-T1s (27.59 ± 4.72° vs. 19.19 ± 3.90°, $p < 0.001$), F/U-T1s (25.10 ± 4.15° vs. 17.92 ± 4.30°, $p < 0.001$), Pre-CL (17.81 ± 4.60° vs. 8.90 ± 5.03°, $p < 0.001$), F/U-CL (12.62 ± 7.78° vs. 6.49 ± 4.22°, $p < 0.001$), Pre-cSVA (22.94 ± 9.16 vs. 23.46 ± 10.16 mm, $p = 0.829$), F/U-cSVA (26.27 ± 9.33 vs. 25.81 ± 9.48 mm, $p = 0.845$), Pre-T1sCL (9.78 ± 2.76° vs. 10.29 ± 5.39°, $p = 0.895$), and F/U-T1sCL (12.48 ± 7.55° vs. 11.43 ± 4.96°, $p = 0.763$). Only T1s and CL showed significant differences between the two groups both preoperatively and during the follow-up period.

Comparison of sagittal alignment and clinical outcome changes according to preoperative SCA

Table 3 summarizes the changes in radiographic parameters and clinical efficacy. The mean values of ΔSCA and ΔCL were 4.61°, −5.18° in the low-SCA group and 1.69°, −2.41° in the high-SCA group, respectively, and all displayed significant differences (ΔSCA: $p = 0.033$, ΔCL: $p < 0.001$). However, the mean values of ΔT1s, ΔcSVA and ΔT1sCL were −2.49°, 3.33°, and 2.70° in the low-SCA group and −1.27°, 2.35°, and 1.14° in the high-SCA group, respectively. No significant differences were noted between the two groups (ΔT1s: $p = 0.179$, ΔcSVA: $p = 0.948$, ΔT1sCL: $p = 0.222$). Similarly, no significant difference occurred in ΔJOA between the two groups ($p = 0.224$).

TABLE 2 Comparison of radiologic and clinical parameters according to preoperative SCA.

	Low-SCA group (lower half)	High-SCA group (upper half)	*p*-value
SCA (°)			
Pre	76.51 ± 4.91	92.94 ± 5.72	<0.001[a]
F/U 2y	81.12 ± 7.63	94.63 ± 6.20	<0.001[a]
Pre vs. F/U	<0.001[b]	0.025[b]	
T1s (°)			
Pre	27.59 ± 4.72	19.19 ± 3.90	<0.001[c]
F/U 2y	25.10 ± 4.15	17.92 ± 4.30	<0.001[a]
Pre vs. F/U	<0.001[b]	0.042[d]	
CA (°)			
Pre	17.81 ± 4.60	8.90 ± 5.03	<0.001[c]
F/U 2y	12.62 ± 7.78	6.49 ± 4.22	<0.001[c]
Pre vs. F/U	<0.001[d]	<0.001[d]	
cSVA (mm)			
Pre	22.94 ± 9.16	23.46 ± 10.16	0.829[a]
F/U 2y	26.27 ± 9.33	25.81 ± 9.48	0.845[a]
Pre vs. F/U	0.010[b]	0.072[b]	
T1sCA (°)			
Pre	9.78 ± 2.76	10.29 ± 5.39	0.895[c]
F/U 2y	12.48 ± 7.55	11.43 ± 4.96	0.763[c]
Pre vs. F/U	0.026[d]	0.301[d]	

Pre, preoperative; F/U, follow up; SCA, spino cranial angle; T1s, T1-slope; CA, C2–7 lordosis angle; cSVA, C2–7 sagittal vertical axis; T1sCA, T1-slope minus C2–7 lordosis angle.
[a]Independent *t*-test.
[b]Paired *t*-test.
[c]Mann-Whitney *U* test.
[d]Wilcoxon Signed Ranks test.

TABLE 3 Comparison of sagittal alignment and clinical outcome changes according to preoperative SCA.

	Low-SCA group (lower half)	High-SCA group (upper half)	*p*-value
ΔSCA (°)	4.61 ± 6.47	1.69 ± 4.18	0.033[a]
ΔT1s (°)	−2.49 ± 3.34	−1.27 ± 3.84	0.179[a]
ΔCA (°)	−5.18 ± 5.20	−2.41 ± 2.36	<0.001[b]
ΔcSVA (mm)	3.33 ± 6.73	2.35 ± 7.35	0.948[b]
ΔT1sCA (°)	2.70 ± 6.59	1.14 ± 4.81	0.222[b]
ΔJOA	4.19 ± 1.60	3.79 ± 1.87	0.224[b]

SCA, spino cranial angle; T1s, T1-slope; CA, C2–7 lordosis angle; cSVA, C2–7 sagittal vertical axis; T1sCA, T1-slope minus C2–7 lordosis angle; JOA, Japanese Orthopaedic Association.
[a]Independent *t*-test.
[b]Mann-Whitney *U* test.

Pearson correlations of cervical sagittal parameters

Table 4 demonstrates the Pearson correlations among preoperative sagittal parameters. Preoperative SCA was significantly correlated with T1s ($r = -0.769$, $p < 0.001$), CL ($r = -0.856$, $p < 0.001$) and preoperative cSVA ($r = 0.430$, $p < 0.001$). Preoperative T1s was positively correlated with preoperative CL ($r = 0.768$, $p < 0.001$). Preoperative CL was negatively correlated with preoperative cSVA ($r = -0.395$, $p = 0.001$) and T1sCL ($r = -0.450$, $p < 0.001$). Preoperative cSVA was positively correlated with preoperative T1sCL ($r = 0.334$, $p = 0.007$).

TABLE 4 Pearson correlations of preoperative cervical sagittal parameters.

		SCA	T1s	CA	cSVA
T1s	*r*	−0.769*			
	p	<0.001			
CA	*r*	−0.856*	0.768*		
	p	<0.001	<0.001		
cSVA	*r*	0.430*	−0.191	−0.395*	
	p	<0.001	0.128	0.001	
T1sCA	*r*	0.231	0.226	−0.450*	0.334*
	p	0.064	0.070	<0.001	0.007

SCA, spino cranial angle; T1s, T1-slope; CA, C2–7 lordosis angle; cSVA, C2–7 sagittal vertical axis; T1sCA, T1-slope minus C2–7 lordosis angle.
*Correlation is significant at the 0.01 level (two-tailed).

TABLE 5 Unvariate analysis between RR and radiological parameters.

	r	*p*
Pre-SCA	−0.247*	0.048
F/U-SCA	−0.189	0.132
ΔSCA	0.108	0.391
Pre-T1s	0.089	0.481
F/U-T1s	0.195	0.119
ΔT1s	0.151	0.230
Pre-CA	0.301*	0.015
F/U-CA	0.247*	0.047
ΔCA	−0.067	0.595
Pre-cSVA	0.036	0.774
F/U-cSVA	0.065	0.609
ΔcSVA	0.036	0.776
Pre-T1sCA	−0.334**	0.006
F/U-T1sCA	−0.098	0.440
ΔT1sCA	0.145	0.250

Pre, preoperative; F/U, follow up; SCA, spino cranial angle; T1s, T1-slope; CA, C2–7 lordosis angle; cSVA, C2–7 sagittal vertical axis; T1sCA, T1-slope minus C2–7 lordosis angle; RR, recovery rate.
*Correlation is significant at the 0.05 level (two-tailed).
**Correlation is significant at the 0.01 level (two-tailed).

TABLE 6 Multivariate analysis of factors associated with RR.

Parameters	*B*	Se	Beta	*t*	*p*
Pre-SCA (°)	−0.002	0.004	−0.114	−0.459	0.648
Pre-CA (°)	0.002	0.008	0.084	0.257	0.798
F/U-CA (°)	<0.001	0.005	−0.003	−0.016	0.987
Pre-T1sCA (°)	−0.010	0.005	−0.272	−1.911	0.061

PRE, preoperative; F/U, follow up; SCA, spino cranial angle; CA, C2–7 lordosis angle; T1sCA, T1s minus CA; RR, recovery rate.

Univariate and multiple linear regression analysis of the relationship between RR and sagittal parameters

The results of univariate and multiple linear regression analyses are summarized in Tables 5, 6. Among all sagittal parameters, Pre-SCA, Pre-CL, F/U-CL and Pre-T1sCL were significantly related to RR (Pre-SCA: $r = -0.247$, $p = 0.048$; Pre-CL: $r = 0.301$, $p = 0.015$; F/U-CL: $r = 0.247$, $p = 0.047$; Pre-T1sCL: $r = -0.334$, $p = 0.006$). Unfortunately, the selected variables above showed no significant correlation with RR in multiple linear regression analysis.

Discussion

Recently, the significance of cervical alignment balance based on sagittal parameters has been gradually realized (4, 5). Cervical sagittal parameters exhibit a close correlation with quality of life (6, 7). Poor cervical equilibrium after the posterior approach is widely recognized as an important influencing factor leading to a decline in quality of life (6, 13). Among numerous sagittal parameters, three parameters stand out: SCA, T1s and cSVA. Previous reports have evaluated sagittal balance by SCA, which fluctuates within a certain range ($83° \pm 9°$) under normal conditions and is significantly correlated with T1s and CL (12). Although the essential sagittal parameter of SCA is being gradually recognized as an important factor, there are limited reports on the role of SCA in sagittal balance. In addition, whether SCA has the ability to predict changes in the sagittal sequence and clinical results, such as T1s and cSVA, remains unclear (10). Moreover, whether the degree of cervical sagittal balance damage after laminoplasty is associated with preoperative sagittal parameters remains controversial (14, 15). In our study, patients with a lower SCA who underwent laminoplasty had more changes in sagittal parameters, such as an increase in the SCA and the loss of CL. Simultaneously, preoperative SCA showed a negative correlation with T1s and CL. Moreover, T1s was significantly positively correlated with CL, which is consistent with previous reports that higher T1s tend to be accompanied by higher CL (5, 15). Studies have shown that patients with higher T1s may have higher CL, and

greater effort is required to maintain cervical alignment balance (14, 15). Our research results seem to apply this hypothetical conclusion to SCA as well, and the results can be generalized to OPLL. In the present study, compared with the preoperative period, all the sagittal parameters involved in the low-SCA group were significantly changed during the follow-up period. However, only T1s and CL were significantly changed in the high-SCA group during the follow-up period, and the changes in SCA and CL in the high-SCA group were significantly smaller than those in the low-SCA group. However, for clinical results, such as JOA and RR, no significant difference was noted between the two groups. This finding may explain why patients with lower SCAs are more susceptible altered sagittal balance after surgery. Sagittal malalignment has been confirmed to be closely associated with a decline in health status, and rational equilibrium could contribute to maintaining posture and ameliorating quality of life (16–18). Moreover, it remains controversial whether cervical kyphosis is associated with RR in patients after laminoplasty (19, 20). Therefore, we hypothesized that SCA might also be associated with clinical prognosis, so we established a univariate regression analysis model to try to correlate various sagittal parameters with RR. Although Pre-SCA, Pre-CL, F/U-CL and Pre-T1sCA were significantly associated with RR, these indicators were not associated with RR in the multivariate regression analysis model. Moreover, neither JOA nor RR significantly differed between the two groups. Therefore, SCA does not seem to be a predictor of clinical outcomes. However, we consider that each specific disease should have a corresponding range of appropriate sagittal parameters, and the relevant conclusions are also applicable to different diseases. Therefore, SCA may not be an appropriate parameter to predict prognostic efficacy in OPLL. Although no significant difference in clinical outcomes was noted between the two groups, the alterations in alignment deserve our attention. Although the loss of cervical lordosis in the low-SCA group was greater than that in the high-SCA group, cervical lordosis could still be maintained. In addition, cervical lordosis was significantly greater than that in the high-SCA group, whereas the change in SCA in the low-SCA group was also larger than that in the high-SCA group. These results indicate that the smaller the SCA and the greater the CL, the more prominent the changes in sagittal balance after laminoplasty. However, the relationship between the surgical effect and SCA changes remains uncertain. No significant differences in cSVA, T1sCL or the incidence of kyphosis were noted between the two groups at the preoperative and follow-up visits, suggesting that patients may be compensated by the global alignment of the spine. Therefore, we believe that cervical alignment is easier to maintain in normal order for patients who can effectively compensate.

Our study has several significant limitations. The first is related to retrospective design. Moreover, the average follow-up time was 28 months, which is too short. In addition, the sample sizes were relatively small. Second, no comprehensive evaluation of clinical and functional results was performed, and only JOA and its RR were statistically evaluated. Third, sagittal x-ray examination of the global spine was not performed, so the relationship between SCA and global sagittal balance could not be further determined. However, despite these limitations, our study is valuable for understanding the relationship between SCA and clinical outcomes after posterior cervical surgery in patients with cervical OPLL.

Conclusion

Our study demonstrated that compared with the high-SCA group, patients with lower SCA tended to have higher T1s and CL before laminoplasty and greater loss of cervical lordosis at the follow-up visit but still maintained a greater lordosis angle. Although preoperative SCA is significantly related to RR, it is not sufficient to indicate that preoperative SCA can be used to predict clinical outcomes. Therefore, further research is needed to confirm the impact of SCA on clinical outcomes for OPLL.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the ethical committee of Hebei province Cangzhou Hospital of integrated traditional and western medicine. All the patients gave written consent to for research applications of their clinical data. The patient data was anonymized in this study. All methods were carried out in accordance with relevant guidelines and regulations in the methods and declaration section.

Author contributions

J-HZ conceived and designed the study. ZL and ZW collected. ZL, PZ, WL, D-FL and XZ analysed and interpreted the patient data. ZL and ZW wrote the paper. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Liu X, Min S, Zhang H, Zhou Z, Wang H, Jin A. Anterior corpectomy versus posterior laminoplasty for multilevel cervical myelopathy: a systematic review and meta-analysis. *Eur Spine J*. (2014) 23(2):362–72. doi: 10.1007/s00586-013-3043-7

2. Tung KL, Cheung P, Kwok TK, Wong KK, Mak KH, Wong WC. Single-door cervical laminoplasty using titanium miniplates alone. *J Orthop Surg*. (2015) 23 (2):174–9. doi: 10.1177/230949901502300211

3. Yeh KT, Yu TC, Chen IH, Peng CH, Liu KL, Lee RP, et al. Expansive open-door laminoplasty secured with titanium miniplates is a good surgical method for multiple-level cervical stenosis. *J Orthop Surg Res*. (2014) 9:49. doi: 10.1186/s13018-014-0049-8

4. Ames CP, Blondel B, Scheer JK, Schwab FJ, Le Huec JC, Massicotte EM, et al. Cervical radiographical alignment: comprehensive assessment techniques and potential importance in cervical myelopathy. *Spine*. (2013) 38(22 Suppl 1): S149–60. doi: 10.1097/BRS.0b013e3182a7f449

5. Knott PT, Mardjetko SM, Techy F. The use of the T1 sagittal angle in predicting overall sagittal balance of the spine. *Spine J*. (2010) 10(11):994–8. doi: 10.1016/j.spinee.2010.08.031

6. Tang JA, Scheer JK, Smith JS, Deviren V, Bess S, Hart RA, et al. The impact of standing regional cervical sagittal alignment on outcomes in posterior cervical fusion surgery. *Neurosurgery*. (2015) 76(Suppl 1):S14–21. doi: 10.1227/01.neu.0000462074.66077.2b

7. Youn MS, Shin JK, Goh TS, Kang SS, Jeon WK, Lee JS. Relationship between cervical sagittal alignment and health-related quality of life in adolescent idiopathic scoliosis. *Eur Spine J*. (2016) 25(10):3114–9. doi: 10.1007/s00586-016-4488-2

8. Ling FP, Chevillotte T, Leglise A, Thompson W, Bouthors C, Le Huec JC. Which parameters are relevant in sagittal balance analysis of the cervical spine? A literature review. *Eur Spine J*. (2018) 27(Suppl 1):8–15. doi: 10.1007/s00586-018-5462-y

9. Kim B, Yoon DH, Ha Y, Yi S, Shin DA, Lee CK, et al. Relationship between T1 slope and loss of lordosis after laminoplasty in patients with cervical ossification of the posterior longitudinal ligament. *Spine J*. (2016) 16(2):219–25. doi: 10.1016/j.spinee.2015.10.042

10. Miyazaki M, Ishihara T, Abe T, Kanezaki S, Notani N, Sato S, et al. Analysis of the reciprocal changes in upper cervical profile and the risk factors for increasing cervical sagittal vertical axis after laminoplasty for ossification of the posterior longitudinal ligament of the cervical spine. *Clin Neurol Neurosurg*. (2020) 194:105788. doi: 10.1016/j.clineuro.2020.105788

11. Miyazaki M, Ishihara T, Notani N, Kanezaki S, Tsumura H. Relationship of T1 slope with loss of lordosis and surgical outcomes after laminoplasty for cervical ossification of the posterior longitudinal ligament. *Clin Neurol Neurosurg*. (2018) 164:19–24. doi: 10.1016/j.clineuro.2017.11.007

12. Le Huec JC, Demezon H, Aunoble S. Sagittal parameters of global cervical balance using eos imaging: normative values from a prospective cohort of asymptomatic volunteers. *Eur Spine J*. (2015) 24(1):63–71. doi: 10.1007/s00586-014-3632-0

13. Tang JA, Scheer JK, Smith JS, Deviren V, Bess S, Hart RA, et al. The impact of standing regional cervical sagittal alignment on outcomes in posterior cervical fusion surgery. *Neurosurgery*. (2012) 71(3):662–9; discussion 9. doi: 10.1227/NEU.0b013e31826100c9

14. Cho JH, Ha JK, Kim DG, Song KY, Kim YT, Hwang CJ, et al. Does preoperative T1 slope affect radiological and functional outcomes after cervical laminoplasty? *Spine*. (2014) 39(26):E1575–81. doi: 10.1097/BRS.0000000000000614

15. Kim TH, Lee SY, Kim YC, Park MS, Kim SW. T1 slope as a predictor of kyphotic alignment change after laminoplasty in patients with cervical myelopathy. *Spine*. (2013) 38(16):E992–7. doi: 10.1097/BRS.0b013e3182972e1b

16. Ferch RD, Shad A, Cadoux-Hudson TA, Teddy PJ. Anterior correction of cervical kyphotic deformity: effects on myelopathy, neck pain, and sagittal alignment. *J Neurosurg*. (2004) 100(1 Suppl):13–9. doi: 10.3171/spi.2004.100.1.0013

17. Glassman SD, Bridwell K, Dimar JR, Horton W, Berven S, Schwab F. The impact of positive sagittal balance in adult spinal deformity. *Spine*. (2005) 30 (18):2024–9. doi: 10.1097/01.brs.0000179086.30449.96

18. Kawakami M, Tamaki T, Ando M, Yamada H, Yoshida M. Relationships between sagittal alignment of the cervical spine and morphology of the spinal cord and clinical outcomes in patients with cervical spondylotic myelopathy treated with expansive laminoplasty. *J Spinal Disord Tech*. (2002) 15(5):391–7. doi: 10.1097/00024720-200210000-00008

19. Iwasaki M, Kawaguchi Y, Kimura T, Yonenobu K. Long-term results of expansive laminoplasty for ossification of the posterior longitudinal ligament of the cervical spine: more than 10 years follow up. *J Neurosurg*. (2002) 96(2 Suppl):180–9. doi: 10.3171/spi.2002.96.2.0180

20. Suda K, Abumi K, Ito M, Shono Y, Kaneda K, Fujiya M. Local kyphosis reduces surgical outcomes of expansive open-door laminoplasty for cervical spondylotic myelopathy. *Spine*. (2003) 28(12):1258–62. doi: 10.1097/01.BRS.0000065487.82469.D9

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The treatment effect of posterior lumbar fusion surgery on patients suffering from lumbar disc herniation concurrent with peroneal nerve paralysis

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Purpose: The purpose of this study is to investigate the clinical effect of posterior lumbar fusion surgery on patients who suffer from lumbar disc herniation concurrent with peroneal nerve paralysis.

Methods: The patients suffering from peroneal nerve paralysis and undergoing posterior lumbar fusion surgery between January 2012 and December 2019 were retrospectively reviewed. The data of the identified patients were then collected and processed. All patients were followed up post-operatively after discharge from the hospital. The data was analyzed in terms of Oswestry disability index (ODI), visual analogue scale (VAS) score, and relative lower-limb muscle strength.

Results: A total of 87 patients (52 males and 35 females) aged 54 ± 11 years met the inclusion criteria for this study. These patients stayed in hospital for 16 ± 6 days and were followed up for 81 ± 24 months. Data analysis showed that muscle strength of the tibialis anterior and extensor digitorum significantly recovered at the last follow-up with a grade of 3 (median), compared to grade 0 at admission ($p < 0.001$). Furthermore, the median VAS score decreased to 1 at the last follow-up from 6 at admission ($p < 0.001$), and the ODI greatly improved with 10% (median) at the last follow-up, while it was 58% at admission ($p < 0.001$). The ODI improvement rate was 60% on average at the last follow-up. Multivariate regression analysis regarding the ODI and muscle strength improvement rates showed that advanced age was a risk factor for postoperative recovery.

Conclusions: Most of the patients suffering from lumbar disc herniation concurrent with peroneal nerve paralysis can improve after undergoing posterior lumbar fusion surgery, but few can reach full recovery. Advanced age might be a risk factor that affects the prognosis of these patients after surgery.

KEYWORDS

lumbar disc herniation, peroneal nerve paralysis, lumbar fusion, lower back pain, risk factor, foot drop

Introduction

In clinical scenarios, lumbar disc herniation (LDH) has a high incidence, most cases being caused by intervertebral disc degeneration (IVDD) (1–3). LDH can lead to lower back pain (LBP), radicular pain and numbness of lower limbs, and even peroneal nerve paralysis (4–7). The clinical symptoms caused by peroneal nerve paralysis include foot and toe (hallux) drop, which results from weakness of ankle (tibialis anterior) and toe dorsiflexion (extensor digitorum) (8). Foot drop has been reported to have an incidence of 0.6%–7.7% in lumbar IVDD diseases, most of which are LDH cases (9).

For these LDH patients with peroneal nerve paralysis, lumbar surgeries are usually performed to remove the herniated nucleus pulposus (the disc), decompress the nerve root and enlarge spinal canal. Nowadays, posterior lumbar surgery, with or without interbody fusion, is widely used to treat LDH, particularly for those cases concurrent with peroneal nerve paralysis (10). However, some previous studies indicated that patients after lumbar surgery might experience prolonged LBP which significantly lowers their quality of life (11–14). Although there have been some studies on LDH-induced peroneal nerve paralysis so far, it is still difficult to make definitive conclusions based on these studies considering the variety of surgical procedures used (4).

Thus, the purpose of this study is to investigate the clinical effect of posterior lumbar fusion surgery on patients who suffered from LDH concurrent with peroneal nerve paralysis.

Patients and methods

Ethics

This retrospective study has been approved by Medical Ethics Council of the Third Hospital of Hebei Medical University (approval no. K2022-127-1). All informed consent was obtained from the patients (or their lawful guardians).

Patients

The patients who were diagnosed with LDH and peroneal nerve paralysis between January 2012 and December 2019 were retrospectively reviewed. All participants in this study underwent posterior lumbar fusion surgery (**Figure 1**) as previously reported (15). The data of the identified patients were then collected and processed. All patients were followed up after discharge from the hospital.

Assessment

The data collected in this study included baseline data and functional parameters. Baseline data consisted of age, gender, hospital stay, blood loss, operation time, follow-up time, and patient satisfaction. Functional parameters included Oswestry disability index (ODI), visual analogue scale (VAS) score, and lower-limb muscle strength. The lower-limb muscle strength was scored and analyzed by assessing muscle strength of the tibialis anterior and extensor digitorum, using the muscle scale established by the Medical Research Council (16). Foot drop and toe drop are defined as muscle strength below or equal to grade 3 (out of 5) (17). Additionally, the patients' satisfaction was collected and graded to three levels; dissatisfied, satisfied, and very satisfied.

ODI improvement rate was calculated using the equation (18, 19):

$$\left(1-\frac{Postoperative\ ODI}{Preoperative\ ODI}\right)\times 100\%$$

Muscle strength improvement rate was calculated using the equation:

$$\frac{Postoperative\ strength-Preoperative\ strength}{5-Preoperative\ \text{strength}}\times 100\%$$

To identify the risk factors that affect postoperative recovery, multivariate regression analyses were performed in terms of the ODI improvement rate and muscle strength improvement rate, respectively.

Statistics

SPSS for Windows 18.0 (SPSS Inc, US) was used for statistical analysis in this study. The data of ODI, VAS score and muscle strength is presented as median and interquartile range (IQR). The other data is presented as mean ± standard deviation (SD). Mann–Whitney *U* tests were used to analyze ODI, VAS score and muscle strength between pre-operation and post-operation. In addition, multivariate regression analyses (Enter method) were performed to identify the risk factors that would affect postoperative recovery in terms of the ODI improvement rate and muscle strength improvement rate, respectively. p values less than 0.05 were regarded as significant.

Results

Baseline data

After screening and review of the patients who had undergone lumbar fusion surgeries between January 2012 and December 2019, a total of 87 patients were identified and included in this study. As shown in **Table 1**, there are 52 males and 35 females.

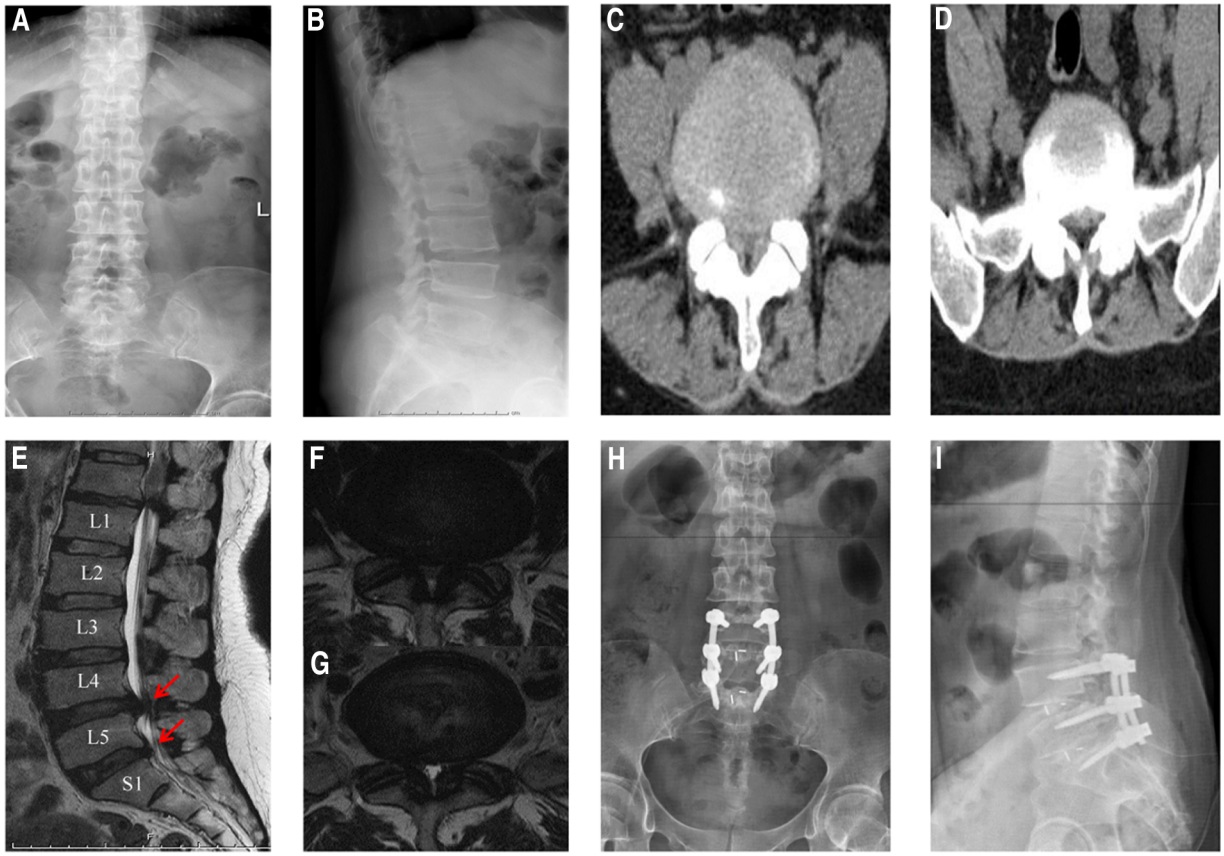

FIGURE 1
A representative case of posterior fusion surgery. (A,B) Preoperative x-ray radiographs; (C,D) preoperative CT scans of L4-5 and L5-S1, respectively; (E) preoperative MRI scan (sagittal plane); (F,G) preoperative MRI scans of L4-5 and L5-S1, respectively (axial plane); (H,I) postoperative x-ray radiographs. The arrows indicate the herniation of intervertebral disc.

The age of these participants was 54 ± 11 years. The hospital stay was 16 ± 6 days, and blood loss was 752 ml on average. Operation time was 196 min on average, and the follow-up time for these patients was 81 ± 24 months. Median time to surgery was 1 month. Among all participants, most were very satisfied or satisfied about their treatment effects (78 in 87) and only 9 patients were dissatisfied.

TABLE 1 Baseline clinical data of patients (n = 87).

Parameters	Mean	SD
Age (years)	54	11
Gender (male/female)	52/35	
Hospital stay (day)	16	6
Blood loss (ml)	752	471
Operation time (min)	196	69
Time to surgery (month)	1 (3)*	
Follow-up time (month)	81	24
Satisfaction (very satisfied/satisfied/dissatisfied)	49/29/9	

SD, standard deviation.
*Median (interquartile range).

Interbody fusions

As shown in Figure 2A, all participants underwent posterior lumbar interbody fusion surgeries. Among all 87 patients, 28 underwent L4-5 fusions, 24 underwent L4-S1 fusions, 14 underwent L3-5 fusions, and 21 underwent other segments' fusions. As shown in Figure 2B, there were a total of 139 interbody fusions performed across all 87 patients. The majority of these fusions were L4-5 fusions and L5-S1 fusions, while the fusions of L3-4 and L2-3 were less common.

Muscle strength and improvement rate

As shown in Figure 3, 66 of 87 patients were at grade 0 muscle strength of the tibialis anterior and extensor digitorum at admission, and 40 of the 87 patients improved to grades 4 or 5 at the last follow-up. Among 87 patients, 56 (64.4%)improved their muscle strength. As shown in Table 2, overall, the median preoperative muscle strength of the tibialis anterior and extensor

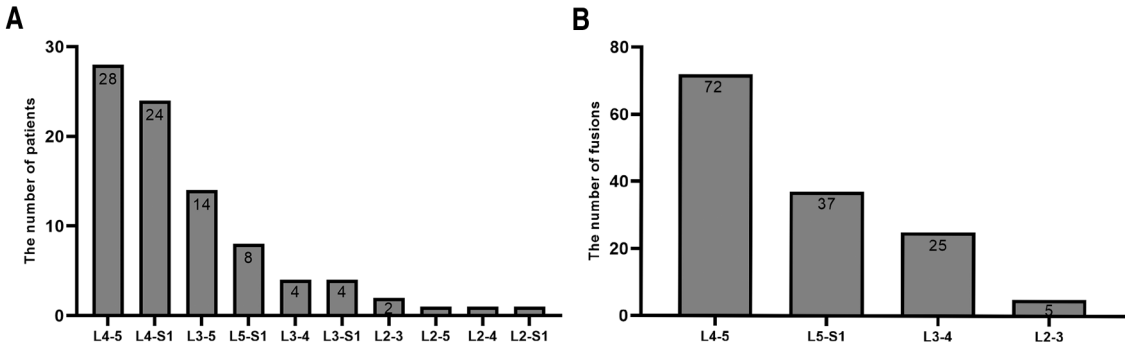

FIGURE 2
Lumbar fusions performed to the patients. (A) The number of patients in terms of fusions; (B) the number of lumbar fusions in terms of every fused segment.

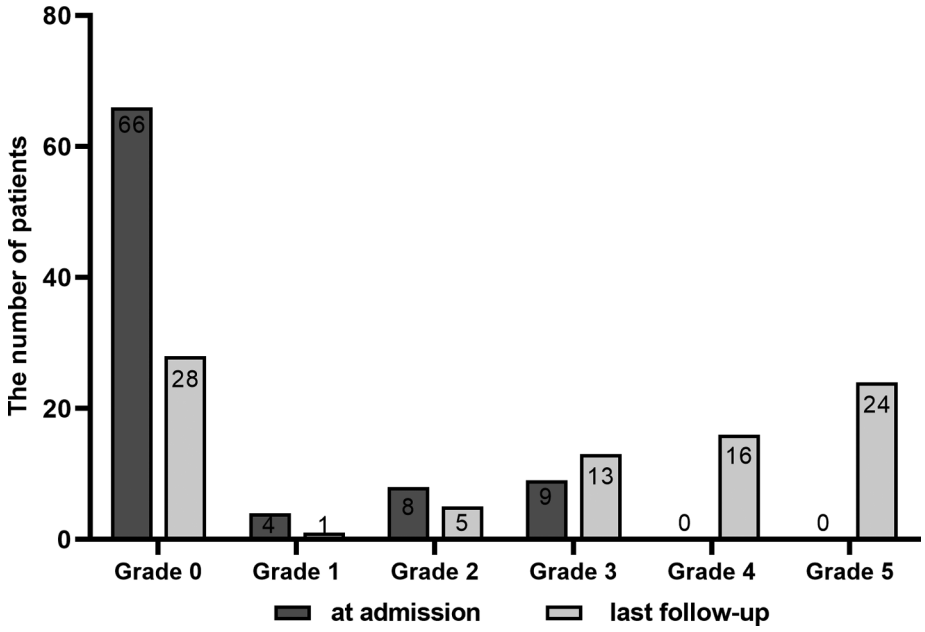

FIGURE 3
Comparison of muscle strength between pre-surgery (at admission) and last follow-up after surgery.

digitorum was grade 0 at admission and grade 3 at the last post-operative follow-up. Compared to the preoperative gradings, the patients' muscle strength significantly recovered after surgery ($p < 0.001$). Muscle strength improvement rate was 50% on average at the last follow-up.

VAS score

As shown in Table 2, the median VAS score of the patients was 6 at admission. By contrast, the median VAS score decreased to 1 at the last post-operative follow-up. Statistical analysis showed that the patients' post-operative VAS score significantly decreased compared with pre-operation ($p < 0.001$).

ODI and ODI improvement rate

As shown in Table 2, the patients' median ODI was 58% at admission, and decreased to 10% at the last post-operative follow-up ($p < 0.001$). The ODI improvement rate was 60% on average at the last follow-up.

Multivariate regression analysis

In this study, multivariate regression analysis was performed to identify risk factors that may influence the recovery of the patients after surgery. In the regression analyses, ODI improvement rate and muscle strength improvement rate were used as the dependent variables, respectively. It showed that advanced age was a risk factor that might affect the final ODI improvement rate and muscle strength improvement rate (both $p < 0.05$), as shown in Tables 3, 4.

TABLE 2 Comparisons regarding muscle strength, VAS, and ODI (median and IQR).

	Muscle strength	VAS	ODI
At admission	0 (0)	6 (5)	58% (60%)
Last follow-up	3 (5)	1 (2)	10% (26%)
P valve	***<0.001***	***<0.001***	***<0.001***

VAS, visual analogue scale; ODI, Oswestry disability index; IQR, interquartile range.

Discussion

Clinically, pathological changes in neural structures that influence the dorsiflexion of ankle would cause peroneal nerve paralysis, such as nerve compression, trauma, infection, tumor, and external oppression (5). LDH is one of the common diseases that lead to peroneal nerve paralysis (7, 8). Clinical symptoms caused by peroneal nerve paralysis usually include foot and toe (hallux) drop, resulting from weakness of

TABLE 3 Multivariate regression analysis regarding ODI improvement rate.

Parameters	Unstandardized		Standardized		
	B	SE	Beta	*t*	*p*
Gender	−5.114	11.745	−0.044	−0.435	0.665
Age	−1.493	0.588	−0.275	−2.540	***0.013***
Hospital stay	−0.301	1.017	−0.030	−0.296	0.768
Number of intervertebral fusions	−16.557	12.021	−0.189	−1.377	0.172
Blood loss	0.020	0.018	0.163	1.099	0.275
Operation time	0.036	0.115	0.044	0.318	0.752
Follow-up time	−0.488	0.262	−0.199	−1.867	0.066
Time to surgery	0.177	0.143	0.128	1.242	0.218
Muscle strength at admission	1.592	5.425	0.029	0.293	0.770
VAS at admission	−1.297	2.709	−0.072	−0.479	0.634
ODI at admission	0.898	0.271	0.510	3.310	***0.001***

VAS, visual analogue scale; ODI, Oswestry disability index.

TABLE 4 Multivariate regression analysis regarding muscle strength improvement rate.

Parameters	Unstandardized		Standardized Beta	*t*	*p*
	B	SE			
Gender	3.289	9.502	0.039	0.346	0.730
Age	−1.015	0.477	−0.258	−2.127	***0.037***
Hospital stay	0.336	0.832	0.046	0.403	0.688
Number of intervertebral fusions	3.000	9.793	0.047	0.306	0.760
Blood loss	−0.003	0.015	−0.031	−0.187	0.852
Operation time	−0.084	0.093	−0.139	−0.902	0.370
Follow-up time	−0.150	0.211	−0.085	−0.713	0.478
Muscle strength at admission	8.068	4.294	0.206	1.879	0.064
VAS at admission	−0.936	2.190	−0.072	−0.427	0.670
ODI at admission	0.272	0.217	0.214	1.254	0.214
Time to surgery	−0.217	0.554	−0.045	−0.392	0.696

VAS, visual analogue scale; ODI, Oswestry disability index.

the ankle (tibialis anterior) and toe (extensor digitorum) dorsiflexion. As previously reported, L4-5 disc herniation is the most common LDH that causes peroneal nerve paralysis, and L5-S1 disc herniation contributes 25% of cases with peroneal nerve paralysis (4, 5). In clinical settings, these LDH patients need to undergo lumbar spine surgeries regardless of interbody fusions. In the current study, we retrospectively collected 87 patients who underwent posterior lumbar fusion surgeries to treat LDH with peroneal nerve paralysis. The purpose of this study is to investigate the clinical effect of posterior lumbar fusion surgery on patients who suffered from LDH concurrent with peroneal nerve paralysis.

After being reviewed and identified, a total of 87 participants are finally enrolled in our study. Compared with pre-surgery, the functional parameters have significantly improved after surgery in terms of VAS score, lower-limb muscle strength, and ODI score. Moreover, most patients are very satisfied or satisfied about their treatment effects after fusion surgery. Our findings are in line with some existing reports indicating postoperative pain relief and functional recovery after the patients underwent lumbar surgeries to remove protruded disc and decompress nerve roots (4, 5, 9).

In our study, 56 out of 87 patients had improvements of muscle strength. Overall, the median muscle strength of the tibialis anterior and extensor digitorum improved to a grade of 3 at the last follow-up from grade 0 at admission. Among all 87 patients, there are 40 (46%) patients with muscle strength of grades 4 or 5 at last follow-up. Liu et al. (17) reported 135 patients who suffered from lumbar degenerative diseases with foot drop, and all these patients underwent posterior lumbar interbody fusion surgery with pedicle screw instrumentation. Their study shows 83.7% cases improved in muscle strength; however, only 15.6% patients improved to grades ≧4. By contrast, our study has shown a higher improvement rate (46%, grades ≧4) in muscle strength for the patients who had undergone lumbar fusion surgeries because of LDH and peroneal nerve paralysis. In addition, a multivariate regression analysis of our study shows that advanced age is a risk factor that may affect the final recovery of postoperative patients. This finding is consistent with Liu et al. (17) who reported that younger patients more often have a better surgical outcome.

To date, some studies have proposed a few risk factors and prognosis factors that influence post-operative recovery, but there is no consensus in this aspect. Shorter duration of peroneal nerve paralysis (17, 20), better pre-operative muscle strength (17, 20–22), shorter time to surgery (22), and younger age (17, 23) have been reported to indicate better recovery outcomes for patients who undergo lumbar surgeries due to lumbar spine diseases with peroneal nerve paralysis. However, it has been reported that there are no significant associations between postoperative recovery and the factors including age, diagnosis (LDH or spinal stenosis), duration of symptoms, and preoperative muscle strength (24).

Previous studies (25–27) have indicated that lower-limb exercise can effectively facilitate post-operative pain relief and promote functional recovery of patients undergoing spinal surgery. However, it still remains controversial regarding whether postoperative lower-limb exercise can really accelerate postoperative recovery. Some studies reported that postoperative lower-limb exercise can increase pain relief, functional improvement and patient satisfaction (25–30), while some others did not show positive effects of postoperative lower-limb exercise on final recovery (31–33).

There are some limitations restricting the data interpretation of this study. To start with, this is a single-center retrospective study, and as such the participants lack extensive representation which may affect the accuracy of the data. In addition, the patient sample size is not large, as only 87 participants were included in this study. The results and conclusions would be more robust if the patient sample size was larger. Hence, a larger and therefore more comprehensive study is needed to address all the issues above. The preferred study design would be multi-center, prospective, blinded and randomly controlled, with a larger sample size.

Conclusions

Most of patients suffering from lumbar disc herniation concurrent with peroneal nerve paralysis can improve after undergoing posterior lumbar fusion surgery, but few can reach full recovery. Advanced age might be a risk factor that affects the prognosis of these patients after surgery.

Data availability statement

The raw data supporting the conclusions of this article is available from the corresponding authors upon request.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Council of the Third Hospital of Hebei Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WD and SY designed and supervised this study. SG, ZL, HW and ZG collected data. ZL and ZG followed up patients. SG, XL and SY performed statistical analysis and data interpretation. XL and SY made tables and figures. SG drafted the manuscript. SY and SR edited the manuscript. SY

finalized the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Wang H, Li Z, Huo Y, Tian T, Yang D, Ma L, et al. 17β-Estradiol Alleviates intervertebral disc degeneration by inhibiting NF-κB signal pathway. *Life Sci*. (2021) 284:119874. doi: 10.1016/j.lfs.2021.119874

2. Yang S, Zhang F, Ma J, Ding W. Intervertebral disc ageing and degeneration: the antiapoptotic effect of oestrogen. *Ageing Res Rev*. (2020) 57:100978. doi: 10.1016/j.arr.2019.100978

3. Huo Y, Yang D, Ma L, Wang H, Ding W, Yang S. Oblique lumbar interbody fusion with stand-alone cages for the treatment of degenerative lumbar spondylolisthesis: a retrospective study with 1-year follow-up. *Pain Res Manag*. (2020) 2020:9016219. doi: 10.1155/2020/9016219

4. Telfeian AE, Oyelese A, Fridley J, Doberstein C, Gokaslan ZL. Prognosis for recovery of foot drop after transforaminal endoscopic decompression of far lateral lumbar 5-sacral 1 herniated disc: case series. *Pain Physician*. (2019) 22: E97–97E103. doi: 10.36076/ppj/2019.22.E97

5. Wang YP, Zhang W, Zhang J, Sun YP, An JL, Ding WY. Analysis of the clinical effects of transforaminal endoscopic discectomy on lumbar disk herniation combined with common peroneal nerve paralysis: a 2-year follow-up retrospective study on 32 patients. *J Pain Res*. (2017) 10:105–12. doi: 10.2147/JPR.S120463

6. Emamhadi M, Naseri A, Aghaei I, Ashrafi M, Emamhadi R, Andalib S. Soleus nerve transfer to deep peroneal nerve for treatment of foot drop. *J Clin Neurosci*. (2020) 78:159–63. doi: 10.1016/j.jocn.2020.04.086

7. Hiramatsu K, Yonetani Y, Kinugasa K, Nakamura N, Yamamoto K, Yoshikawa H, et al. Deep peroneal nerve palsy with isolated lateral compartment syndrome secondary to peroneus longus tear: a report of two cases and a review of the literature. *J Orthop Traumatol*. (2016) 17:181–5. doi: 10.1007/s10195-015-0373-8

8. Marciniak C. Fibular (peroneal) neuropathy: electrodiagnostic features and clinical correlates. *Phys Med Rehabil Clin N Am*. (2013) 24:121–37. doi: 10.1016/j.pmr.2012.08.016

9. Nakashima H, Ishikawa Y, Kanemura T, Kato F, Satake K, Ito K, et al. Neurological function following early versus delayed decompression surgery for drop foot caused by lumbar degenerative diseases. *J Clin Neurosci*. (2020) 72:39–42. doi: 10.1016/j.jocn.2020.01.039

10. van Erp R, Jelsma J, Huijnen I, Lundberg M, Willems PC, Smeets R. Spinal Surgeons' opinions on Pre- and postoperative rehabilitation in patients undergoing lumbar spinal fusion surgery: a survey-based study in The Netherlands and Sweden. *Spine*. (2018) 43:713–9. doi: 10.1097/BRS.0000000000002406

11. Jansson KA, Németh G, Granath F, Jönsson B, Blomqvist P. Health-related quality of life (EQ-5D) before and one year after surgery for lumbar spinal stenosis. *J Bone Joint Surg Br*. (2009) 91:210–6. doi: 10.1302/0301-620X.91B2.21119

12. Jansson KA, Németh G, Granath F, Jönsson B, Blomqvist P. Health-related quality of life in patients before and after surgery for a herniated lumbar disc. *J Bone Joint Surg Br*. (2005) 87:959–64. doi: 10.1302/0301-620X.87B7.16240

13. Mannion AF, Denzler R, Dvorak J, Grob D. Five-year outcome of surgical decompression of the lumbar spine without fusion. *Eur Spine J*. (2010) 19:1883–91. doi: 10.1007/s00586-010-1535-2

14. Martin BI, Mirza SK, Comstock BA, Gray DT, Kreuter W, Deyo RA. Reoperation rates following lumbar spine surgery and the influence of spinal fusion procedures. *Spine*. (2007) 32:382–7. doi: 10.1097/01.brs.0000254104.55716.46

15. Kong LD, Zhang YZ, Wang F, Kong FL, Ding WY, Shen Y. Radiographic restoration of sagittal spinopelvic alignment after posterior lumbar interbody fusion in degenerative spondylolisthesis. *Clin Spine Surg*. (2016) 29:E87–92. doi: 10.1097/BSD.0000000000000104

16. Compston A. Aids to the investigation of peripheral nerve injuries. Medical research council: nerve injuries research committee. His majesty's stationery office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By michael O'Brien for the guarantors of brain. Saunders elsevier: 2010; pp. [8] 64 and 94 figures. *Brain*. (2010) 133:2838–44. doi: 10.1093/brain/awq270

17. Liu K, Zhu W, Shi J, Jia L, Shi G, Wang Y, et al. Foot drop caused by lumbar degenerative disease: clinical features, prognostic factors of surgical outcome and clinical stage. *PLoS One*. (2013) 8:e80375. doi: 10.1371/journal.pone.0080375

18. Chen Y, Yang H, Zhang L, Wang Y, Zou J. Analyzing the influence of modic changes on patients with lower back pain undergoing conservative treatment. *Pain Res Manag*. (2019) 2019:8185316. doi: 10.1155/2019/8185316

19. Du JP, Fan Y, Liu JJ, Zhang JN, Huang YS, Zhang J, et al. The analysis of MSTMOVCF (multi-segment thoracolumbar mild osteoporotic fractures surgery or conservative treatment) based on ASTLOF (the assessment system of thoracolumbar osteoporotic fracture). *Sci Rep*. (2018) 8:8185. doi: 10.1038/s41598-018-26562-7

20. Aono H, Iwasaki M, Ohwada T, Okuda S, Hosono N, Fuji T, et al. Surgical outcome of drop foot caused by degenerative lumbar diseases. *Spine*. (2007) 32: E262–6. doi: 10.1097/01.brs.0000259922.82413.72

21. Iizuka Y, Iizuka H, Tsutsumi S, Nakagawa Y, Nakajima T, Sorimachi Y, et al. Foot drop due to lumbar degenerative conditions: mechanism and prognostic factors in herniated nucleus pulposus and lumbar spinal stenosis. *J Neurosurg Spine*. (2009) 10:260–4. doi: 10.3171/2008.12.SPINE08500

22. Macki M, Syeda S, Kerezoudis P, Gokaslan ZL, Bydon A, Bydon M. Preoperative motor strength and time to surgery are the most important predictors of improvement in foot drop due to degenerative lumbar disease. *J Neurol Sci*. (2016) 361:133–6. doi: 10.1016/j.jns.2015.12.035

23. Ghahreman A, Ferch RD, Rao P, Chandran N, Shadbolt B. Recovery of ankle dorsiflexion weakness following lumbar decompressive surgery. *J Clin Neurosci*. (2009) 16:1024–7. doi: 10.1016/j.jocn.2008.10.017

24. Girardi FP, Cammisa Jr FP, Huang RC, Parvataneni HK, Tsairis P. Improvement of preoperative foot drop after lumbar surgery. *J Spinal Disord Tech*. (2002) 15:490–4. doi: 10.1097/00024720-200212000-00010

25. Wang H, Huo Y, Zhao Y, Zhang B, Yang D, Yang S, et al. Clinical rehabilitation effect of postoperative lower-limb training on the patients undergoing OLIF surgery: a retrospective study. *Pain Res Manag*. (2020) 2020:1065202. doi: 10.1155/2020/1065202

26. Liu SK, Song YL, Ding WY, Yang DL, Ma L, Yang SD. The effect of systematic lower-limb rehabilitation training in elderly patients undergoing lumbar fusion surgery: a retrospective study. *Oncotarget*. (2017) 8:112720–6. doi: 10.18632/oncotarget.22746

27. Yang SD, Ning SH, Zhang LH, Zhang YZ, Ding WY, Yang DL. The effect of lower limb rehabilitation gymnastics on postoperative rehabilitation in elderly patients with femoral shaft fracture: a retrospective case-control study. *Medicine*. (2016) 95:e4548. doi: 10.1097/MD.0000000000004548

28. Ostelo RW, Costa LO, Maher CG, de Vet HC, van Tulder MW. Rehabilitation after lumbar disc surgery: an update cochrane review. *Spine*. (2009) 34:1839–48. doi: 10.1097/BRS.0b013e3181abbfdf

29. Nielsen PR, Jørgensen LD, Dahl B, Pedersen T, Tønnesen H. Prehabilitation and early rehabilitation after spinal surgery: randomized clinical trial. *Clin Rehabil*. (2010) 24:137–48. doi: 10.1177/0269215509347432

30. Canbulat N, Sasani M, Ataker Y, Oktenoglu T, Berker N, Ercelen O, et al. A rehabilitation protocol for patients with lumbar degenerative disk disease treated with lumbar total disk replacement. *Arch Phys Med Rehabil*. (2011) 92:670–6. doi: 10.1016/j.apmr.2010.10.037

31. Aalto TJ, Leinonen V, Herno A, Alen M, Kröger H, Turunen V, et al. Postoperative rehabilitation does not improve functional outcome in lumbar spinal stenosis: a prospective study with 2-year postoperative follow-up. *Eur Spine J*. (2011) 20:1331–40. doi: 10.1007/s00586-011-1781-y

32. McGregor AH, Doré CJ, Morris TP, Morris S, Jamrozik K. ISSLS Prize winner: function after spinal treatment, exercise, and rehabilitation (FASTER): a factorial randomized trial to determine whether the functional outcome of spinal surgery can be improved. *Spine*. (2011) 36:1711–20. doi: 10.1097/BRS.0b013e318214e3e6

33. Ilves O, Häkkinen A, Dekker J, Pekkanen L, Piitulainen K, Järvenpää S, et al. Quality of life and disability: can they be improved by active postoperative rehabilitation after spinal fusion surgery in patients with spondylolisthesis? A randomised controlled trial with 12-month follow-up. *Eur Spine J*. (2017) 26:777–84. doi: 10.1007/s00586-016-4789-5

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Comparison of the feasibility and validity of a one-level and a two-level erector spinae plane block combined with general anesthesia for patients undergoing lumbar surgery

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Background: Spinal surgery causes severe postoperative pain. An erector spinae plane (ESP) block can relieve postoperative pain, but the optimal blocking method has not been defined. The aim of this study is to compare the feasibility of a one-level and a two-level lumbar ESP block and their effect on intraoperative and postoperative analgesia in lumbar spinal surgery.
Methods: A total of 83 adult patients who were scheduled for posterior lumbar interbody fusion were randomly divided into two groups. Patients in Group I ($n = 42$) received an ultrasound-guided bilateral one-level ESP block with 0.3% ropivacaine, while patients in Group II ($n = 41$) received a bilateral two-level ESP block. Blocking effectiveness was evaluated, including whether a sensory block covered the surgical incision, sensory decrease in anterior thigh, and quadriceps strength decrease. Intraoperative anesthetic dosage, postoperative visual analogue scale scores of pain, opioid consumption, rescue analgesia, and opioid-related side effects were analyzed.
Results: Of the total number, 80 patients completed the clinical trial and were included in the analysis, with 40 in each group. The time to complete the ESP block was significantly longer in Group II than in Group I (16.0 [14.3, 17.0] min vs. 9.0 [8.3, 9.0] min, $P = 0.000$). The rate of the sensory block covering the surgical incision at 30 min was significantly higher in Group II than in Group I (100% [40/40] vs. 85.0% [34/40], $P = 0.026$). The rate of the sensory block in the anterior thigh was higher in Group II (43.8% [35/80] vs. 27.5% [22/80], $P = 0.032$), but the rate of quadriceps strength decrease did not differ significantly between the groups. The mean effect–site remifentanil concentration during intervertebral decompression was lower in Group II than in Group I (2.9 ± 0.3 ng/ml vs. 3.3 ± 0.5 ng/ml, $P = 0.007$).There were no significant differences between the groups in terms of intraoperative analgesic consumption, postoperative analgesic consumption, and postoperative VAS pain scores at rest and with movement within 24 h. There were no block failures, block-related complications, and postoperative infection.

Conclusions: Among patients undergoing posterior lumbar interbody fusion, the two-level ESP block provided a higher rate of coverage of the surgical incision by the sensory block when compared with the one-level method, without increasing the incidence of procedure-related complications.

Clinical Trial Registration: www.chictr.org.cn, identifier: ChiCTR2100043596

KEYWORDS

erector spinae plane block, one-level and two-level ESP block, pain sensorial blockage, lumbar surgery, perioperative analgesia

Introduction

Posterior lumbar surgery is a common procedure to treat lumbar degenerative diseases (1). The surgery is traumatic and causes postoperative pain, which confines patients to the bed at the early stage, resulting in delayed recovery, prolonged hospital stays, and increased costs (2–4). Perioperative pain management is important for achieving both anesthesia and surgical outcomes (5, 6).

Multimodal analgesia includes intravenous opioids, local anesthetic infiltration, and regional nerve blocking. NSAIDS has also been used in spinal surgery (7). An erector spinae plane (ESP) block is a paraspinal fascial plane block, first reported by Forero et al. in 2016 (8). Local anesthetic (LA) is administered between the thoracic transverse processes and the erector spinae muscle, blocking the dorsal and ventral rami of the thoracic and abdominal spinal nerves (8–10). It has been reported that the ESP block can provide analgesia for lumbar spinal surgery and has opioid-sparing effects (5, 11, 12). Different ESP block methods have been used in previous studies, with different concentrations (0.25%–0.4%) and volumes of bupivacaine or ropivacaine at T10, T12, and L4 or the midpoint of the incision (5, 7, 12–15). There is no systematic evaluation for determining the effects of a lumbar ESP block. It is not clear whether different volumes and injection sites will lead to different outcomes in a lumbar ESP block. We hypothesized that a two-level ESP block would have a higher rate of coverage of the surgical incision by the sensory block compared with a one-level ESP block.

The purpose of this study was to compare the feasibility of the one-level and two-level lumbar ESP block and their effect on intraoperative and postoperative analgesia in lumbar spinal surgery.

Materials and methods

Patients

This study was a randomized controlled trial conducted in Beijing Jishuitan Hospital. The study was approved by the Ethics Committee of Beijing Jishuitan Hospital (Review No. 20191202-J02) and was registered at the Chinese Clinical Trial Registry (ChiCTR2100043596). Written informed consent was obtained from all participants.

The patients' inclusion criteria were the American Society of Anesthesiologists (ASA) physical status class I or II, age ≥18 years, and those scheduled for posterior lumbar interbody fusion. Exclusion criteria included severe heart, kidneys, liver, and life-threatening hematologic diseases; central or peripheral neurologic disease; non-sinus heart rate; pacemaker or antiarrhythmic drug use; allergy to amide-type local anesthetics; infection in the intervention region; a history of lumbar surgery and consuming narcotic substances or alcohol dependence.

Random allocation was performed by using SPSS software Version 22.0 (IBM Corp., Armonk, NY, United States). The inclusion orders 1–80 were inputted, the corresponding random numbers were generated by "COMPUTE random = RV.UNIFORM(0,1)," 40 smaller numbers were assigned to Group I, and the rest were included in Group II. The anesthesiologist who performed the ESP block was given an envelope containing group information when a patient was included. The patients were not informed of their group assignments. Orthopedists were unware of their group assignments. General anesthesia and postoperative assessment was performed by researchers blinded to the group assignment.

Anesthesia management

Conduct of the ESP block

The patients were transferred to the regional anesthesia room 45 min before surgery. A standard monitor was established with pulse oximetry, non-invasive arterial blood pressure measurement, and electrocardiogram. The patients were placed in the right lateral position and given intravenous midazolam of 2 mg and sufentanil of 5 μg for preprocedure sedation.

The ultrasound probe was placed at the sagittal axis, scanning from 5 cm to the midline and moving toward the midline. In sequence, the vertebral transverse process, lamina, and the spinous process were seen. Vertebral level T_{12} could be identified by the 12th rib, followed by each lumbar process.

L_1–L_5 lumbar spinous processes were marked on the skin to identify operative vertebrae. The objective site of injection was decided according to the surgical incision. The upper site was one vertebral above the operative vertebrae. The lower site was defined as the lowest operative vertebrae. For patients in Group I, the ESP block was performed only at the upper level. For patients in Group II, it was performed at both upper and lower levels. In Group I, each patient received bilateral blocking at the upper level, while in Group II, each received bilateral upper- and lower-level injections. As a result, there were 80 injections in Group I and 160 injections in Group II. The ESP block was performed by the same anesthesiologist.

Ultrasound probe and the region scheduled for the procedure were sterilized. The probe was installed along the sagittal axis at the midline of the targeted vertebral level. The spinous processes were first visualized, and then with the probe moving to the lateral side, the transverse processes and the erector spinae muscle were visualized approximately 3–4 cm to the midline. A 100 mm needle was inserted using the in-plane technique. The needle was targeted between the transverse process and the deep fascia of the erector spinae muscle. The location of the needle was confirmed with 2 ml saline solution, followed by 0.3% ropivacaine injection. The same procedure was also performed on the opposite side. At the upper level, the needle was inserted from the cranial side to the caudal side, and 0.3% local anesthetic of 25 ml was injected. At the lower level, the needle was inserted from the caudal to the cranial side, and the LA volume was set at 10 ml. Therefore, the total LA volume was 35 in Group II and 25 ml in Group I.

General anesthesia and operation

After the patients arrived in the operating room, pulse oximetry, invasive arterial blood pressure measurement, electrocardiogram, Bispectral Index (BIS), and Pain Rating Index (Pti) monitor were established. General anesthesia was performed in all patients with a target-controlled infusion (TCI) of propofol and remifentanil. The initial plasma concentration of propofol was set at 3.5 μg/ml and increased by 0.3 μg/ml gradually until eyelash reflex disappeared. When the BIS was lower than 60, the effect compartment concentration was recorded. When the effect compartment concentration of remifentanil reached 3.0 ng/ml, rocuronium of 0.6 mg/kg was injected, and then endotracheal intubation was performed. Propofol and remifentanil were titrated to keep the BIS at 40–60 and PTI at 40–79. If it was necessary, rocuronium of 0.2 mg/kg would be added for muscle relaxation. During the intraoperative period, vasoactive drugs were administrated to maintain the heart rate and blood pressure within 20% of baseline. The operation was performed by the same surgical team using the same technique for all patients.

At 30 min before the end of surgery, parecoxib sodium of 40 mg and tropisetron hydrochloride of 5 mg were injected intravenously. After 15 min, sufentanil of 0.1 μg/kg was administered. The total dosage of intraoperative propofol, remifentanil, and rocuronium were recorded. Postoperatively, neostigmine of 2 mg and atropine of 1 mg were administered to antagonize the residual muscle relaxation. The patients were extubated after all extubation criteria were met and then transferred to the postanesthesia care unit (PACU). Patients with Aldrete scores ≥9 were transferred to the surgical ward.

Postoperative analgesia

Patients in both groups were provided with the same postoperative analgesia. Parecoxib sodium of 40 mg was given every 12 h within 72 h after surgery. The protocol of the patient-controlled analgesia (PCA) devices was set with sufentanil of 180 μg, tropisetron hydrochloride of 15 mg, and normal saline of 120 ml and initiated at the PACU. The PCA parameters were set as a basal infusion of 1 ml/h, lockout interval of 30 min, and bolus of 2 ml. For rescue analgesia, tramadol of 100 mg was intravenously administered to patients with visual analog scale (VAS) scores of more than 4 at rest.

Data collection

General information of the patients was recorded, such as sex, age, height, weight, ASA classification, and duration of surgery. The objective vertebra and time to complete the block were also recorded.

The primary endpoint was the rate of complete coverage of the surgical incision site by the sensory block. The plane of the sensory block was detected with a pinprick along the site of surgical incision at 15 and 30 min following the procedure. To confirm the boundary, it was necessary to ensure that the distance between each test point was less than 1 cm. The line between the targeted operative vertebra and the spinous process of the vertebra above was the surgical incision. If the blockage plane totally covered the surgical incision site, it would be recorded as complete blocking. If not, the incision length and vertical diameter of hypoalgesia were measured and the coverage rate was calculated as shown in **Figure 1**. According to the ultrasound image, the reliability of blocking was classified into three levels and recorded. (Level 0: the needle tip and the diffusion of LA were invisible; Level 1: the needle tip was invisible, the diffusion of LA was visible; Level 2: both the needle tip and the diffusion of LA were visible.) Local anesthetic allergy, toxicity, total spinal anesthesia or epidural block, hematoma, and postoperative infection were recorded. The treatments were also recorded.

Secondary endpoints included sensory decrease in the anterior thigh and quadriceps strength decrease. Pinprick

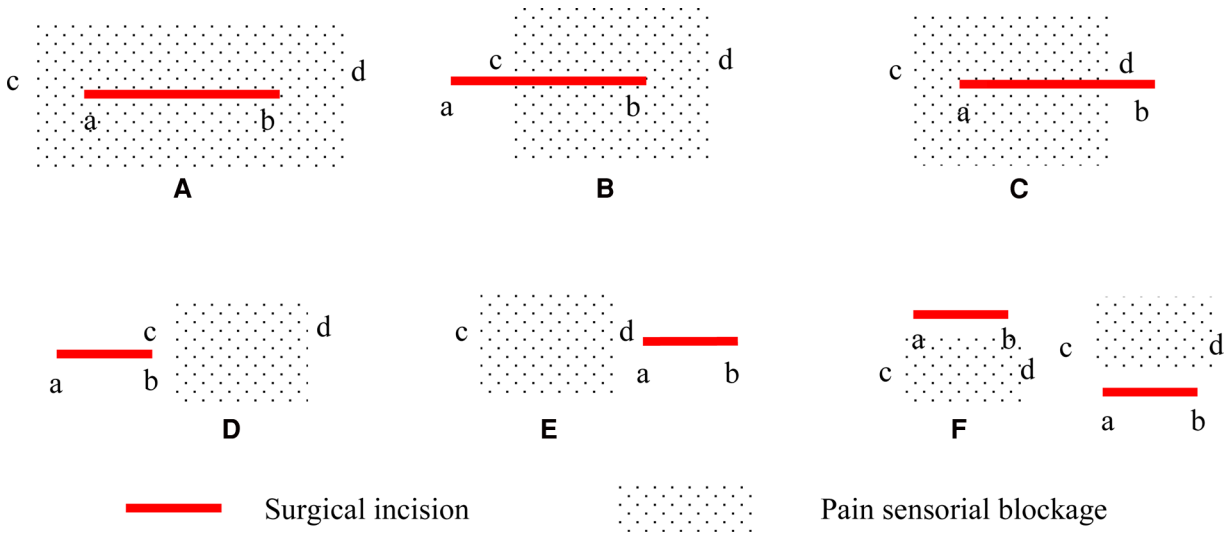

FIGURE 1
Surgical incision and pain sensorial blockage. (A) the coverage rate is defined as complete blocking (100%); (B) the coverage rate is defined as cb/ab * 100%; (C) the coverage rate is defined as ad/ab * 100%; (D) or (E) the coverage rate is defined as 0%; (F) or no hypoalgesia: blocking failure. a, the upper bound of the surgical incision; b, the lower bound of the surgical incision; c, the upper bound of pain sensorial blockage; d, the lower bound of pain sensorial blockage.

sensation of the bilateral anterior thigh and quadriceps strength were evaluated at 30 min after the completion of the ESP block, and the results were recorded. Decreased quadriceps femoris strength was defined as less than grade 4. All examinations were performed by the same investigator who was unaware of group assignment. Intraoperative and postoperative data were recorded. The TCI concentration was recorded at the following timepoints: endotracheal intubation, skin incision, pedicle screw implantation, decompression, and skin closure. The consumption of anesthetics such as propofol, sufentanil, remifentanil, and rocuronium bromide was recorded. Postoperative pain was assessed at 2, 4, 8, 12, and 24 h using VAS scores of pain at rest and active movement. Moving from the supine to the lateral position was defined as active movement. Sufentanil consumption was recorded at the above-mentioned timepoints. Postoperative nausea and vomiting (PONV) and rescue analgesia were recorded.

Statistical analysis

Sample size determination

The primary purpose of the study was to evaluate the rate of complete coverage of the surgical incision by the sensory block after the completion of a single-level or two-level ESP block. On the basis of a pilot study of 10 patients, the rate after the one-level ESP block was 80%. Assuming that the rate after the two-level ESP block was 100%, the number of patients required for each group was determined as 39, using PASS 11.0 software (NCSS, LLC. Kaysville, Utah, USA) on "Tests for two proportions [proportions]" with 90% power and 0.05 alpha error.

Outcome analysis

Statistical analysis was performed on SPSS software Version 22.0 (IBM Corp, Armonk, NY, United States). Continuous variables data were expressed as mean ± standard deviation (SD) if the measurement data were in line with normal distribution. If not, it would be presented as median (interquartile). Statistics of data normality test was performed for continuous variables. Distributed data comprising continuous variables were analyzed using Student's *t*-test, otherwise, the Mann–Whitney *U* test was used. Categorical data were analyzed using the χ^2 test. If the expected value was less than 5, the Fisher's Exact Test was used. A value of $P < 0.05$ was considered statistically significant.

Result

A total of 83 patients were enrolled between March 2021 and August 2021. Two patients from Group I and one patient from Group II were excluded owing to a change in the surgery type or cancelation, and data from the remaining 80 patients were included in the analysis, with 40 in each group (**Figure 2**).

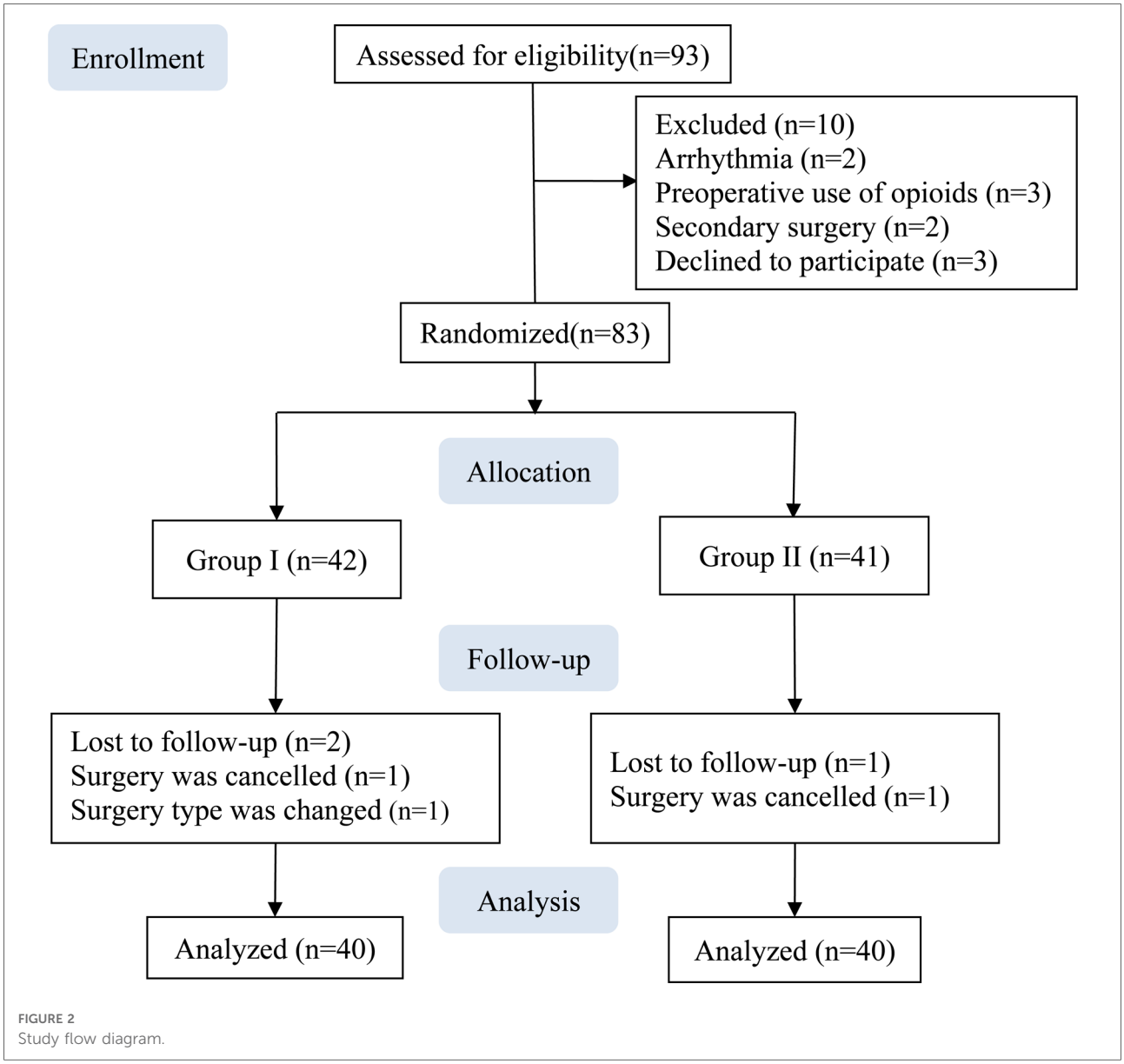

FIGURE 2
Study flow diagram.

Demographic characteristics are presented in Table 1. There was no significant difference in terms of sex, age, height, weight, ASA classification, and duration of surgery between the groups.

At 30 min after the ESP block procedure, all patients in Group II received a complete sensory block over the surgical incision site. The rate of the complete coverage of the surgical incision by the sensory block was significantly higher in Group II than in Group I (100% [40/40] vs. 85.0% [34/40], $P = 0.026$). Six patients in Group I did not receive complete coverage as described (III) in Figure 1, and the coverage rates were 72.9%, 83.2%, 87.3%, 83.9%, 88. 4%, and 91.4%. At 30 min after the completion of the block, hypoesthesia and muscle strength were assessed for both the left and the right lower limbs, and 80 evaluations were performed in each group. The rate of the sensory block in the anterior thigh was higher in Group II (43.8% [35/80] vs. 27.5% [22/80], $P = 0.032$), but the rate of quadriceps strength decrease did not differ significantly between the groups. The time to complete the ESP block was significantly longer in Group II than in Group I (16.0 [14.3, 17.0] min vs. 9.0 [8.3, 9.0] min, $P = 0.000$). After 15 min of the ESP block procedure, the rate of coverage of the surgical incision by the sensory block was significantly higher in Group II than in Group I (80.0% [32/40] vs. 57.5% [23/40], $P = 0.030$). Group I patients received 80 injections and Group II received 160 injections as described above. There was no significant difference with regard to the reliability of blockage and the targeted vertebral of the upper level (Table 2).

TABLE 1 Demographic and operative characteristics of the study patients.

	Group I ($n = 40$)	Group II ($n = 40$)	*P*-value
Sex (M/F)[a]	11/29	15/25	0.340
Age (year)[b]	59.1 ± 8.6	59.8 ± 8.6	0.737
Height (cm)[b]	164.5 ± 6.4	163.0 ± 5.4	0.279
Weight (kg)b	68.3 ± 8.4	68.8 ± 9.1	0.800
ASA status (I/II)[a]	23/17	19/21	0.370
Duration of surgery (min)[c]	120 (110–120)	120 (103–120)	0.505

Data are presented as mean ± SD or median (interquartile range).
[a]χ^2 test was used.
[b]Student's *t*-test was used.
[c]Mann–Whitney *U* test was used.

The targeted infusion concentration of remifentanil in Group II was lower than in Group I during intervertebral decompression (2.9 ± 0.3 ng/ml vs. 3.3 ± 0.5 ng/ml, $P = 0.007$). No significant difference was found between the two groups with regard to the target concentration of propofol and remifentanil during the operation (Table 3). There was also no significant difference with regard to the intraoperative anesthetic dosage between the two groups (Table 4). Postoperative rest and active movement VAS scores within 24 h are given in Table 5. There was no significant difference in the total consumption dosage of sufentanil within 24 h postoperatively (Table 6).

No block failures, local anesthetic allergy, toxicity, total spinal anesthesia or epidural blocking, hematoma, and postoperative infection were detected. There was no difference with regard to rescue analgesia, nausea, and vomiting among these patients (Table 7).

TABLE 3 Comparison of the TCI concentration of propofol and remifentanil during the maintenance of anesthesia.

	Group I ($n = 40$)	Group II ($n = 40$)	*P*-value
Propofol (μg/ml)			
Intubation	3.1 ± 0.4	3.1 ± 0.4	0.873
Skin incision	3.6 ± 0.4	3.6 ± 0.5	0.651
Pedicle screw implantation	3.7 ± 0.4	3.8 ± 0.5	0.219
Decompression	3.7 ± 0.4	3.7 ± 0.5	0.581
Skin closure	3.7 ± 0.5	3.8 ± 0.5	0.828
Remifentanil (ng/ml)			
Intubation	1.6 ± 0.2	1.5 ± 0.2	0.726
Skin incision	2.8 ± 0.7	2.7 ± 0.6	0.985
Pedicle screw implantation	2.9 ± 0.7	2.8 ± 0.5	0.390
Decompression	3.3 ± 0.5	2.9 ± 0.3*	0.007
Skin closure	2.7 ± 0.6	2.8 ± 0.5	0.923

Data are presented as mean ± SD.
Mann–Whitney *U* test was used.
*$P < 0.05$ compared with Group I.

Discussion

Skin, muscle, and bone will be damaged during posterior lumbar surgery (11). The surgical incision and paravertebral muscles were innervated by the dorsal rami of the spinal nerves, which runs downward and backward after passing through the transverse process of the lower vertebrae. A segmental and crossed distribution is the feature of the dorsal spinal nerve rami. An ideal regional block should block several dorsal ramies of the spinal nerve, especially the nerve from the cranial vertebrae, so we chose one level above the operative vertebrae as the site of the ESP block (9, 15–17). Previous studies have shown that a median of 5 ml of injectate was needed to cover one vertebral level. When the ESP block was performed in the lumbar region in our study, 0.3% ropivacaine of 25 ml was injected (18). In the pilot study, we evaluated the pain sensorial blockage after the ESP block, which did not cover the lower part of the incision. A larger volume of LA might result in a broader block site, but it might cause epidural anesthesia (19). On the other hand,

TABLE 2 Target vertebra of the block and block effect.

	Group I ($n = 40$)	Group II ($n = 40$)	*P*-value
Objective vertebral of the upper level ($T_{12}/L_1/L_2/L_3/L_4$)[a]	0/11/18/11/1	1/14/20/5/0	0.364
Objective vertebral of the lower level ($/L_4/L_5/S_1$)	None	12/15/13	None
Duration of ESP blocking manipulation (min)[b]	9.0 (8.3–9.0)	16.0 (14.3–17.0)*	0.000
Reliability of blockage (0/1/2)[c]	0/45/35	0/94/66	0.712
Coverage rate ≥ 100% at 15 min after ESP blocking[c]	23 (57.5)	32 (80.0)*	0.030
Coverage rate ≥ 100% at 30 min after ESP blocking[a]	34 (85.0)	40 (100.0)*	0.026
Hypoalgesia of lap[c]	22 (27.5)	35 (43.8)*	0.032
Quadriceps strength weakening[c]	17 (21.3)	26 (32.5)	0.108

Data are presented as median (interquartile range) or number (%).
[a]Fisher's Exact Test was used.
[b]Mann–Whitney *U* test.
[c]χ^2 test was used was used.
*$P < 0.05$ compared with Group I.

TABLE 4 Comparison of anesthetics consumption dosage between the two groups during the maintenance of anesthesia.

	Group I ($n = 40$)	Group II ($n = 40$)	*P*-value
Propofol (mg)[a]	1041.3 ± 185.4	1057.0 ± 136.5	0.667
Sufentanil (μg)[b]	22 (21–22)	22 (21–23)	0.682
Remifentanil (μg)[a]	861.2 ± 142.3	898.3 ± 128.4	0.225
Rocuronium Bromide (μg)[b]	40 (40–50)	40 (40–48)	0.278

Data are presented as mean ± SD or median (interquartile range).
[a]Student's *t*-test was used.
[b]Mann–Whitney *U* test was used.

the lumbar ESP block has a more localized spread compared with the thoracic ESP block because of a more complex, multilayered thoracolumbar fascia and the arrangement and thickness of the lumbar musculature (20, 21). The iliolumbar ligament, which passes from the tip of the transverse process of the L5 vertebra to the iliac crest, forms a thickened lower border of the two layers of the TLF and limits caudal spread (22, 23). Because of the reasons cited above, we performed a two-level ESP block, rather than increasing the volume of LA. Different LA-injected levels might result in different blocking sites. We recorded the injected level of the upper ESP block. Because the injected upper level was the same between the two groups, the added lower-level injection site was the reason for better coverage. To make sure LA was injected correctly, the reliability of the block was evaluated. The diffusion of LA was visible on ultrasound image. The result showed that the two-level ESP block provided a better pain sensorial blockage. Similar to our study, Silnha et al. (24) found that the two-level ESP block resulted in a better cranio-caudal spread of LA in a patient undergoing kyphosis correction surgery.

The spread of LA after the ESP block may follow different pathways, such as between the transverse process and the erector spinae muscle, between the QL muscle and the psoas muscle, and between the QL and the erector spinae muscle, which could block both the ventral and the dorsal rami of the spinal nerve (25). Previous studies have shown that different LA volumes, block levels, and needle tip positions lead to different sensory block areas (10, 18, 22, 26–28). In a cadaveric study, 20 ml of contrast solution was injected at L4, and then CT scan and dissection were performed. It was found that the solution spread from L2 to L5 in the erector spinae muscle, reaching the facet joints and the thoracolumbar fascia. In 33% of patients, the solution did not spread anterior to the transverse process, and in 16% patients, the contrast solution reached the corresponding spinal nerves (28). Harbell et al. (22) found that 20 ml of methylene blue injected at L4 could consistently spread to the dorsal rami, but there was no anterior spread to the ventral rami or paravertebral space. Azevedo et al. (27) performed the ESP block at L4 in fresh cadavers, injecting different volumes of LA, and found that the lumbar ESP block was effective in reaching the dorsal rami of the lumbar spinal nerves with a low volume injection of 20 ml. However, the anterior spread reaching the ventral rami or paravertebral space was better achieved with larger volumes of solution (30–40 ml). In our study, an LA of 35 ml was injected for patients in Group II, which yielded a higher rate of anterior thigh analgesia, indicating that LA had spread to the ventral rami. The lumbar disc is innervated by the anterior rami and the sinusoidal vertebral nerve. Better ventral rami blocking might account for a lower target infusion concentration of remifentanil needed in Group II patients during intraoperative decompression.

TABLE 5 Comparison of visual analog pain scores at postoperative timepoints.

	Group I ($n = 40$)	Group II ($n = 40$)	*P*-value
At rest			
2 h	1.6 ± 1.1	1.6 ± 1.0	0.884
4 h	1.6 ± 1.0	1.5 ± 1.0	0.831
8 h	1.5 ± 0.8	1.3 ± 1.9	0.559
12 h	1.7 ± 0.8	1.6 ± 0.9	0.813
24 h	1.5 ± 0.8	1.4 ± 0.7	0.473
During active movement			
2 h	2.5 ± 0.9	2.3 ± 0.9	0.577
4 h	2.7 ± 0.7	2.7 ± 0.9	0.875
8 h	2.6 ± 0.7	2.6 ± 0.9	0.925
12 h	2.9 ± 0.6	2.7 ± 0.7	0.132
24 h	2.7 ± 0.7	2.8 ± 0.9	0.587

Data are presented as mean ± SD.
Mann–Whitney *U* test was used.

TABLE 6 Comparison of sufentanil consumption dosage in the first 24 h following surgery.

	Group I ($n = 40$)	Group II ($n = 40$)	*P*-value
0–2 h (μg)	4.4 ± 1.9	4.5 ± 2.1	0.987
2–4 h (μg)	4.4 ± 2.1	4.8 ± 2.4	0.483
4–8 h (μg)	8.9 ± 2.2	8.4 ± 2.0	0.304
8–12 h (μg)	10.4 ± 2.9	9.8 ± 2.5	0.382
12–24 h (μg)	22.6 ± 3.3	21.8 ± 2.4	0.411
Total 24 h (μg)	50.7 ± 6.5	49.3 ± 7.0	0.273

Data are presented as mean ± SD.
Mann–Whitney *U* test was used.

TABLE 7 Comparison of rescue analgesia and PONV between the two groups.

	Group I ($n = 40$)	Group II ($n = 40$)	*P*-value
Rescue analgesia	2 (5.0)	1 (2.5)	0.500
PONV	3 (7.5)	4 (10)	0.500

Data are presented as number (%).
Fisher's Exact Test was used. PONV, postoperative nausea and vomiting.

Multimodal analgesia was used in our study to relieve postoperative pain. In Group I, there were six patients who did not reach 100% incision blockage with the ESP block, but the coverage rate was more than 70%, which could be considered effective for intraoperative and postoperative pain control. There was no difference in terms of the degree of postoperative pain and sufentanil dosage between the two groups, which might be attributed to effective administration of incisional analgesia, and the result may also be limited by the sample size.

This study has some limitations. First, for patients in Group II, a larger volume of LA was injected, and it might result in a wider site of the block. The added injected position in Group II was another factor that might lead to better coverage. However, we could not distinguish whether it was the larger volume, LA-injected position, or both that led to the increased blockage rate. In addition, in our study, the injection point of Group I patients was similar to the upper injection point of Group II. For the one-level ESP block, injection in the midpoint of the incision might result in better coverage. Further study is needed to confirm this result. Second, the dressing covering the incision after surgery made it difficult to evaluate sensory loss of the block, and therefore, the duration of the block was not evaluated. Third, the patients in this study could not be blinded to the intervention, and this might lead to additional bias.

In conclusion, when compared with the one-level ESP block, the two-level ESP block with a larger-volume LA provided better craniocaudal spread and a higher rate of complete coverage of the surgical incision by the sensory block. However, there is no difference in intraoperative and postoperative opioid-sparing effects between the one-level and the two-level ESP blocks. The optimal method of the ESP block in patients undergoing lumbar surgery remains to be explored.

Data availability statement

The original contributions presented in the study are included in the article further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Jishuitan Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TW and GW designed and conducted the study. SZ performed the ESP block, and YZ evaluated the block effect. LH and SZ performed the surgical procedure. WZ and YZ were responsible for the collection of data. TW revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Nashibi M, Tafrishinejad A, Safari F, Asgari S, Sezari P, Mottaghi K. Evaluation of ultrasound guided erector spinae plane block efficacy on post operative pain in lumbar spine surgery: a randomized clinical trial. *Agri*. (2022) 34(3):174–9. doi: 10.14744/agri.2021.04864

2. Bajwa SJ, Haldar R. Pain management following spinal surgeries: an appraisal of the available options. *J Craniovertebr Junction Spine*. (2015) 6(3):105–10. doi: 10.4103/0974-8237.161589

3. Lin H, Guan J, Luo S, Chen S, Jiang J. Bilateral erector spinae plane block for quality of recovery following posterior lumbar interbody fusion: a randomized controlled trial *Pain Ther*. (2022) 113:861–71. doi: 10.1007/s40122-022-00395-9

4. van den Broek RJC, van de Geer R, Schepel NC, Liu WY, Bouwman RA, Versyck B. Evaluation of adding the erector spinae plane block to standard anesthetic care in patients undergoing posterior lumbar interbody fusion surgery. *Sci Rep*. (2021) 11(1):7631. doi: 10.1016/j.jclinane.2021.11026810.1038/s41598-021-87374-w

5. Oh SK, Lim BG, Won YJ, Lee DK, Kim SS. Analgesic efficacy of erector spinae plane block in lumbar spine surgery: a systematic review and meta-analysis. *J Clin Anesth*. (2022) 78:110647. doi: 10.1016/j.jclinane.2022.110647

6. Oezel L, Hughes AP, Onyekwere I, Wang Z. Procedure-specific complications associated with ultrasound-guided erector spinae plane block for lumbar spine

surgery: a retrospective analysis of 342 consecutive cases *J Pain Res*. (2022) 15:655–61. doi: 10.2147/jpr.s354111

7. Yayik AM, Cesur S, Ozturk F, Ahiskalioglu A, Ay AN, Celik EC, et al. Postoperative analgesic efficacy of the ultrasound-guided erector spinae plane block in patients undergoing lumbar spinal decompression surgery: a randomized controlled study. *World Neurosurg*. (2019) 126:e779–85. doi: 10.1016/j.wneu.2019.02.149

8. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. *Reg Anesth Pain Med*. (2016) 41(5):621–7. doi: 10.1097/AAP.0000000000000451

9. Tulgar S, Aydin ME, Ahiskalioglu A, De Cassai A, Gurkan Y. Anesthetic techniques: focus on lumbar erector spinae plane block. *Local Reg Anesth*. (2020) 13:121–33. doi: 10.2147/LRA.S233274

10. Tulgar S, Ahiskalioglu A, Aydin ME, Jadon A, Forero M, Gurkan Y. Lumbar erector spinae plane block: a miracle or self-persuasion? *Reg Anesth Pain Med*. (2021) 46(7):638–9. doi: 10.1136/rapm-2020-102336

11. Vergari A, Frassanito L, Mariangela DIM, Nestorini R, Chierichini A, Rossi M, et al. Bilateral lumbar ultrasound-guided erector spinae plane block versus local anesthetic infiltration for perioperative analgesia in lumbar spine surgery: a randomized controlled trial. *J Pain Res*. (2022) 88(6):465–71. doi: 10.2147/jpr.s35411110.23736/s0375-9393.22.15950-x

12. Rizkalla JM, Holderread B, Awad M, Botros A, Syed IY. The erector spinae plane block for analgesia after lumbar spine surgery: a systematic review. *J Orthop*. (2021) 24:145–50. doi: 10.1016/j.jor.2021.02.006

13. Schwartz RH, Urits I, Viswanath O, Urman RD, Kaye AD, Eskander JP. Successful combination of thoracodorsal interfascial plane block and erector spinae pain block for peri-operative pain control after lumbar laminectomy. *J Clin Anesth*. (2020) 62:109705. doi: 10.1016/j.jclinane.2020.109705

14. Liu MJ, Zhou XY, Yao YB, Shen X, Wang R, Shen QH. Postoperative analgesic efficacy of erector spinae plane block in patients undergoing lumbar spinal surgery: a systematic review and meta-analysis. *Pain Ther*. (2021) 10 (1):333–47. doi: 10.1007/s40122-021-00256-x

15. Singh S, Choudhary NK, Lalin D, Verma VK. Bilateral ultrasound-guided erector spinae plane block for postoperative analgesia in lumbar spine surgery: a randomized control trial. *J Neurosurg Anesthesiol*. (2020) 32(4):330–4. doi: 10.1097/ana.0000000000000603

16. Selvi O, Tulgar S, Serifsoy TE, Lance R, Thomas DT, Gürkan Y. Quadrant and dermatomal analysis of sensorial block in ultrasound- guided erector spinae plane block. *Eurasian J Med*. (2022) 54(2):121–6. doi: 10.5152/eurasianjmed.2022.21151

17. Zhang Q, Wu Y, Ren F, Zhang X, Feng Y. Bilateral ultrasound-guided erector spinae plane block in patients undergoing lumbar spinal fusion: a randomized controlled trial. *J Clin Anesth*. (2020) 68:110090. doi: 10.1016/j.jclinane.2020.110090

18. De Cassai A, Andreatta G, Bonvicini D, Boscolo A, Munari M, Navalesi P. Injectate spread in esp block: a review of anatomical investigations. *J Clin Anesth*. (2020) 61:109669. doi: 10.1016/j.jclinane.2019.109669

19. Guna Pratheep K, Sonawane K, Rajasekaran S, Shetty AP, Subramanian BJ, Kanna RM. Transient paraplegia in lumbar spine surgery-a potential complication following erector spinae plane block. *Eur Spine J*. (2021). doi: 10.1007/s00586-021-07059-w

20. Kose HC, Kose SG, Thomas DT. Lumbar versus thoracic erector spinae plane block: similar Nomenclature, different mechanism of action. *Can J Anaesth*. (2018) 48:1. doi: 10.1007/s12630-018-1145810.1016/j.jclinane.2018.03.026

21. Ivanusic J, Konishi Y, Barrington MJ. A cadaveric study investigating the mechanism of action of erector spinae blockade. *Reg Anesth Pain Med*. (2018) 43(6):567–71. doi: 10.1097/AAP.0000000000000789

22. Harbell MW, Seamans DP, Koyyalamudi V, Kraus MB, Craner RC, Langley NR. Evaluating the extent of lumbar erector spinae plane block: an anatomical study. *Reg Anesth Pain Med*. (2020) 45(8):640–4doi: 10.1136/rapm-2020-101523

23. Elsharkawy H, Bajracharya GR, El-Boghdadly K, Drake RL, Mariano ER. Comparing two posterior quadratus lumborum block approaches with low thoracic erector spinae plane block: an anatomic study. *Reg Anesth Pain Med*. (2019)28:rapm-2018-10047. doi: 10.1136/rapm-2018-100147

24. Sinha C, Kumar A, Kumar A, Kumari P, Agrawal P, Sk A. Two-level bilateral ultrasound-guided erector spinae plane block for kyphosis corrective surgery – a case report. *Anesth Pain Med (Seoul)*. (2022) 17(3):327–30. doi: 10.1007/s00586-022-07212-z10.17085/apm.21107

25. Pascarella G, Costa F, Strumia A, Agrò FE, Del Buono R. The multiple pathways of local anaesthetic during lumbar erector spinae plane block: an ultrasound finding. *Anaesthesia*. (2021) 76(1):142–3. doi: 10.1016/j.wneu.2020.10.17510.1111/anae.15216

26. Kokar S, Ertaş A, Mercan Ö, Yildirim FG, Taştan Ö A, Akgün K. The lumbar erector spinae plane block: a cadaveric study. *Turk J Med Sci*. (2022) 52 (1):229–36. doi: 10.7759/cureus.1866610.3906/sag-2107-83

27. Azevedo AS, Silva VTG, Xavier AL, da Silva LFF, Hojaij FC, Ashmawi HA, et al. Comparison of different injection volumes on spread of lumbar erector spinae plane block: an anatomical study. *Global Spine J* (2021) 72:110268. doi: 10.1177/2192568221101074010.1016/j.jclina-ne.2021.110268

28. De Lara Gonzalez SJ, Pomes J, Prats-Galino A, Gracia J, Martinez-Camacho A, Sala-Blanch X. Anatomical description of anaesthetic spread after deep erector spinae block at L-4. *Rev Esp Anestesiol Reanim*. (2019) 66(8):409–16. doi: 10.1016/j.redar.2019.07.001

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Continuous cryotherapy vs. traditional cryotherapy after total knee arthroplasty: A systematic review and meta-analysis of randomized controlled trials

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Background: Cryotherapy is widely applied to relieve pain and improve functional outcomes after total knee arthroplasty (TKA). New cryotherapy devices have recently been developed to guarantee a fixed temperature for a prolonged time. Therefore, we conducted a systematic review and meta-analysis to compare continuous cryotherapy and traditional cryotherapy (ice bag or gel pack) for patients after TKA.

Methods: This study was conducted according to a predefined protocol registered on PROSPERO. Two independent reviewers performed an electronic database search of PubMed, Embase, Cochrane, Web of Science, Google Scholar, and ClinicalTrials.gov. Dichotomous outcomes were reported as risk difference (RD) with 95% confidence intervals (CIs), and continuous outcomes were reported as mean difference (MD), or standardized mean difference (SMD) with 95% CIs.

Results: Seven trials enrolling a total of 519 patients were included. There were no differences in pain intensity (MD: −0.54, 95% CI: −1.55 to 0.47; $P = 0.30$), analgesics consumption (MD: −0.37, 95% CI: −1.28 to 0.55; $P = 0.43$), postoperative range of motion (MD: 0.47, 95% CI: −4.09 to 5.03; $P = 0.84$), swelling of the knee joint, blood loss, change in hemoglobin, or transfusion rate. Meanwhile, there were no differences in length of hospital stay (MD: −0.77, 95% CI: −1.62 to 0.08; $P = 0.07$) and adverse events (RD: 0, 95% CI: −0.02 to 0.03; $P = 0.74$). In addition, continuous cryotherapy leads to extra costs and resources than traditional cryotherapy.

Conclusions: Continuous cryotherapy does not appear to offer significant benefits for TKA when compared with traditional cryotherapy. Based on currently available evidence, traditional cryotherapy is still recommended as continuous cryotherapy is not cost-effective. Further well-designed studies with larger sample sizes are warranted to further confirm these preliminary results.

PROSPERO Registration: Identifier [CRD42022308217].

KEYWORDS

cryotherapy, total knee arthroplasty, postoperative pain, analgesics consumption, swelling, range of motion, cost

1. Introduction

Total knee arthroplasty (TKA) is an effective surgical intervention for end-stage arthritis of the knee joint, which could provide better overall improvements in function, mobility, pain, and health-related quality of life (1, 2). Despite several studies with short- to mid-term follow-up have reported excellent results with high rates of satisfaction, the postoperative period after TKA may be pretty challenging: patients may experience acute pain, potential blood loss, local swelling, and edema resulting from tissue damage and acute inflammatory responses, restricted motion, and stiffness of the knee joint, reduced quadriceps strength, and finally lead to delayed recovery and prolonged hospital stay (3–5). Thus, even with the latest advances in multimodal pain management protocols, surgical and anesthetic techniques, TKA remains a difficult procedure for most patients. It is, therefore, a pressing need for the introduction and implementation of the enhanced recovery after surgery (ERAS) principles, which aim to optimize perioperative care, reduce complications, shorten the length of hospital stay, and reduce readmission rates and costs (6–8). Cryotherapy, as a nonpharmaceutical treatment, plays a vital role in addressing immediate postoperative complications, mainly for severe pain and significant swelling (9, 10).

Cryotherapy, also known as cold therapy, was utilized for inflammation and infection treatment as early as 3,000 BC, and was utilized for anesthesia before operations and amputations for its analgesic and numbing effects in the 1800s (11, 12). At present, cryotherapy is still commonly recommended and widely applicated following orthopaedic procedures, which is also utilized to enhance recovery and outcomes after TKA (13). Despite many advances in postoperative rehabilitation, cryotherapy remains popular and is universally considered appealing for its minimal disadvantages compared with the possible benefits. External application of cryotherapy in TKA is the application of external cold mediums to the skin around the knee joint and is supposed to reduce the intra-articular temperature, which on the one hand, could slow the conduction velocity of nerve fibers and potentially reduce pain transmission, and on the other hand, could reduce peripheral blood flow due to circulating vasoconstriction and therefore decrease the local inflammation and swelling (13). Traditionally, ice bag or gel pack is the most common and economical cryotherapy method, which is typically discontinuous with unregulated cold temperature and demands a manual replacement by the staff nurses (14). Therefore, continuous cryotherapy devices have been developed to deliver a steady cooling temperature for a prolonged time (15). However, it remains unclear whether the newly developed continuous cryotherapy devices were superior to traditional ice/gel pack for TKA.

A broad scope of the literature has suggested that the volume of randomized controlled trials (RCTs) specifically focusing on continuous cryotherapy vs. traditional cryotherapy has increased, and findings are conflicting (16–22). The aim of this study was to perform a comprehensive systematic review and use a meta-analytic approach to pool outcomes to compare the efficacy, safety, and cost-effectiveness of continuous cryotherapy to traditional cryotherapy for TKA.

2. Methods

The present systematic review and meta-analysis was designed in accordance with the guidelines proposed by the Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org) and completed according to a predefined protocol, which has been listed on the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42022308217) (23). The study was completed in adherence with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (24).

2.1 Literature search

We searched the following electronic bibliographic databases from inception to March 2,022 to capture all recent relevant studies: PubMed, Embase, The Cochrane Library (Cochrane Database of Systematic Reviews), Web of Science, and Google Scholar,. We performed electronic searches using exploded Medical Subject Headings (MeSH) terms with corresponding keywords. The search was broad and applied no language restriction. A detailed description can be found in Appendix 1. In addition, we further searched the ClinicalTrials.gov registry (https://clinicaltrials.gov/) and checked the reference lists of all included full-text articles and previous systematic reviews to identify any additional eligible studies. Corresponding authors of included articles were contacted, where possible, to obtain detailed information or numerical data.

2.2 Study eligibility and selection

Two investigators independently conducted the initial electronic databases search and carefully reviewed all yielded records for inclusion using pre-determined eligibility criteria. All records were screened by title, abstract, and keywords for possible inclusion, and subsequently, identified as “included”, “excluded”, or “required further retrieval” to identify

eligibility. No language or publication database filter was applied. Any discrepancies were resolved through discussion by the review team.

The inclusion criteria were:

(i) Population: adult patients undergoing TKA;
(ii) Intervention: received continuous cryotherapy (without compression) after TKA;
(iii) Comparison: received traditional cryotherapy after TKA;
(iv) Outcomes: reporting at least one of the outcomes of interest listed below;
(v) Study type: RCT.

Exclusion criteria were non-RCT interventional studies, observational studies, conference abstracts, editorials, correspondence, expert opinions, case series or reports, and unavailable full texts.

2.3 Data review and extraction

Two independent reviewers extracted details pertaining to the participants from each included trial. The following data were extracted from each included study: first author; year of publication; study location; publication journal; study design; clinical settings; study population; demographic data; intervention management; control management; outcomes of interest. These extracted data were entered into a standardized data extraction form. When the information was unclear or missing, we attempted to contact the corresponding authors of the original studies. The differences in the extracted data were discussed and resolved by referring to the original article by the panel of all the reviewers. The main outcomes of interest were the efficacy, safety, and cost-effectiveness of continuous cryotherapy when compared with traditional cryotherapy. In detail, the primary outcomes include pain intensity, analgesics consumption, postoperative range of motion (PROM), and swelling of the knee joint; while the secondary outcomes include blood loss, change in hemoglobin, transfusion rate, adverse events, length of hospital stay, and cryotherapy costs.

2.4 Quality assessment

Two reviewers independently evaluated the risk of bias of each study using the assessment tool from the Cochrane Handbook (25). The major domains of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias) in each trial were reviewed. Each study was graded as "low risk of bias", "unclear risk of bias", or "high risk of bias". The highest risk score from any one domain was used to inform the overall risk. If the highest risk score was "unclear risk of bias" but occurred across multiple domains, it was classed as high risk of bias. Therefore, to be of low risk of bias overall, the trial had to be at low risk of bias across all domains. The disagreements between the two reviewers were resolved *via* discussion and consensus.

2.5 Statistical analysis

This meta-analysis was performed using Review Manager version 5.3 (Nordic Cochrane Center) for all prespecified outcomes if three or more studies reported the outcome (23). The risk differences (RDs) with 95% confidence intervals (CIs) were calculated for dichotomous data; and the mean differences (MDs) or standardized mean difference (SMD) with 95% CIs were calculated for continuous data. When the mean values are not available for continuous outcomes, the median values was utilized for estimation; other potential missing data will be estimated using the methods described in the Cochrane Handbook (23). A random-effects model was used due to anticipated heterogeneity. Results were reported in a Forest plot with 95% CIs. Heterogeneity was assessed *via* three means: visual inspection of overlapping confidence intervals, the statistical heterogeneity across studies quantified using I^2 statistics, with $P \geq 0.05$ considered statistically non-significant. Heterogeneity will be considered to be substantial if the I^2 value $> 50\%$. All P values were two-sided, and a P value < 0.05 was considered to be statistically significant evidence.

3. Results

3.1 Study selection

In total, 1,387 articles were obtained from the electronic search strategy, with an additional 16 articles identified through other resources. After the removal of duplicates and irrelevant references, 35 publications were thought to be potentially eligible for inclusion and further assessed for eligibility. Overall we excluded 28 publications for not meeting the inclusion criteria, and seven RCTs were included. The flow diagram with the number of and reasons for exclusions at each stage is provided in **Figure 1**.

3.2 Characteristics of included studies

The characteristics of included studies can be found in the study characteristics tables (**Tables 1**, **2**). Seven trials were included in our meta-analysis, which randomized 519 patients into continuous cryotherapy group ($n = 263$) and

traditional cryotherapy ($n = 256$). These studies were published between 2012 and 2019, with a sample size ranging from 44 to 100. Notably, the application protocols between the continuous and traditional cryotherapy groups differed significantly with respect to the applied time and intervals, and the difference is even more significant among studies.

3.3 Risk of bias in included studies

No trials were considered to be at low risk of bias. Three studies were judged to be at high risk of bias, and four studies were felt to be at unclear risk of bias (Figures 2, 3). More specifically, adequate randomized sequence generation was reported in six trials, while appropriate allocation concealment was conducted in one trial. Blinding of outcome assessments was achieved by three trials, thus, the primary efficacy outcome and other outcomes assessment may have been affected by lack of blinding to some extent.

4. Outcomes

4.1 Primary outcomes

4.1.1 Pain

Data for pain intensity were reported by six trials that recruited 475 patients ($n = 241$ vs. $n = 234$ in the continuous cryotherapy group and traditional cryotherapy group, respectively). Meta-analysis was performed on studies that reported a pain score for participants at 48 h postoperatively (Figure 4). There was no statistically significant difference in the pain score at 48 h between the continuous cryotherapy group and the traditional cryotherapy group (MD: −0.54, 95% CI: −1.55 to 0.47; $P = 0.30$). A high level of heterogeneity was observed ($I^2 = 96\%$). Data for analgesics consumption were reported by three trials that recruited 268 patients ($n = 138$ vs. $n = 130$ in the continuous cryotherapy group and traditional cryotherapy group, respectively). SMD was used as there were differences in the calculating conversations of analgesics consumption. There was no statistically significant difference in

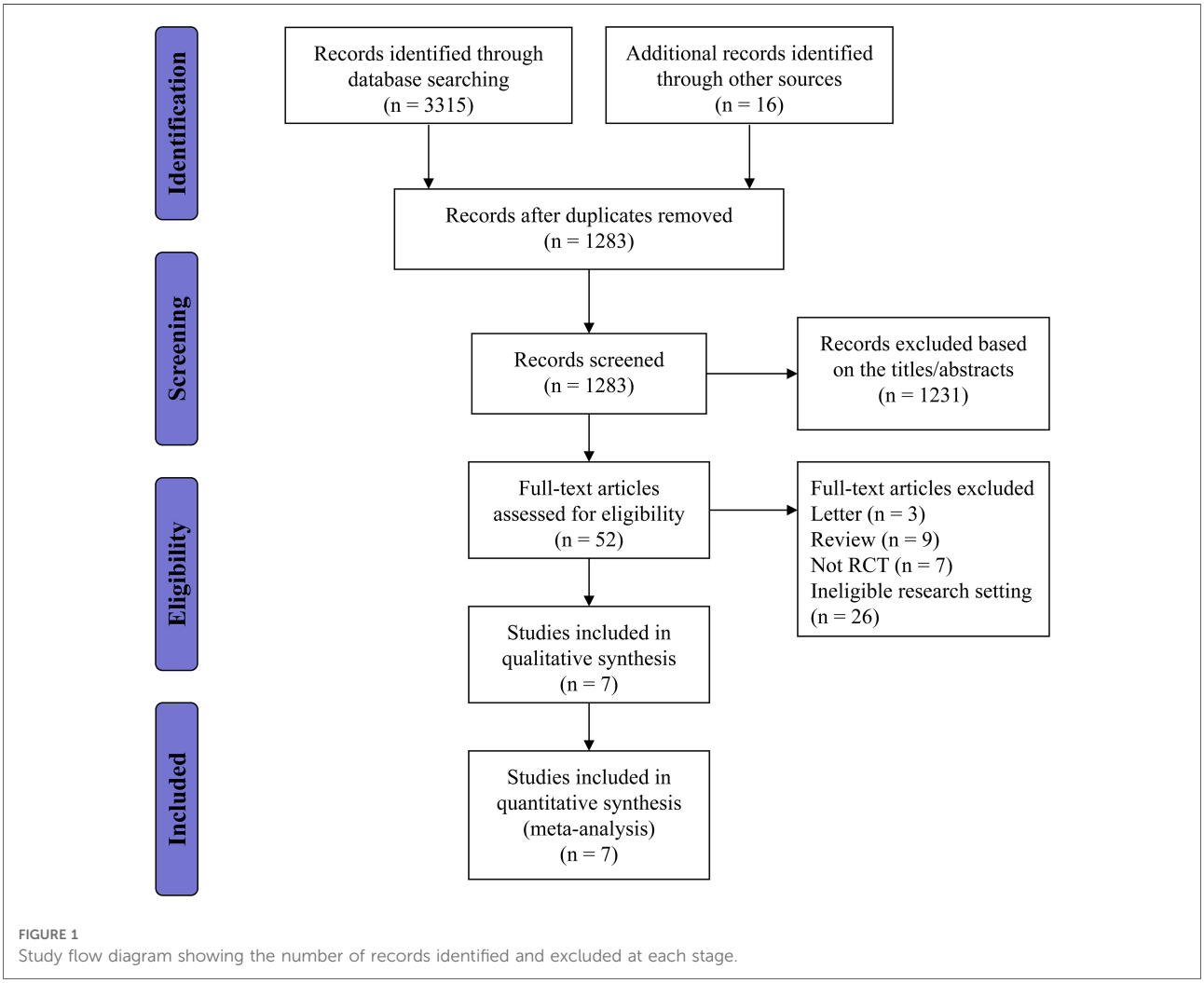

FIGURE 1
Study flow diagram showing the number of records identified and excluded at each stage.

TABLE 1 Baseline characteristics of the included studies.

Author	Year	Region	Journal	Study Dates	Sample size
Demoulin (16)	2012	Belgium	Annals of Physical and Rehabilitation Medicine	Not reported	44
Thienpont (17)	2014	Belgium	Clinical Orthopaedics and Related Research	January 2012–October 2012	100
Bech (18)	2015	Canada	Physiotherapy Canada	February 2009–May 2012	71
Schinsky (19)	2016	US	Orthopaedic Nursing	June 2012–September 2013	97
Ruffilli (20)	2017	Italy	Journal of Knee Surgery	2013–2014	50
Sadoghi (21)	2018	Austria	International Orthopaedics	December 2011–April 2013	97
Karaduman (22)	2019	Turkey	Medicina (Kaunas)	January 2015–January 2016	60

analgesics consumption between the continuous cryotherapy group and the traditional cryotherapy group (SMD: −0.37, 95% CI: −1.28 to 0.55; $P = 0.43$) (Figure 5). A high level of heterogeneity was observed ($I^2 = 92\%$).

4.1.2 Swelling

Data for PROM were reported by six trials that recruited 475 patients ($n = 241$ vs. $n = 234$ in the continuous cryotherapy group and traditional cryotherapy group, respectively). There was no statistically significant difference in the PROM between the continuous cryotherapy group and the traditional cryotherapy group (MD: 0.47, 95% CI: −4.09 to 5.03; $P = 0.84$) (Figure 6). A high level of heterogeneity was observed ($I^2 = 84\%$).

Knee circumference is another parameter that reflects swelling of the knee joint and was reported in three trials. Meta-analysis was not performed as two trials reported the postoperative knee circumference while one trial reported the difference in knee circumference. Overall, all three trials found no statistically significant difference in knee circumference between the continuous cryotherapy group and the traditional cryotherapy group.

4.2 Secondary outcomes

4.2.1 Blood loss

Only one study reported blood loss and there was no statistically significant difference between the continuous cryotherapy group and the traditional cryotherapy group.

4.2.2 Change in hemoglobin

Three trials reported data for hemoglobin changes, and meta-analysis was not performed because two trials reported the preoperative and postoperative hemoglobin while one trial reported the change in hemoglobin. Only one study detected a statistically significant difference between the continuous cryotherapy group and the traditional cryotherapy group (22).

4.2.3 Transfusion rate

Data for transfusion rate was reported by three trials, and meta-analysis was not performed as two trials reported the number of transfusions while one study reported the number of units of allogeneic blood transfusions. Overall, all three trials found no statistically significant difference in transfusion rate between the continuous cryotherapy group and the traditional cryotherapy group.

4.2.4 Length of hospital stay

Data for the length of hospital stay were reported by four trials that recruited 265 patients ($n = 187$ vs. $n = 178$ in the continuous cryotherapy group and traditional cryotherapy group, respectively). There was no statistically significant difference in the length of hospital stay between the continuous cryotherapy group and the traditional cryotherapy group (MD: −0.77, 95% CI: −1.62 to 0.08; $P = 0.07$) (Figure 7). A high level of heterogeneity was observed ($I^2 = 84\%$).

4.2.4 Safety

Data for adverse events were reported by six trials that recruited 362 patients ($n = 184$ vs. $n = 178$ in the continuous cryotherapy group and traditional cryotherapy group, respectively). There was no statistically significant difference in the incidence of adverse events between the continuous cryotherapy group and the traditional cryotherapy group (RD: 0, 95% CI: −0.02 to 0.03; $P = 0.74$) (Figure 8).

4.2.4 Cost

Data for cryotherapy costs were reported by three trials. Thienpont et al. reported that the cost of continuous cryotherapy is $ 520, Schinsky et al. reported that continuous cryotherapy costs $97.34 than traditional cryotherapy per patient, while Karaduman reported that they found no significant additional costs associated with the use of continuous cryotherapy.

TABLE 2 Baseline characteristics of the included population.

Author	Group size	Groups	Cold treatment	Device	Tourniquet use	Outcomes	Follow-up
Demoulin et al. 2012 (16)	22	Cryotherapy device	Applied for 20 min, five times a day. From POD 2 to discharge, except the weekend.	Aircast Cryocuff combined with AutoChill System (Aircast, Inc., Summit, New Jersey)	Used for 45–55 min	Pain intensity; swelling of the phatologic knee; ROM; cutaneous temperature of the knee	Not reported
	22	Ice/gel pack	Applied for 20 min, five times a day. From POD 2 to discharge, except the weekend.				
Thienpont et al. 2014 (17)	50	Cryotherapy device	The cTreatment device was used immediately after surgery for 4 h of continuous cooling at 11°C (range, 6–15°C). The day after surgery, the device was applied for 2 h after standard physiotherapy and repeated in the afternoon. During the evening and night, patients were allowed to continuously used during the night.	cTreatment system (Waegener, Beerse, Belgium)	Used for 55 ± 9 min	VAS score; analgesics consumption; ROM; swelling of the knee; blood loss	6 weeks for data collection and 3 months for adverse events
	50	Ice/gel pack	Patients received 15 min of cold pack (conserved at −17°C) treatment on arrival to the recovery room and again on arrival to the ward, and repeated 2 h and 4 h after surgery. The following days patients received cold pack cryotherapy 15 min after their physiotherapy session (11 AM and 3 PM) and during the evening and night whenever they considered it useful for comfort and pain control.				
Bech et al. 2015 (18)	37	Cryotherapy device	The device was applied immediately after surgery and remained in place for 48 h, except for brief periods: after 1 h, and every 4 h thereafter, for nursing assessment for skin or nerve damage; during exercise; and during ambulation.	DonJoy Iceman (DJO Canada, Mississauga, ON)	Not reported	Pain intensity; ROM, nausea or vomiting, opioid use, blood loss, lower limb function, hospital length of stay, patient-reported compliance and satisfaction	6 weeks after TKA
	34	Ice/gel pack	The operated limb was wrapped with an elastic bandage for 48 h after surgery to help control the degree of compression between groups. In the PACU and on the unit, the control group received ice bags at a frequency requested by the patient (usual care) for 48 h.				
Schinsky et al. 2016 (19)	49	Cryotherapy device	POD 1–3 continuous; POD4-10 1 h on and 1 h off while awake and continuous while asleep; POD11 as needed for pain control, continuous for 1-hour intervals; not to exceed 12 h/day while awake; may be used continuously as needed for pain control while asleep.	Polar Care Glacier (Breg, Inc.)	Used	Analgesics consumption; Length of stay; drain output; change in hemoglobin; change in hematocrit; allogeneic blood transfusions; ROM.	3 weeks and 6 weeks after TKA
	48	Ice/gel pack	POD 1–3 continuous; POD4-10 1 h on and 1 h off while awake and continuous while asleep; POD11 as needed for pain control: continuous for 1-hour intervals; not to exceed 12 h/day while awake; may be used continuously as needed for pain control while asleep. (replace the gel packs with fresh, frozen packs every 3–4 h)				

(*continued*)

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TABLE 2 Continued

Author	Group size	Groups	Cold treatment	Device	Tourniquet use	Outcomes	Follow-up
Ruffilli et al. 2017 (20)	24	Cryotherapy device	Hilotherm device was applied in the operating room and the device was turned on in the ward. The day after surgery, the elasto-compressive bandage was removed and the Hilotherm device was applied over the skin.	Hilotherm (Hilotherm GmbH, Germany)	Used for 92.5 ± 15.2 min and 93.8 ± 16.7 min, respectively	Edema reduction; blood loss, transfusion requirement, pain, ROM	1 week after TKA
	26	Ice/gel pack	Ice cold packs were applied over the elasto-compressive bandage, and changed every 30 min. The day after surgery, the elasto-compressive bandage was removed and the ice packs was applied over the skin.				
Sadoghi et al. 2018 (21)	51	Cryotherapy device	The device was applied immediately after TKA in the postanaesthesia care unit for six hours in total, applied each day for four hours in total, two hours in the morning and two hours in the afternoon.	cTreatment system (Waegener, Beerse, Belgium)	Not reported	Pain intensity; ROM; analgesics consumption; swelling of the knee; hospitalisation length; adverse effect	Not reported
	46	Ice/gel pack	Cold packs were applied three times per day for 20 min each throughout the whole trial.				
Karaduman et al. 2019 (22)	30	Cryotherapy device	Cryotherapy was applied for the first 6 h after TKA; On POD1, it was applied at 2 h intervals. On POD2–3, it was applied every 6 h for 2 h.	cTreatment system (Waegener, Beerse, Belgium)	Used	Hemoglobin levels; VAS pain scores; analgesic requirement; ROM; swelling of the knee; length of hospital stay	Monitored for 12–24 months after TKA
	30	Ice/gel pack	A cold pack (gel ice) was applied as standard treatment for 20 min every 2 h for 3 days postoperatively.				

PACU, post-anesthesia care unit; POD, postoperative day; ROM, range of motion; VAS, visual analog scale.

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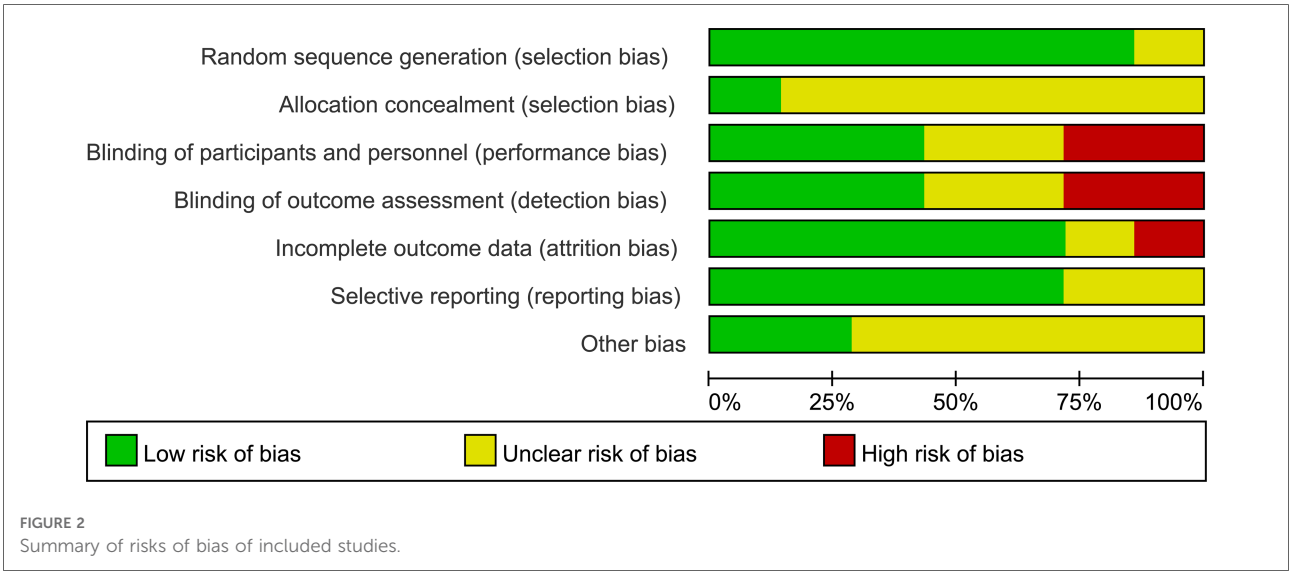

FIGURE 2
Summary of risks of bias of included studies.

5. Discussion

5.1 Main findings

Our meta-analysis comprehensively and systematically reviewed the currently available literature, and the study results suggest that continuous cryotherapy does not appear to offer significant clinical benefits for TKA compared with traditional cryotherapy. There were no significant differences in pain intensity, analgesics consumption, postoperative range of motion, swelling of the knee joint, blood loss, change in hemoglobin, transfusion rate, length of hospital stay, and adverse events. In addition, continuous cryotherapy may lead to extra costs and resources than traditional cryotherapy.

5.2 Implication for clinical practice

Although TKA shows long-lasting clinical and structural improvement for the management of severe osteoarthritis, patients in the immediate postoperative period are often associated with acute pain, hidden bleeding, severe edema, and reduced range of motion. Cryotherapy has been shown to appreciably reduce the intraarticular temperature, especially in the knee, blood flow by vasoconstriction, the local inflammatory reaction, postoperative bleeding and swelling, pain transmission, and the length of hospital stay (26–29). In the clinic, several cryotherapy options are available, including: (i) the first-generation cold therapy such as ice bag or gel pack; (ii) second-generation cryotherapy devices with circulating ice water with or without compression; (iii) third-generation devices with advanced computer-assisted devices to provide continuous controlled cold therapy (17). Compared with ice/gel pack, advanced cryotherapy devices are developed and are expected to be even more efficient as they maintain a steady low temperature for an extended time. Thus, in theory, continuous cryotherapy could play a better role in fast-track rehabilitation after TKA by reducing inflammation, pain, and swelling. However, this meta-analysis observed no differences in clinical outcomes between continuous cryotherapy and traditional cryotherapy, which could be caused by several factors such as the level of tissue penetration of cold therapy, method of cryotherapy, time of application, and types of outcome measurement. TKA-induced inflammation leads to a significant increase in temperature deep inside the knee joint, and the effect of cryotherapy after TKA is closely related to the temperature-dependent mechanism (13). After the cold temperature penetrates tissues and reaches the intended area, which reduces inflammation, reduces nerve conduction velocity, induces local vasoconstriction, and reduces blood flow to muscles (30–35). Although continuous cryotherapy is a more effective treatment to consistently maintain the temperature of the knee joint below the body temperature, the findings of this study suggested that traditional cryotherapy using ice/gel pack could achieve a similar decrease in temperature and reach similar clinical effects. However, a significant weakness of these trials is that neither the skin temperature nor the intraarticular temperature was persistently measured and monitored to confirm effective cooling (17–22). Currently, the optimal cold treatment protocol remains unclear, including the cold temperature, application time and interval, and whether it needs relevant adjustment for different joints. Therefore, further exploration of the application of cryotherapy should

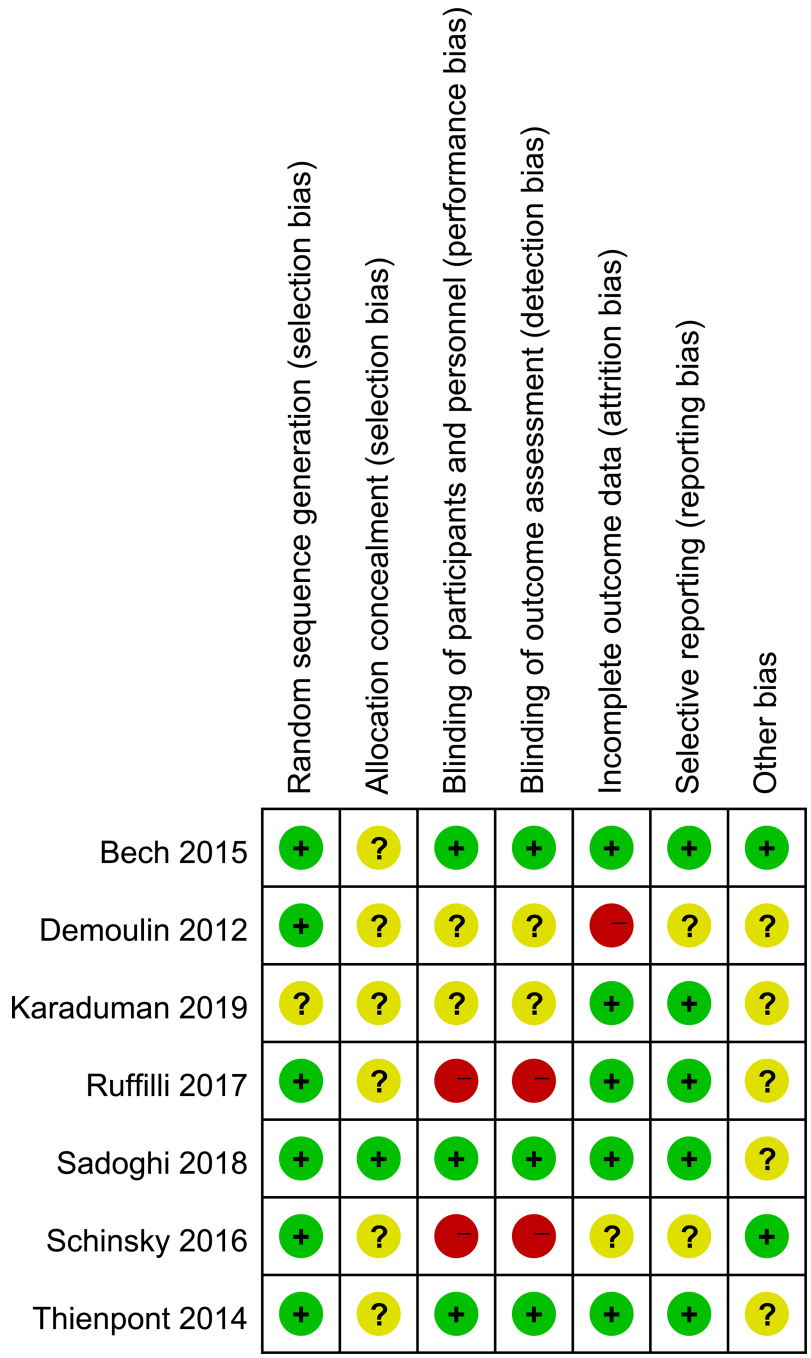

FIGURE 3
Risk of bias in individual studies.

be considered, and attention should also be paid that statistically significant findings may not translate into clinically significant results.

On the other hand, as healthcare providers, it is our duty to appropriately allocate finite resources to evidence-based approaches that are efficacious in an era of increasing expenses. Therefore, apart from the convenience that continuous cryotherapy devices provide prolonged continuous cooling and do not need to change the ice/gel pack, which does not offer any extra clinical advantage for patients undergoing TKA when compared with traditional cryotherapy (13). However, continuous cryotherapy

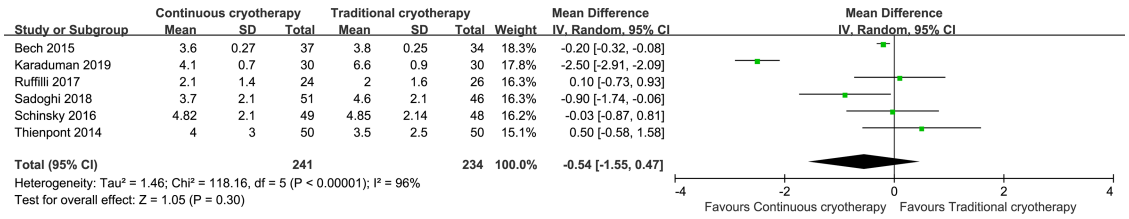

FIGURE 4
Forest plot for pain intensity.

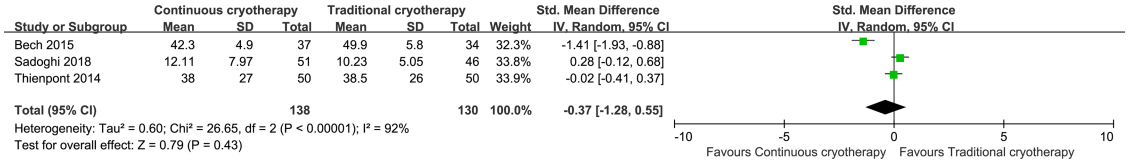

FIGURE 5
Forest plot for analgesics consumption.

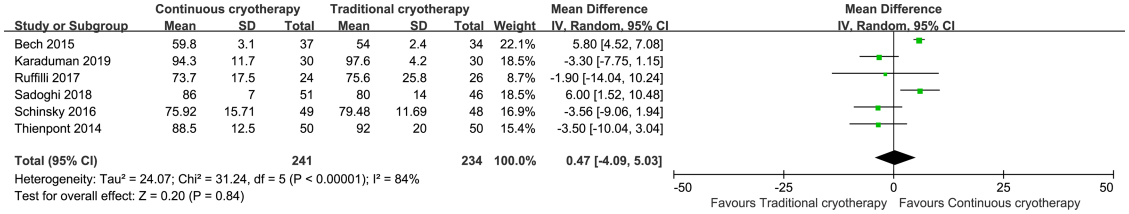

FIGURE 6
Forest plot for postoperative range of motion.

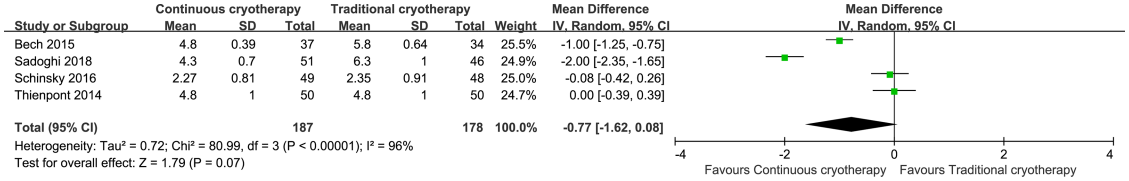

FIGURE 7
Forest plot for the length of hospital stay.

warrants additional costs and resources associated with providing the cooling devices, which may not be covered by insurance (13, 17, 19, 22). In comparison, the cost of traditional cryotherapy is almost neglectable but achieves similar clinical effects. Thus, the currently available evidence does not support the theoretical cost-effectiveness of utilizing continuous cryotherapy after TKA, and future high-level prospective studies are needed to verify these findings.

In addition, the current available RCTs only applied continuous cryotherapy and traditional cryotherapy during hospitalization and not after discharge, which is a relatively

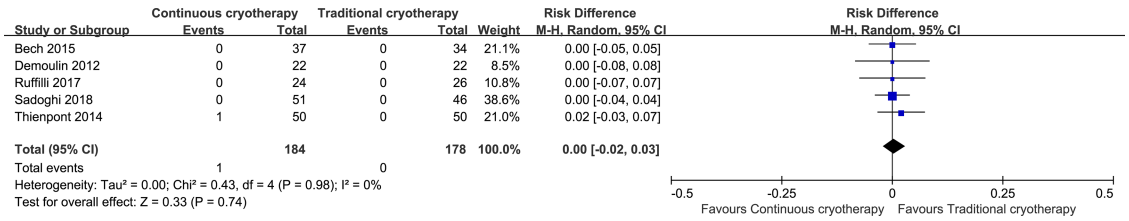

FIGURE 8
Forest plot for adverse events.

short duration, and the minimal difference between continuous cryotherapy and traditional cryotherapy may not be detected (17, 29). Therefore, the extended application of cryotherapy at home could also be explored in future studies.

5.3 Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis that systemically and comprehensively reviewed currently available evidence to compare the efficacy, safety, and cost-effectiveness of continuous cryotherapy vs. traditional cryotherapy for TKA.

Our study also has several potential limitations. First of all, in more than half of included studies, neither patients nor healthcare providers were blinded to group allocation and outcome assessment, hence, subjective assessments such as pain level are subject to potential bias. Second, the comparison of continuous cryotherapy vs. traditional cryotherapy was specialized to the TKA procedure, which may not be generalizable to other surgical procedures, such as arthroscopic surgery. Third, substantial heterogeneity across studies was noticed, which may be explained by the considerable difference in cryotherapy protocols. Lastly, almost all eligible trials included in the meta-analysis had relatively modest sample sizes (<100 patients), and overestimation of the treatment effect is more likely than in larger trials.

6. Conclusion

Our systematic review and meta-analysis suggested that continuous cryotherapy showed no superiority in reducing pain intensity, analgesics consumption, swelling, blood loss, length of hospital stay, and improving ROM compared with traditional cryotherapy in the acute postoperative setting after TKA. Continuous cryotherapy may further lead to extra costs and resources, so the currently available evidence does not support continuous cryotherapy could be added as an adjunct therapy. Additional well-designed studies with larger sample sizes are needed to confirm these preliminary results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conceived and designed the study: M-ML, MT, SW, LS. Acquired, analyzed, and interpreted the data: M-ML, MT, CL, SW, LS. Drafted or revised the article: M-ML, MT, CL, SW, LS. Final approval of the version to be published: M-ML, MT, CL, SW, LS. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. (2007) 89(4):780–5. doi: 10.2106/JBJS.F.00222

2. Patel A, Pavlou G, Mújica-Mota RE, Toms AD. The epidemiology of revision total knee and hip arthroplasty in England and Wales: a comparative analysis with projections for the United States. A study using the national joint registry dataset. *Bone Joint J*. (2015) 97-B(8):1076–81. doi: 10.1302/0301-620X.97B8.35170

3. Matsen 3rd FA, Questad K, Matsen AL. The effect of local cooling on postfracture swelling. A controlled study. *Clin Orthop Relat Res*. (1975) 109:201–6. doi: 10.1097/00003086-197506000-00029

4. Hecht PJ, Bachmann S, Booth Jr RE, Rothman RH. Effects of thermal therapy on rehabilitation after total knee arthroplasty. A prospective randomized study. *Clin Orthop Relat Res*. (1983) 178:198–201. doi: 10.1097/00003086-198309000-00023

5. Grosu I, Lavand'homme P, Thienpont E. Pain after knee arthroplasty: an unresolved issue. *Knee Surg Sports Traumatol Arthrosc*. (2014) 22(8):1744–58. doi: 10.1007/s00167-013-2750-2

6. Andersen LØ, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. *Anaesthesia*. (2009) 64(5):508–13. doi: 10.1111/j.1365-2044.2008.05831.x

7. Kehlet H. Fast-track hip and knee arthroplasty. *Lancet*. (2013) 381 (9878):1600–2. doi: 10.1016/S0140-6736(13)61003-X

8. Hansen TB. Fast track in hip arthroplasty. *EFORT Open Rev*. (2017) 2 (5):179–88. doi: 10.1302/2058-5241.2.160060

9. Martin SS, Spindler KP, Tarter JW, Detwiler KB. Does cryotherapy affect intraarticular temperature after knee arthroscopy? *Clin Orthop Relat Res*. (2002) 400:184–9. doi: 10.1097/00003086-200207000-00023

10. Zhong Y, Zheng C, Du W, Zheng J, Xu S, Tong P. Mirabilite with ice pack after total knee arthroplasty: a randomized controlled trial study. *Evid Based Complement Alternat Med*. (2021) 2021:6611614. doi: 10.1155/2021/6611614

11. Maranda E, Simmons BJ, Romanelli P. Cryotherapy-As ancient as the pharaohs. *JAMA Dermatol*. (2016) 152(6):730. doi: 10.1001/jamadermatol.2015.1616

12. Wang H, Olivero W, Wang D, Lanzino G. Cold as a therapeutic agent. *Acta Neurochir (Wien)*. (2006) 148(5):565–70; discussion 569–70. doi: 10.1007/s00701-006-0747-z

13. Kunkle BF, Kothandaraman V, Goodloe JB, Curry EJ, Friedman RJ, Li X, et al. Orthopaedic application of cryotherapy: a comprehensive review of the history, basic science, methods, and clinical effectiveness. *JBJS Rev*. (2021) 9(1): e20.00016. doi: 10.2106/JBJS.RVW.20.00016

14. Ruffilli A, Buda R, Castagnini F, Di Nicolantonio D, Evangelisti G, Giannini S, et al. Temperature-controlled continuous cold flow device versus traditional icing regimen following anterior cruciate ligament reconstruction: a prospective randomized comparative trial. *Arch Orthop Trauma Surg*. (2015) 135 (10):1405–10. doi: 10.1007/s00402-015-2273-z

15. Chughtai M, Sodhi N, Jawad M, Newman JM, Khlopas A, Bhave A, et al. Cryotherapy treatment after unicompartmental and total knee arthroplasty: a review. *J Arthroplasty*. (2017) 32(12):3822–32. doi: 10.1016/j.arth.2017.07.016

16. Demoulin C, Brouwers M, Darot S, Gillet P, Crielaard JM, Vanderthommen M. Comparison of gaseous cryotherapy with more traditional forms of cryotherapy following total knee arthroplasty. *Ann Phys Rehabil Med*. (2012) 55 (4):229–40 (English, French). doi: 10.1016/j.rehab.2012.03.004

17. Thienpont E. Does advanced cryotherapy reduce pain and narcotic consumption after knee arthroplasty? *Clin Orthop Relat Res*. (2014) 472 (11):3417–23. doi: 10.1007/s11999-014-3810-8

18. Bech M, Moorhen J, Cho M, Lavergne MR, Stothers K, Hoens AM. Device or ice: the effect of consistent cooling using a device compared with intermittent cooling using an ice bag after total knee arthroplasty. *Physiother Can*. (2015) 67 (1):48–55. doi: 10.3138/ptc.2013-78

19. Schinsky MF, McCune C, Bonomi J. Multifaceted comparison of two cryotherapy devices used after total knee arthroplasty: cryotherapy device comparison. *Orthop Nurs*. (2016) 35(5):309–16. doi: 10.1097/NOR.0000000000000276

20. Ruffilli A, Castagnini F, Traina F, Corneti I, Fenga D, Giannini S, et al. Temperature-Controlled continuous cold flow device after total knee arthroplasty: a randomized controlled trial study. *J Knee Surg*. (2017) 30 (7):675–81. doi: 10.1055/s-0036-1593874

21. Sadoghi P, Hasenhütl S, Gruber G, Leitner L, Leithner A, Rumpold-Seitlinger G, et al. Impact of a new cryotherapy device on early rehabilitation after primary total knee arthroplasty (TKA): a prospective randomised controlled trial. *Int Orthop*. (2018) 42(6):1265–73. doi: 10.1007/s00264-018-3766-5

22. Karaduman ZO, Turhal O, Turhan Y, Orhan Z, Arican M, Uslu M, et al. Evaluation of the clinical efficacy of using thermal camera for cryotherapy in patients with total knee arthroplasty: a prospective study. *Medicina (Kaunas)*. (2019) 55(10):661. doi: 10.3390/medicina55100661

23. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0*. (updated March 2011). Available at: http://www.cochrane.org/handbook

24. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6(7):e1000097. doi: 10.1371/journal

25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *Br Med J*. (2011) 343:d5928. doi: 10.1136/bmj.d5928

26. Markert SE. The use of cryotherapy after a total knee replacement: a literature review. *Orthop Nurs*. (2011) 30(1):29–36. doi: 10.1097/NOR.0b013e318205749a

27. Ewell M, Griffin C, Hull J. The use of focal knee joint cryotherapy to improve functional outcomes after total knee arthroplasty: review article. *PM&R*. (2014) 6(8):729–38. doi: 10.1016/j.pmrj.2014.02.004

28. Ni SH, Jiang WT, Guo L, Jin YH, Jiang TL, Zhao Y, et al. Cryotherapy on postoperative rehabilitation of joint arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. (2015) 23(11):3354–61. doi: 10.1007/s00167-014-3135-x

29. Thacoor A, Sandiford NA. Cryotherapy following total knee arthroplasty: what is the evidence? *J Orthop Surg (Hong Kong)*. (2019) 27 (1):2309499019832752. doi: 10.1177/2309499019832752

30. Lindsay A, Carr S, Cross S, Petersen C, Lewis JG, Gieseg SP. The physiological response to cold-water immersion following a mixed martial arts training session. *Appl Physiol Nutr Metab*. (2017) 42(5):529–36. doi: 10.1139/apnm-2016-0582

31. White GE, Wells GD. Cold-water immersion and other forms of cryotherapy: physiological changes potentially affecting recovery from high-intensity exercise. *Extrem Physiol Med*. (2013) 2(1):26. doi: 10.1186/2046-7648-2-26

32. Kang JI, Jeong DK, Choi H. Effects of microcurrent and cryotherapy on C-reactive protein levels and muscle tone of patients with rotator cuff reconstruction. *J Phys Ther Sci*. (2018) 30(1):37–41. doi: 10.1589/jpts.30.37

33. Algafly AA, George KP. The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. *Br J Sports Med*. (2007) 41 (6):365–9; discussion 369. doi: 10.1136/bjsm.2006.031237

34. Stålman A, Berglund L, Dungnerc E, Arner P, Felländer-Tsai L. Temperature-sensitive release of prostaglandin $E_2$and diminished energy requirements in synovial tissue with postoperative cryotherapy: a prospective randomized study after knee arthroscopy. *J Bone Joint Surg Am*. (2011) 93 (21):1961–8. doi: 10.2106/JBJS.J.01790

35. Vieira Ramos G, Pinheiro CM, Messa SP, Delfino GB, Marqueti Rde C, Salvini Tde F, et al., Cryotherapy reduces inflammatory response without altering muscle regeneration process and extracellular matrix remodeling of rat muscle. *Sci Rep*. (2016) 6:18525. doi: 10.1038/srep18525

Appendix 1. Literature search strategy.

Database			
PubMed	Search	Query	Results
	#1	"Cryotherapy"[Mesh]	26,791
	#2	Cryotherapy[Title/Abstract]	8,064
	#3	Cryopneumatic[Title/Abstract]	4
	#4	Cryo*[Title/Abstract]	101,381
	#5	Cold[Title/Abstract]	132,678
	#6	Cold therapy[Title/Abstract]	359
	#7	Cold treatment[Title/Abstract]	1,157
	#8	Ice[Title/Abstract]	35,670
	#9	Ice Bag*[Title/Abstract]	146
	#10	Ice pack*[Title/Abstract]	619
	#11	Icing[Title/Abstract]	914
	#12	Cooling[Title/Abstract]	43,608
	#13	Cooling water[Title/Abstract]	562
	#14	Cold Effects[Title/Abstract]	1,096
	#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	310,602
	#16	"Arthroplasty, Replacement, Knee"[Mesh]	28,337
	#17	Knee Arthroplasty[Title/Abstract]	27,828
	#18	Knee Replacement[Title/Abstract]	9,811
	#19	#16 OR #17 OR #18	40,053
	#20	#15 AND #19	180
Embase	**Search**	**Query**	**Results**
	#1	“cryotherapy”/exp	38,217
	#2	0ôcryotherapy device”/exp	97
	#3	cryotherapy:ab,ti	11,183
	#4	cryopneumatic:ab,ti	4
	#5	cryo*:ab,ti	130,360
	#6	cold:ab,ti	165,147
	#7	“cold therapy”:ab,ti	273
	#8	“cold treatment”:ab,ti	1,064
	#9	“ice”:ab,ti	40,261
	#10	“ice bag*”:ab,ti	182
	#11	“ice pack*”:ab,ti	922
	#12	“icing”:ab,ti	904
	#13	cooling:ab,ti	46,673
	#14	“cooling water”:ab,ti	938
	#15	temperature:ab,ti	661,805

(*continued*)

Continued

Database			
PubMed	Search	Query	Results
	#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	972,974
	#17	"replacement arthroplasty"/exp	50,510
	#18	"hip arthroplasty":ab,ti	28,377
	#19	"hip replacement":ab,ti	15,115
	#20	"knee arthroplasty":ab,ti	30,517
	#21	"knee replacement":ab,ti	12,500
	#22	#17 OR #18 OR #19 OR #20 OR #21	92,662
	#23	#16 AND #22	895
	#24	#16 AND #22 AND [animals]/lim	63
	#25	#16 AND #22 AND [pubmed-not-medline]/lim	4
	#26	#16 AND #22 AND [erratum]/lim	5
	#27	#16 AND #22 AND ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)	34
	#28	#24 OR #25 OR #26 OR #27	69
	#29	#23 NOT #28	826
Cochrane	**Search**	**Query**	**Results**
	#1	MeSH descriptor: [Cryotherapy] explode all trees	1,683
	#2	(Cryopneumatic):ti,ab,kw (Word variations have been searched)	2
	#3	(Cryo*):ti,ab,kw (Word variations have been searched)	5,990
	#4	(Cold therapy):ti,ab,kw (Word variations have been searched)	4,323
	#5	(Cold treatment):ti,ab,kw (Word variations have been searched)	5,247
	#6	(Ice):ti,ab,kw (Word variations have been searched)	2,506
	#7	(Ice Bag*):ti,ab,kw (Word variations have been searched)	160
	#8	(Ice pack*):ti,ab,kw (Word variations have been searched)	395
	#9	(Cold):ti,ab,kw (Word variations have been searched)	11,820
	#10	(Cryotherapy):ti,ab,kw (Word variations have been searched)	2,309
	#11	(Icing):ti,ab,kw (Word variations have been searched)	2,457
	#12	(Cooling):ti,ab,kw (Word variations have been searched)	4,568
	#13	(Cooling water):ti,ab,kw (Word variations have been searched)	678
	#14	(Temperature):ti,ab,kw (Word variations have been searched)	23,270
	#15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	40,683
	#16	MeSH descriptor: [Arthroplasty] explode all trees	5,389
	#17	(Knee Replacement):ti,ab,kw (Word variations have been searched)	6,062
	#18	(Hip Arthroplasty):ti,ab,kw (Word variations have been searched)	5,506
	#19	(Hip Replacement):ti,ab,kw (Word variations have been searched)	5,550
	#20	(Knee Arthroplasty):ti,ab,kw (Word variations have been searched)	7,703
	#21	#16 or #17 or #18 or #19 or #20	16,065
	#22	#15 and #21	381

(*continued*)

Continued

Database			
PubMed	Search	Query	Results
Web of Science	**Search**	**Query**	**Results**
	#1	TS = (Cryotherapy)	9,906
	#2	TS = (Cryopneumatic)	5
	#3	TS = (Cryo*)	201,930
	#4	TS = (Cold)	463,731
	#5	TS = (Cold therapy)	8,786
	#6	TS = (Cold treatment)	51,183
	#7	TS = (Ice)	222,234
	#8	TS = (Ice Bag*)	554
	#9	TS = (Ice pack*)	6,152
	#10	TS = (Icing)	222,269
	#11	TS = (Cooling)	457,798
	#12	TS = (Cooling water)	88,667
	#13	TS = (Cold Effects)	124,148
	#14	#13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	1,241,609
	#15	TS = (Knee Arthroplasty)	47,281
	#16	TS = (Knee Replacement)	33,322
	#17	#16 OR #15	57,951
	#18	#14 AND #17	338
Google Scholar	**Search**	**Query**	**Results**
	#1	("Cryotherapy" OR "Cryopneumatic" OR "Cold therapy" OR "Cold treatment" OR "Ice Bag" OR "Ice pack" OR "Cooling water") AND ("total knee replacement" OR "total knee Arthroplasty") AND ("Randomized Controlled Trial" OR "Controlled Clinical Trial")	1,590

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Incidence and risk factors for postoperative nosocomial pneumonia in elderly patients with hip fractures: A single-center study

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Objective: Postoperative nosocomial pneumonia is a terrible complication, especially for elderly patients. This study attempts to investigate the incidence and risk factors for postoperative nosocomial pneumonia and its influence on hospitalization stay in elderly patients with hip fractures.

Methods: This study retrospectively retrieved hospitalization records of patients who presented a hip fracture and underwent surgeries in our institution between January 2014 and December 2021. Postoperative new-onset pneumonia was determined in accordance with discharge diagnosis. Multivariate logistic regression analysis was performed to identify the associated risk factors with pneumonia, and its influence on total hospitalization stay or postoperative hospitalization stay was investigated by multivariate linear regression analyses.

Results: Totally, 808 patients were included, among whom 54 developed a pneumonia representing the incidence rate of 6.7% (95% CI, 5.0%–8.4%). Six factors were identified as independently associated with pneumonia, including advanced age (OR, 1.50 for each 10-year increment), history of chronic respiratory disease (OR, 4.61), preoperative DVT (OR, 3.51), preoperative delay to operation (OR, 1.07 for each day), surgical duration ≥120 min (OR, 4.03) and arthroplasty procedure (OR, 4,39). When adjusted for above confounders, pneumonia was significantly positively associated with total hospitalization stay (standardized coefficient, 0.110; $p < 0.001$) and postoperative hospitalization stay (standardized coefficient, 0.139; $p < 0.001$).

Conclusions: This study identified multiple factors associated with postoperative pneumonia and its influence on prolonging hospitalization stay, which would facilitate preventive targeted intervention into implementation for individuals with different risk profiles.

KEYWORDS

hip fracture, clinical epidemiology, influence, risk factors, geriatric population, nosocomial pneumonia

Introduction

Surgical treatment, *via* either arthroplasty or osteosynthesis, has been well established as the gold standard for management of hip fracture in elderly patients, who are generally frail and comorbid (1). This strategy allows early mobility and initiation of postoperative exercises, and thus helps to prevent or reduce many complications that often occur after conservative

Abbreviations
DVT, deep venous thrombosis; BMI, body mass index; ASA, American society of anesthesiologists; WBC, white blood cell; RBC, red blood cell; HCRP, hypersensitivity C-reactive protein; OR, odd ratio; 95% CI, 95% confidence interval; VTE, venous thromboembolism.

treatments, e.g., deep venous thrombosis (DVT) of lower extremities, neuromuscular dysfunction or even mortality within early period (2, 3). Despite that, postoperative nosocomial pneumonia, which would cause systemic dysfunction and even death, is prevalent in 4.7%–16.3% of elderly hip fracture patients (4–7). Not only the direct adverse events, but also the great costs from prolonged hospitalization stay and re-admission to hospital constitute a substantial burden for patients and the public health-care systems (4, 8, 9).

From the cost-effective point of view, to prevent is most favorable than to treat. Indeed, during the past decade, researchers have made substantial attempts to address the prevention, and numerous influential factors have been well established, e.g., male sex, advanced age, obesity, history of a chronic respiration disease, active smoking, undernutrition, greater comorbidity index (American Society of Anesthesiologists score ≥ III) or presence of a specific comorbidity or condition (diabetes, renal insufficiency, dementia, anemia, hypoalbuminemia, lower oxygen status), delay to surgery, surgical method (arthroplasty vs. osteosynthesis) and mechanical ventilation (4, 6, 8, 10–12). However, some limitations should be noted, including but not limited to relatively small sample size, inadequate confounders for adjustment, and inaccuracy in data collection. In addition, one may neglect that, up to 35%, of elderly patients with hip fracture had preoperative DVT, despite prophylactic thromboembolic drugs were routinely administered (13). It is possible that the hypercoagulability and the relatively poor venous status associated with DVT in elderly trauma patients might also be contributors for nosocomial pneumonia, however, this has not been investigated in literature. Furthermore, in China, for seeking better surgical treatment, patients generally are transferred or admitted to higher-level tertiary referral hospitals, easily leading to centralization of hip fracture surgery and the delay to surgery, which is a well-known risk factor for many complications, even mortality.

Given the above, we performed this study, with aims to investigate the incidence and risk factors associated with postoperative nosocomial pneumonia in elderly patients with hip fractures, and its influence on hospitalization stay, a direct factor related to the total health care costs.

Materials and methods

The study was performed in accordance with the Declaration of Helsinki and the study protocol was approved by the ethics committee of the Second Hospital of Tangshan prior to its commencement, which waived the requirement for informed consent due to the retrospective nature.

We reviewed patients who presented with and underwent a surgery for an acute hip fracture between January 2018 and December 2021 in the Second Hospital of Tangshan, an 800-bed orthopaedics-specialized hospital serving a population of 7.7 million people. The inclusion criteria were age of 60 years or older, diagnosis of hip fracture (femoral neck or intertrochanteric) definitely surgically treated and complete medical records. The exclusion criteria were injury mechanism of high-energy impact (fall from a height, traffic accident or others), subtrochanteric fracture, open fracture, pathological fractures, polytrauma or concurrent fractures, non-operative treatment or delay to operation >21 days after fracture, history of any operation on the affected hip, malignancies, presence of preoperative pneumonia, long-term use of glucocorticoid or missing information on variables of interest.

Definition and identification of pneumonia

Two researchers (X Tong and C Ci) were responsible for data exaction, *via* review of the hospital' electronic database. Postoperative nosocomial pneumonia was defined as a postoperative pneumonia occurring ≥48 h after hospital admission, which was documented in the discharge abstract. It was diagnosed in accordance with the Guidelines (14), on basis of following criteria: (1) typical clinical presentations and physical examination findings, showing cough, expectoration, fever or hypothermia (body temperature >38 °C or body temperature < 36 °C), chest pain, moist rale on lung auscultation or lung consolidation signs; (2) blood tests showing increase or decrease of number of white blood cell (WBC) (>$10 * 10^9$/L or white cell count <$4 * 10^9$/L) and the percentage of neutrophils; (3) Chest x-ray or CT scanning showing signs of pneumonia; and 4, blood or sputum culture revealing the same causative pathogens for two consecutive times.

Variables of interest

Demographics features and potential risk factors were extracted from the records by the same investigators (X Tong and C Ci). These variables included sex, age, height and weight and the calculated body mass index (BMI), lifestyles (active smoking, alcohol drinking), comorbidities or conditions (hypertension, diabetes, chronic respiratory disease, heart disease, cerebrovascular disease, liver disease, renal disease, presence of preoperative DVT), fracture location (femoral neck or intertrochanteric), surgery-related data (delay to operation after fracture, anesthesia pattern, surgical duration, American Society of Anesthesiologists (ASA) score, intraoperative bleeding, allogeneic blood transfusion and operative procedure (arthroplasty or osteosynthesis). In addition, some blood test indexes immediately after admission were also extracted, including serum albumin level, albumin/globulin ration, WBC count, neutrophil count, lymphocyte count, red blood cell (RBC), hemoglobin, hematocrit, hypersensitivity C-reactive protein (HCRP), lactate dehydrogenase (LDH), creatinine and fasting blood glucose (FBG).

In accordance with the criteria proposed specifically for Chinese adults (15), obesity was defined as BMI ≥28 kg/m^2. Active smoking or alcohol drinking was defined as regular consumption of cigarettes or alcohol within 6 months before the index operation (16). Preoperative DVT was diagnosed by duplex ultrasonography or venography, which was a routine procedure for patients with hip fracture before surgery. Comorbidities or conditions were self-reported by patients after admission and documented by the initial clinicians on-duty. The blood test indexes were categorized according to the manufacturer-recommended reference ranges.

Statistical analysis

Continuous variables were presented with mean and standard deviation (SD), and were explored for their normality distribution status by Kolmogorov–Smirnov test; and the difference between patients with and without pneumonia was detected by Student-*t* test for normally distributed data or by Mann Whitney-*U* test for skewedly distributed data. Categorical variables were presented as number and percentage, and the between-group difference was detected by Chi-square or Fisher exact test, as appropriate.

The incidence rate of postoperative nosocomial pneumonia was calculated by dividing the total number of patients by the number of those who developed pneumonia during hospitalization stay. Variables that tested with *P* values <0.10 in the above univariate analyses were further entered into the multivariate logistic regression analysis to identify their potential independent effect on incidence of postoperative nosocomial pneumonia. During this procedure, the stepwise backward mode was applied to eliminate the less associated factors, and those with *P* value <0.10 were retained in the final model. The magnitude of association was indicated by the odd ratio (OR) and its 95% confidence interval (95% CI). To evaluate the goodness-of-fit of the final model, Hosmer–Lemeshow test was applied with $P > 0.05$ indicating the acceptable result; also, adjusted Nagelkerke R^2 value was used to quantify the magnitude of goodness-of-fit, with <0.750 deemed as acceptable result, with lower value suggesting a better model fit.

For investigation of effect of pneumonia on the hospitalization stay, we performed the multiple linear regression, with hospitalization stay in days as outcome variable and pneumonia as independent variables and above-mentioned variables tested with *p* value <0.10 as co-variables for adjustment. The "enter" mode was applied. The collinearity between independent variables was examined by variance inflation factor (VIF), with VIF ≥ 3 suggestive of multicollinearity and the related factors were not included. Regression coefficient (B) with 95% CI and the standard regression coefficient (Beta) were used to indicate the association magnitude.

For all analyses, $P < 0.05$ was considered as significant. All statistical analyses were performed by SPSS25.0 package (IBM, Armonk, NY, United States).

Results

Within the study period, there were 1,563 elderly hip fractures treated in our institution, and 755 were excluded due to various reasons, e.g., high-energy impact (134), subtrochanteric fracture (116), open fracture (45), pathological fractures (28), polytrauma or concurrent fractures (107), non-operative treatment or delay to operation >21 days (72), history of any operation on the affected hip (39), malignancies (27), presence of preoperative pneumonia (22), long-term use of glucocorticoid (13) or missing information on variables of interest (152). This left 808 eligible patients for data analysis (**Figure 1**).

Fifty-four patients developed pneumonia after operation, indicating an incidence rate of 6.7% (95% CI, 5.0%–8.4%). Compare to those without developing pneumonia, patients who had pneumonia had an older age (76.9 ± 8.2 vs. 72.7 ± 8.6; 38.9% vs. 24.8% for age ≥80 years), higher prevalence rate of hypertension (61.1% vs. 46.0%), diabetes (33.3% vs. 20.7%), respiratory disease (13.0% vs. 3.2%), presence of preoperative DVT of bilateral extremities (29.6% vs. 13.7%) and a longer preoperative waiting (7.2 ± 4.7 vs. 5.4 ± 3.4 days; 46.3% vs. 27.7% for preoperative waiting over 7 days), needed a longer surgical duration (131.7 ± 40.0 vs. 112.7 ± 41.8 min; 79.6% vs. 47.2% for procedure lasting over 120 min), a higher proportion of arthroplasty procedure (75.9% vs. 54.9%) and a higher proportion of elevated WBC (38.9% vs. 25.5%) (**Table 1**). Two (3.7%) patients in pneumonia group and 14 (1.9%) in non-pneumonia group died during the index hospitalization, without significant difference ($P = 0.290$).

In the multivariate logistics regression analysis, age (OR,1.50% and 95% CI, 1.10–1.92 for each 10-year increment), history of chronic respiratory disease (OR, 4.61; 95% CI, 1.70–12.54), preoperative DVT (OR, 3.51; 95% CI, 1.74–10.48), preoperative waiting (OR, 1.07; 95% CI, 1.01–1.15 for each day increment), surgical duration ≥120 min (OR, 4.03; 95% CI, 1.96–8.27) and arthroplasty procedure (OR, 4,39; 95% CI, 1.87–10.31) (**Table 2**). The Hosmer–Lemeshow test showed the good fitness ($X^2 = 6.328$, $P = 0.556$, Nagelkerke $R^2 = 0.197$).

The total hospitalization stay was 20.3 ± 10.3 days in patients developing pneumonia, significantly longer than that (14.1 ± 6.6) in those without ($P < 0.001$). The postoperative hospitalization stays (calculated by subtracting the preoperative stay from the total hospitalization stay) was significantly longer in patients developing pneumonia than those without (13.1 ± 8.9 vs. 8.8 ± 5.0 days, $P < 0.001$) (**Table 1**). The multivariate linear regression analyses showed pneumonia was significantly positively with the total hospitalization stay (B, 3.11; 95% CI, 1.67–4.84; Beta, 0.110; $P < 0.001$) and the postoperative hospitalization stay (B, 3.93; 95% CI, 2.35–5.49; Beta, 0.139; $P < 0.001$) (**Tables 3**, **4**). The VIFs were ranging 1.034–2.923, and 1.036–3.088, respectively; indicating no multicollinearity for any factor.

Discussion

In the present study, we found the incidence of postoperative nosocomial pneumonia was 6.7% in elderly patients with a hip fracture and identified 6 independent factors, including elder age, history of chronic respiratory disease, present preoperative DVT of bilateral extremities, prolonged preoperative waiting, surgical duration ≥120 min and arthroplasty procedure. We also identified that pneumonia was positively associated with total hospitalization stay and postoperative hospitalization stay.

The rate of postoperative nosocomial pneumonia of 6.7% in elderly patients with a hip fracture was in range of those reported in literature on this subject, which, however, varied greatly between 4.7% and 16.3% (4–7). The reasons for such variation might be various, primarily from patient selection, treatment pattern (surgery or conservation), wide definitions of pneumonia, study design and sample size. For example, in one study of 418 hip fracture patients aged 60 years or older, Yan et al. (7) reported a

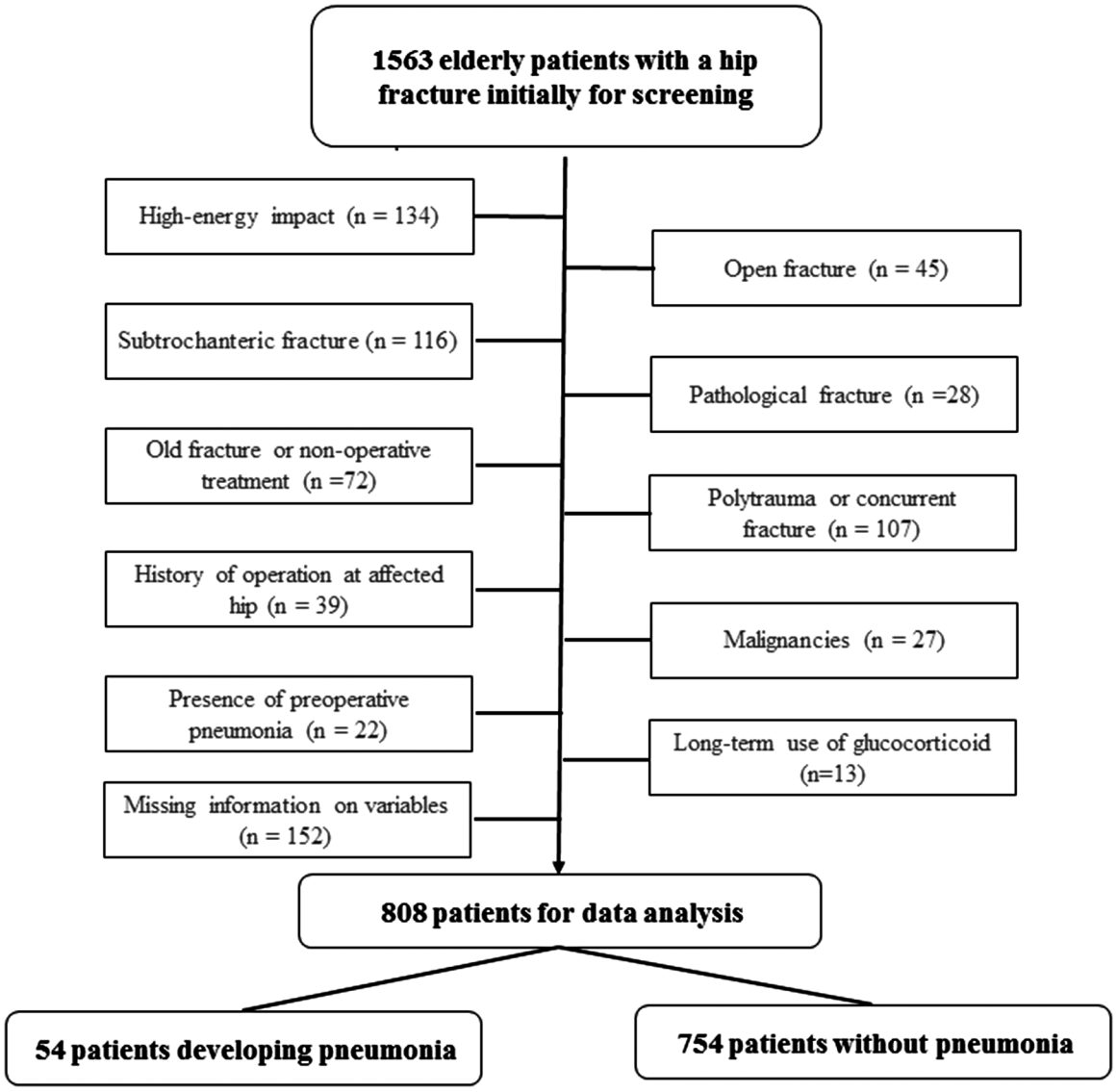

FIGURE 1
The flowchart showing the screening of eligible participants.

highest incidence of 16.3% for postoperative pneumonia. That might be explained by the greater proportion (29.0%, 7-times as ours) of previous respiratory system disease in their population, a substantial risk (OR, 4.61) for pneumonia identified in our study. Another important factor might be that 15.8% of included patients were conservatively treated, also a well-established risk factor for various complications and adverse outcomes, including pneumonia and even morality (3, 17). In contrast, in the study there the lowest incidence rate (4.7%) was reported, the lower proportion of smokers (4.4%, about 1/4 as ours) and relatively low proportion of femoral neck fracture, a substantial proportion of which requires arthroplasty, might contribute greatly (6).

In consistence with previous findings (1, 18), postoperative pneumonia was re-confirmed as a risk factor for prolonged hospitalization stay in this study, and was associated with additional 6.2 day and 4.3 day for total and postoperative hospitalization stay, respectively. Their influence on costs from public health care system and patients is remarkable, which, exactly, underscores the importance of prevention of postoperative pneumonia.

Among 6 factors identified, most have been well established, e.g., elder age (2, 6, 19), history of chronic respiratory disease (20, 21), prolonged preoperative waiting (22, 23) and longer surgical duration (24) and arthroplasty procedure (6). The first two factors related to the patients' systemic functional decline and the poorer cardiorespiratory reserves, e.g., decline of breathing strength, lung compliance, cough reflex and respiratory defense, providing the basis and intrinsic conditions for pneumonia (25, 26). The prolonged preoperative waiting, on one hand, might reflect the frail systemic conditions, comorbidities or severe injury that require more time to optimize to improve the tolerance to surgery. On the other hand, the physical and psychological changes (e.g., anxiety and sleep disorder) secondary to prolonged preoperative hospitalization stay should also contribute to lowering the resistance to surgical trauma (27), thus increasing the risk of pneumonia. Therefore, for those older, especially aged >80 years,

TABLE 1 Univariate analysis of variables between pneumonia and non-pneumonia patients.

Variables	Pneumonia ($n = 54$)	Non-Pneumonia ($n = 754$)	*P*
	Mean ± SD or count (%)	Mean ± SD or count (%)	
Sex (males)	19 (35.2)	280 (37.1)	0.774
Age	76.9 ± 8.2	72.7 ± 8.6	<0.001
≥80 years	21 (38.9)	187 (24.8)	0.022
BMI (kg/m^2)	23.3 ± 3.8	23.6 ± 3.7	0.600
Obesity	8 (14.8)	78 (10.3)	0.304
Hypertension	33 (61.1)	347 (46.0)	0.032
Diabetes mellitus	18 (33.3)	156 (20.7)	0.029
Respiratory disease	7 (13.0)	24 (3.2)	<0.001
Heart disease	15 (27.8)	183 (24.3)	0.563
Cerebrovascular disease	15 (27.8)	212 (28.1)	0.957
Liver disease	3 (5.6)	18 (2.4)	0.332
Renal disease	6 (11.1)	53 (7.0)	0.399
Preoperative DVT	16 (29.6)	103 (13.7)	<0.001
Cigarette smoking	11 (20.4)	129 (17.1)	0.541
Alcohol drinking	18 (33.3)	236 (31.3)	0.756
Fracture location			0.089
Femoral neck	43 (79.6)	517 (68.6)	
Intertrochanteric	11 (20.4)	237 (31.4)	
Preoperative stay (days)	7.2 ± 4.7	5.4 ± 3.4	<0.001
≥7d	25 (46.3)	209 (27.7)	0.004
Hospital stay (days)	20.3 ± 10.3	14.1 ± 6.6	<0.001
Intraoperative bleeding (ml)	179.6 ± 340.0	109.6 ± 255.6	0.058
Intraoperative blood transfusion	14 (25.9)	152 (20.2)	0.311
Surgical duration (min)	131.7 ± 40.0	112.7 ± 41.8	<0.001
≥120	43 (79.6)	356 (47.2)	<0.001
Procedure			0.003
Arthroplasty	41 (75.9)	414 (54.9)	
Osteosynthesis	13 (24.1)	340 (45.1)	
ASA			0.083
I-II	28 (51.9)	480 (63.7)	
III-IV	26 (48.1)	274 (36.3)	
Anesthesia (general)	34 (63.0)	450 (59.7)	0.635
Albumin (<35 g/L)	30 (55.6)	425 (56.4)	0.908
A/G			0.284
1.2–2.4	37 (68.5)	587 (77.9)	
<1.2	17 (31.5)	167 (22.1)	
HCRP (>8 mg/L)	43 (79.6)	624 (82.8)	0.558
LDH (>250 U/L)	21 (38.9)	226 (30.0)	0.170
Sodium concentration (<135 mmol/L)	18 (33.3)	309 (41.0)	0.269
FBG (>6.1 mmol/L)	28 (51.9)	371 (49.2)	0.707
Creatinine (>111 μmol/L)	8 (14.8)	65 (8.6)	0.198
WBC (>10 * 10^9/L)	21 (38.9)	192 (25.5)	0.031
Neutrophil count (>6.3 * 10^9/L)	29 (53.7)	384 (50.9)	0.693
Lymphocyte count (<1.1 * 10^9/L)	29 (53.7)	371 (49.2)	0.523
#RBC (<Lower limit)	22 (40.7)	376 (49.9)	0.195
#Hemoglobin (<Lower limit)	20 (37.0)	367 (48.7)	0.098
#Hematocrit (<Lower limit)	32 (59.3)	519 (68.8)	0.145
Platelet count (>300 * 10^9/L)	9 (16.7)	85 (11.3)	0.232

(*continued*)

TABLE 1 Continued

SD, standard deviation; BMI, body mass index; ASA, american society of anesthesiologists; WBC, white blood cell; A/G, albumin/globulin; HCRP, hypersensitive c-reactive protein; LDH, lactate dehydrogenase; FBG, fasting blood glucose; RBC, red blood cell.

#Reference range was applied stratified by sex: RBC: Female, 3.5–5.0 * 10^{12}/L and males, 4.0–5.5 * 10^{12}/L; Hemoglobin: Females, 110–150 g/L and males, 120–160 g/L; Hematocrit: Females, 35%–45%; males, 40%–50%.

and having chronic respiratory disease, simplification of procedure to admit and multidisciplinary intervention to achieve a fastest medical optimization might be more effective, e.g., setting of dedicated, organized and comprehensive orthogeriatric care wards (28).

Greater surgical trauma meant the increased body inflammatory/immune response, and the prolonged surgical duration and

TABLE 2 Multivariate analysis of factors associated with postoperative nosocomial pneumonia in patients with a hip fracture.

Variables	OR	95% CI		*P*
		Lower limit	Upper limit	
Age (each 10-year increment)	1.50	1.10	1.92	0.011
Diabetes	1.77	0.91	3.43	0.092
Chronic respiratory disease	4.61	1.70	12.54	0.003
Presence of preoperative DVT	3.51	1.74	10.48	0.001
Preoperative waiting (in each day increment)	1.07	1.01	1.15	0.039
Surgical duration >120 min	4.03	1.96	8.27	<0.001
Procedure (arthroplasty vs. osteosynthesis)	4.39	1.87	10.31	0.001

TABLE 3 [&]Multivariate linear regression analysis showing pneumonia significantly positively associated with total hospitalization stay, together with other 3 factors.

Variables	*B*	95% CI	Beta	*T*	*P*
Pneumonia	3.119	1.672 to 4.849	0.110	3.986	<0.001
Preoperative stay (day)	1.101	0.988 to 1.123	0.549	19.223	<0.001
Surgical duration ≥120 min	1.820	1.040 to 2.600	0.129	4.580	<0.001
Procedure (osteosynthesis vs. arthroplasty)	2.205	1.348 to 3.063	0.155	5.047	<0.001

B, unstandardized coefficient; Beta, standardized coefficient indicating the strength of influence; and T, statistic of the regression.
[&]Covariables included in this multivariate model were pneumonia, age in continuous variable, diabetes, history of respiratory disease, preoperative DVT, surgical duration, procedure pattern.

TABLE 4 ^Multivariate linear regression analysis showing pneumonia significantly positively associated with postoperative hospitalization stay, together with other 3 factors.

Variables	*B*	95% CI	Beta	*T*	*P*
Pneumonia	3.934	2.351 to 5.493	0.139	4.104	<0.001
Preoperative stay (day)	0.181	0.075 to 0.287	0.117	3.348	0.001
Surgical duration ≥120 min	1.575	0.837 to 2.313	0.144	4.191	<0.001
Procedure (osteosynthesis vs. arthroplasty)	2.254	1.444 to 3.065	0.205	5.462	<0.001

B, unstandardized coefficient; Beta, standardized coefficient indicating the strength of influence; and T, statistic of the regression.
^Covariables included in this multivariate model were pneumonia, age in continuous variable, diabetes, history of respiratory disease, preoperative DVT, surgical duration, procedure pattern.

arthroplasty procedure (vs. osteosynthesis), undoubtedly, contributed predominantly to this effect (6, 7). Despite the international guidelines recommending specific surgical procedure for different fracture patterns of hip fractures, taking age and systemic conditions into consideration, but that seemed more applicable for femoral neck fractures. Because, for intertrochanteric fracture, more options were available, including dynamic hip screw, Gamma screw and proximal femoral nail and variants, which possibly caused less-experienced surgeons to be trapped in the dilemma of choose (29). Thus, out results emphasize the importance of thorough understanding and grasping the indications for hip fracture surgery, thereby choosing a simple and fast surgical method to shorten the surgical duration and reduce the risk of intraoperative exposure.

Preoperative DVT of bilateral lower extremities were detected in 6.8%–35% of patients with a hip fracture, even if prophylactic thromboembolic agents are routinely administered (13). However, no studies linked this to the risk of pneumonia. In this study, we got the relatively strong relationship magnitude (OR, 3.51). The underlying mechanism is unclear, but we can obtain some useful information from other studies. Minno et al. (30) conducted a meta-analysis of studies on relationship between COVID-19 and venous thromboembolism (VTE), and found the incidence of VTE was 31.3% in COVID-19 patients far greater than that for general patients, also for hip fracture patients (14.7% in this study). Factors that contribute to developing DVT, such as endothelial injury, venous blood stasis and hypercoagulability, are also potentially playing a role in pneumonia. In addition, platelet activation (a component in DVT) would promote the release of vasoactive mediators and thus increase the pulmonary vascular resistance (31), potentially creating an improved condition for bacterial colonization. Regardless, patients detected with preoperative DVT should be placed more attention on the risk of postoperative pneumonia, and preventive targeted measures to eliminate embolus and enhance respiratory dynamics and muscle function should be considered into practice for this population.

Strengths and limitations

The strengths of this study included the relatively sample and inclusion of numerous variables for adjustment. However, the potential limitations should also be noted. First, the retrospective design had the intrinsic limitations in data collection, especially that comorbidities or conditions were self-reported by patients. Second, the single-center design might have compromised the representativeness of sample, and our institution was an orthopaedics-specialized hospital, thus further deteriorating the issue of selection bias. Also, the generalizability of these finding might be less applicable to other settings. Third, as with every logistic regression analysis, the unknown, unmeasured or not considered factors make the confounding effects remain. Fourth, due to the observational nature, the findings were associative rather than causative, and therefore should be interpreted with caution.

Conclusion

Nosocomial pneumonia was prevalent in 6.7% of patients following surgical treatment, and was positively associated with total and postoperative hospitalization stay. Six factors were identified, including elder age, history of chronic respiratory disease, preoperative DVT, prolonged preoperative waiting, surgical duration ≥120 min and arthroplasty procedure. These findings help stratify patients regarding the risk of pneumonia and more importantly, facilitating preventive targeted intervention into implementation for individuals with different risk profiles.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the ethics committee of the Second Hospital of Tangshan, which waived the requirement for informed consent due to the retrospective nature.

Author contributions

XT designed the study. XT and CC searched relevant studies and collected data on variables of interest. JC, MS and HZ analyzed and interpreted the data. HW, TY. and HW prepared the Tables and Figures. XT and CC grafted the manuscript and WY revised. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Bolton D, Bush C, Wallace MT. Nonagenarian hip fractures: morbidity and mortality at a single institution. *J Clin Orthop Trauma*. (2021) 14:69–73. doi: 10.1016/j.jcot.2020.09.020

2. Flikweert ER, Wendt KW, Diercks RL, Izaks GJ, Landsheer D, Stevens M, et al. Complications after hip fracture surgery: are they preventable? *Eur J Trauma Emerg Surg*. (2018) 44:573–80. doi: 10.1007/s00068-017-0826-2

3. Pradhan A, Aboelmagd T, Richardson L, Olivarius-McAllister J, Ralhan S, Deakin M. Outcomes for non-operatively managed fracture neck of femur patients: a single-institution study. *Injury*. (2022) 53:626–30. doi: 10.1016/j.injury.2021.11.007

4. Lv H, Yin P, Long A, Gao Y, Zhao Z, Li J, et al. Clinical characteristics and risk factors of postoperative pneumonia after hip fracture surgery: a prospective cohort study. *Osteoporos Int*. (2016) 27:3001–9. doi: 10.1007/s00198-016-3624-5

5. Shin KH, Kim JJ, Son SW, Hwang KS, Han SB. Early postoperative hypoalbuminaemia as a risk factor for postoperative pneumonia following hip fracture surgery. *Clin Interv Aging*. (2020) 15:1907–15. doi: 10.2147/CIA.S272610

6. Tang MT, Li S, Liu X, Huang X, Zhang DY, Lei MX. Early detection of pneumonia with the help of dementia in geriatric hip fracture patients. *Orthop Surg*. (2022) 14:129–38. doi: 10.1111/os.13199

7. Yan JC, Chen JY, Wang YQ, Wang HX, Chen XL. Renis factors analysis and intervention of hospital acquired pneumonia in elderly patients with hip fracture. *Modern Pract Med*. (2017) 29:16–8. doi: 10.3969/j.issn.1671-0800.2017.01.007

8. Bohl DD, Sershon RA, Saltzman BM, Darrith B, Della Valle CJ. Incidence, risk factors, and clinical implications of pneumonia after surgery for geriatric hip fract ure. *J Arthroplasty*. (2018) 33:1552–1556.e1. doi: 10.1016/j.arth.2017.11.068

9. Salarbaks AM, Lindeboom R, Nijmeijer W. Pneumonia in hospitalized elderly hip fracture patients: the effects on length of hospital-stay, in-h ospital and thirty-day mortality and a search for potential predictors. *Injury*. (2020) 51:1846–50. doi: 10.1016/j.injury.2020.05.017

10. Wang X, Dai L, Zhang Y, Lv Y. Gender and low albumin and oxygen levels are risk factors for perioperative pneumonia in geriatric hi p fracture patients. *Clin Interv Aging*. (2020) 15:419–24. doi: 10.2147/CIA.S241592

11. Shin WC, Do MU, Woo SH, Choi SH, Moon NH, Suh KT. C-reactive protein for early detection of postoperative systemic infections in intertrochanteric femo ral fractures. *Injury*. (2018) 49:1859–64. doi: 10.1016/j.injury.2018.07.029

12. Sheehan KJ, Guerrero EM, Tainter D, Dial B, Milton-Cole R, Blair JA, et al. Prognostic factors of in-hospital complications after hip fracture surgery: a scoping review. *Osteoporos Int*. (2019) 30:1339–51. doi: 10.1007/s00198-019-04976-x

13. Zhang BF, Wei X, Huang H, Wang PF, Liu P, Qu SW, et al. Deep vein thrombosis in bilateral lower extremities after hip fracture: a retrospective study of 463 patients. *Clin Interv Aging*. (2018) 13:681–9. doi: 10.2147/CIA.S161191

14. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilatorassociated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. (2005) 171:388–416. doi: 10.1164/rccm.200405-644ST

15. Xiong M, Li J, Yang S, Zeng F, Ji Y, Liu J, et al. Influence of gender and reproductive factors on liver fibrosis in patients with chronic hepatitis B infection. *Clin Transl Gastroenterol*. (2019) 10:e00085. doi: 10.14309/ctg.0000000000000085

16. Liu Y, Zou J, Li X, Zhao X, Zou J, Liu S, et al. Effect of the interaction between obstructive sleep apnea and lipoprotein(a) on insulin resistance: a large-scale cross-sectional study. *J Diabetes Res*. (2019) 2019:9583286. doi: 10.1155/2019/9583286

17. Malhotra R, Huq SS, Chong M, Murphy D, Daruwalla ZJ. Outcomes in nonagenarians with hip fractures treated conservatively and surgically. *Malays Orthop J*. (2021) 15:21–8. doi: 10.5704/MOJ.2111.004

18. Salarbaks AM, Lindeboom R, Nijmeijer W. Pneumonia in hospitalized elderly hip fracture patients: the effects on length of hospital-stay, in-hospital and thirty-day mortality and a search for potential predictors. *Injury*. (2020) 51:1846–50. doi: 10.1016/j.injury.2020.05.017

19. Shen J. Prognostic implications of preoperative pneumonia for geriatric patients undergoing hip fracture surgery or arthroplasty. *Orthop Surg*. (2020) 12(6):1890–9. doi: 10.1111/os.12830.

20. McAlister FA, Khan NA, Straus SE, Papaioakim M, Fisher BW, Majumdar SR, et al. Accuracy of the preoperative assessment in predicting pulmonary risk after nonthoracic surgery. *Am J Respir Crit Care Med*. (2003) 167:741–4. doi: 10.1164/rccm.200209-985BC

21. Warner DO, Warner MA, Offord KP, Schroeder DR, Maxson P, Scanlon PD. Airway obstruction and perioperative complications in smokers undergoing abdominal surgery. *Anesthesiology*. (1999) 90:372–9. doi: 10.1097/00000542-199902000-00007

22. Borges FK, Bhandari M, Patel A, Avram V, Guerra-Farfán E, Sigamani A, et al. Rationale and design of the HIP fracture accelerated surgical TreaTment and care tracK (HIP ATTACK) trial: a protocol for an international randomised controlled trial evaluating early surgery for hip fracture patients. *BMJ Open*. (2019) 9:e028537. doi: 10.1136/bmjopen-2018-028537

23. Moja L, Piatti A, Pecoraro V, Ricci C, Virgili G, Salanti G, et al. Timing matters in hip fracture surgery: patients operated within 48 h have better outcomes. A meta-analysis and meta-regression of over 190,000 patients. *PLoS One*. (2012) 7:e46175. doi: 10.1371/journal.pone.0046175

24. Jiang LY, Huang XY, Xie W, Cen JW, Li Y, Wang MY, et al. Retrospective analysis of risk factors and prognosis of postoperative aspiration pneumonia in elderly patients with hip fracture. *J Pract Med*. (2020) 36:2264–68. doi: 10.3969/j.issn.1006-5725.2020.16.019

25. Murao M, Honma Y. [Aging and diseases: pneumonia]. *Nihon Rinsho*. (1974) 32:87–91.

26. Li W, Ding C, Yin S. Aging increases the expression of lung CINCs and MCP-1 in senile patients with pneumonia. *Oncotarget*. (2017) 8:108604–09. doi: 10.18632/oncotarget.21285

27. Bowman AM. Sleep satisfaction, perceived pain and acute confusion in elderly clients undergoing orthopaedic procedures. *J Adv Nurs*. (1997) 26:550–64. doi: 10.1046/j.1365-2648.1997.t01-16-00999.x

28. Prestmo A, Hagen G, Sletvold O, Helbostad JL, Thingstad P, Taraldsen K, et al. Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial. *Lancet*. (2015) 385:1623–33. doi: 10.1016/S0140-6736(14)62409-0

29. Bhandari M, Swiontkowski M. Management of acute hip fracture. *N Engl J Med*. (2017) 377:2053–62. doi: 10.1056/NEJMcp1611090

30. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost*. (2020) 46:763–71. doi: 10.1055/s-0040-1715456

31. Díaz JM, Boietti BR, Vazquez FJ, Waisman GD, Giunta DH, Rojas LP, et al. Mean platelet volume as a prognostic factor for venous thromboembolic disease. *Rev Med Chil*. (2019) 147:145–52. doi: 10.4067/s0034-98872019000200145

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Constructing intervertebral disc degeneration animal model: A review of current models

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Low back pain is one of the top disorders that leads to disability and affects disability-adjusted life years (DALY) globally. Intervertebral disc degeneration (IDD) and subsequent discogenic pain composed major causes of low back pain. Recent studies have identified several important risk factors contributing to IDD's development, such as inflammation, mechanical imbalance, and aging. Based on these etiology findings, three categories of animal models for inducing IDD are developed: the damage-induced model, the mechanical model, and the spontaneous model. These models are essential measures in studying the natural history of IDD and finding the possible therapeutic target against IDD. In this review, we will discuss the technical details of these models, the duration between model establishment, the occurrence of observable degeneration, and the potential in different study ranges. In promoting future research for IDD, each animal model should examine its concordance with natural IDD pathogenesis in humans. We hope this review can enhance the understanding and proper use of multiple animal models, which may attract more attention to this disease and contribute to translation research.

KEYWORDS

intervertebral disc degeneration, nucleus pulposus, intervertebral disc, animal model, surgery technique, orthopedics surgery

1. Introduction

Low back pain (LBP) is one of the most common disorders affecting elder and middle-aged persons. It has been estimated that low back pain is the fourth most prevalent disease that causes disability worldwide (1). In the last 30 years, DALYs of low back pain has increased by approximately 33% (2). In the US, the total cost of LBP is 7.4 billion US dollars in 2008 (3). Given the high prevalence and high cost of LBP, it is urgent to search for the pathogenesis of LBP and develop treatments for alleviating LBP (4).

Intervertebral disc degeneration (IDD) is one of the major causes of LBP (5–7). Approximately 40% of LBP presented with the feature of IDD (8). The Intervertebral disc consists of three major histological distinct components: annulus fibrosus (AF), nucleus pulposus (NP), and cartilage endplate (EP). In undegenerated intervertebral disc, NP was surrounded by AF with CEP covering the interface between AF and bony vertebrae. Known risk factors for IDD include excessive mechanical loading, obesity, spine imbalance, diabetes mellitus, and genetic predisposition (9–13). When the process of IDD commences, internal and external stimuli triggers inflammation and oxidative stress. The overproduction of inflammatory mediators, such as tumor tumor necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), and interleukin 6 (IL-6), led to increased expression of extracellular matrix

(ECM) degradation enzymes (14, 15). The overproduction of ECM degradation enzymes leads to loss of collagen type II and aggrecan in NP and subsequently compromises the water-retaining ability (16). Loss of water and ECM components leads to biomechanical changes in the intervertebral disc and exacerbates IDD (17, 18).

It is of great significance to develop and utilize IDD animal models to understand the pathogenesis mechanism and test novel treatments. We elaborate on currently available animal models and provide an overview of the utility of these models. In this review, we tried to present the advantages and disadvantages of these models, discuss the duration of constructing these models, and include some necessary technical details of model construction (**Figure 1**). Finally, we hope this review will contribute to the appropriate selection of IDD models and promote the development of new therapeutic strategies.

2. Methods for constructing IDD animal model

2.1. Damage-induced model

2.1.1. Needle puncture model

The needle puncture model was established through puncture of the intervertebral disc from either the posterior or anterior direction. This model is most commonly used in small animals, including rats, mice, and rabbits. However, needle puncture is also applicable in establishing the IDD model on larger animals like dog (19), sheep (20), bovine (21), and rhesus monkeys (22). The needle puncture model is easy to install by inserting the needle into AF without disrupting NP. The insertion depth can be determined by radiography monitoring or the length of the needle emerged. After insertion, the needles are usually placed in the disc for a period of 30 s to 1 min (23, 24). A proportion of studies rotated the needle for 180°–360° before being placed in the disc (25, 26).

Different diameters of needles are used to induce the IDD animal model. Chen et al. inserted a 21G needle into the AF of rats and IDD was observed in the corresponding level 4 weeks post-operation (27). Our experiments also confirmed the successful induction of IDD histologically and radiographically four weeks after 21G needle insertion (28). Smaller and larger needles are also demonstrated to induce IDD in rats post-surgery. Issy et al. showed that 30G needles insertion can cause IDD 6 weeks post-operative (29). Matta et al. performed the puncture model with 32G needles, and the animals were euthanized ten weeks after modeling (30). In rats inserted with larger needles (20G), the occurrence of IDD is more rapid than minor needle insertion as the histological IDD was observed one week after injury (31, 32). Masuda et al. compared the histological damage of needle puncture using 16G, 18G, and 21G needles in the rabbit model of IDD. Generally, these studies suggested that the radiographic and histologic damage is more severe in mice punctured with a larger needle (33). In large animals, a larger size of needles is needed to induce the IDD model. Tellegen et al. inserted 18G needles on the AF of dogs under the monitoring of intra-operative fluoroscopy. These studies suggested that the development of IDD is closed related to the diameter of needles and choosing the appropriate needle and sampling time are crucial to the conclusion.

Punctures in both lumbar (L) discs and coccygeal (Co) discs can induce IDD. In the lumbar disc puncture model, skin incisions are needed to expose the lumbar disc. Kim et al. performed a right hemilaminectomy to expose the L5/6 disc and inserted a needle. Von Frey test, Basso-Beattie-Bresnahan scale, and the horizontal ladder test found that the rats emerged behavior in response to pain as early as 1-week post-surgery (34). Coccygeal disc puncture can be performed with or without fluoroscopy (35, 36). Co5/6, Co6/7, Co7/8, Co8/9, and Co9/10 levels are usually selected for the IDD modeling (37, 38). Isa et al. established the IDD model by puncturing Co4/5 and Co5/6 discs and then investigated the pain response in the ventral base of the tail by Hargreaves test, von Frey test, and tail-flick test (39). Interestingly, lumbar discs and coccygeal discs puncture may represent the different modeling scenarios. In evaluating the behavioral parameters of IDD, lumbar disc puncture seems more resemble with IDD in patients since it may induce both leg and back pain. The coccygeal discs puncture

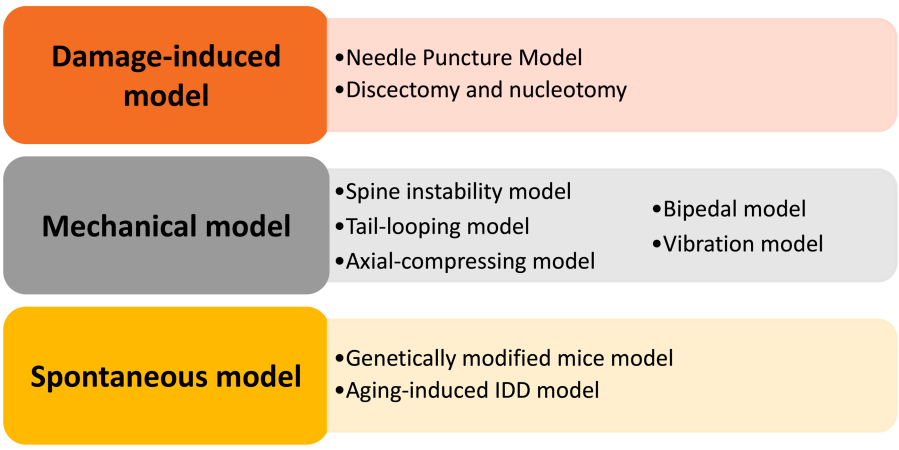

FIGURE 1
Summary of the animal models demonstrated in this review, including the damage-induced, mechanical, and spontaneous models.

models are easier to perform and may benefit the research for alleviating the disc degeneration process.

Needle puncture combined with intradiscal injection of reagents also represents a method for constructing the IDD model. Since pro-inflammatory factors contribute to the onset of IDD (5), injection of pro-inflammatory factors such as TNF-α and IL-1β into the intervertebral disc can induce IDD in different animal models (34, 40). Notably, the pain response to needle puncture is associated with the expression level of pro-inflammatory cytokines in the dorsal root ganglion (41). Norcross et al. compared injection of chondroitinase ABS or phosphate-buffered saline into the intervertebral disc of rats. Disc height and histological examination showed that chondroitinase injection leads to the observable degeneration on day 14 of experiment (42). Complete Freund's adjuvant (CFA), a tissue destruction reagent, was injected into to intervertebral disc to induce IDD (43). The rats were subjected to the behavioral test and found CFA injection successfully induced back pain and inflammatory factors accumulation (44). Wei et al. injected pingyangmycin or bleomycin into the subchondral bone adjacent to the lumbar intervertebral disc of rhesus monkeys, and degeneration was observed by MRI 3 months after injection (45, 46).

2.1.2. Discectomy and nucleotomy model

Discectomy is the standard surgical procedure for treating intervertebral disc herniation caused by IDD (47). Discectomy can relieve the nerve root compression by disc herniation, but the loss of NP tissue may cause the subsequent collapse of the intervertebral space (48). Therefore, discectomy model is suitable for studying disc-healing therapy, especially implants or biomaterials. The discectomy was performed on multiple animals, including rats (49), rabbits (50), sheep (51), pigs (52), and bovine (53). Since many studies suggested that goats and sheep possess similar biomechanical properties that are similar and comparable to the human spine, both animals are considered to be suitable for investigating spine mechanical properties (54, 55). Sloan et al. performed the discectomy in 3-4-year-old Finn sheep by performing a 3×10 mm annulotomy and then removing 200 mg of NP tissue (56). The intervertebral discs were subjected to histological examination six weeks after surgery. NP heterogeneity, AF lesions, and increased proteoglycan staining were observed in AF (56). Oehme et al. investigated a mini-invasive approach in sheep by making a 3×5 mm rectangular annular incision on AF using an 11-blade scalpel (57). A mixture of NF and AF tissue weighing 200 mg was removed.

Nucleuotomy refers to the partial excision of NP tissue with little disturbance of AF structure (58). Schwan et al. introduced a novel surgical approach to performing nucleotomy (59). A skin incision was made, and the corresponding disc level was determined with x-ray fluoroscopy. The discs were punctured with a straight awl through the whole layer of AF, and surgical channels were created. A 12 cm long rongeur was inserted through the tunnel, and approximately 0.15 cm^3 of NP tissue was removed (59, 60). Partial nucleotomy resulted in the loss of disc height six weeks after surgery. Takeoka et al. performed percutaneous nucleotomy in rats according to the method by Nishimura et al., and loss of disc height was observed as early as seven days post-surgery (61).

2.2. Mechanical model

2.2.1. Spine instability model

In 1991, Miyamoto et al. proposed a model of constructing cervical spondylosis by surgically induced spine instability (62). The posterior paravertebral muscles were separated, and the cervical, thoracic and lumbar spine was exposed. Then the spinous processes and attached supraspinous and interspinous ligaments were resected. The model was commonly used in constructing the IDD model in the lumbar spine and is therefore referred to lumbar spine instability (LSI) model. Zheng et al. applied the L3–L4 LSI to investigate the contributory role of parathyroid hormone in maintaining intervertebral disc homeostasis (63). Xue et al. further exploited the model to examine the role of skeletal interoception in causing EP degeneration and spinal-associated pain (64). Recently, Liu et al. demonstrated that the LSI model leads to spinal hypersensitivity in DRG, which explains the pain caused by IDD (65).

As for constructing the caudal spine instability model, Bian et al. stapped through the full depth of the Co7/8 AF, and then removed the NP (66). The adjacent Co8/9 intervertebral disc was subjected to histological analysis four weeks post-surgery and confirmed the successful establishment of the IDD model. Another study by the same group also made an incision into the whole layer of AF and performed NP removal to induce IDD. The bony EP was then analyzed and found that CSI leads to bony EP porosity of the same level (67).

2.2.2. Tail-looping model

Clinical observations suggested spinal deformities such as adolescent idiopathic scoliosis (AIS) and Scheuermann's disease are associated with IDD (68, 69). The spine deformity alters the normal pattern of force distribution and undermines the mechanical property. Tail-looping model is a novel method to construct the IDD model by creating force imbalance within the intervertebral disc. Saikai et al. looped the tail of mice and made fixation between Co5 and Co13 vertebrae with 0.8-mm stainless steel wire (70). The extra vertebrae were excised. The NP of Co7/8, and Co8/9 discs were aspirated to generate more severe degeneration. In this model, the Co2/3 and Co3/4 discs were selected as control discs, while Co10/11 and Co11/12 discs were chosen as mildly degeneration discs. The researchers demonstrated that histological severity correlates with previous treatment, and degeneration occurred as early as eight weeks after looping (70). Nakamichi et al. established the tail-looping induced IDD model by joining Co2 and Co9 vertebrae together (71). In this study, outer AF was removed, and the role of Mohawk-induced AF regeneration was explored. Further, Huang et al. modified the looping method by tying the tail with thin wire instead of stitching the vertebrae. The model was successfully constructed after two months of fixation and continued with the adenovirus treatment for one month before sample collection (72).

2.2.3. Axial-compressing external fixation devices

Under the condition of compression and angulation, the intervertebral discs may become narrowed and stiffer (73).

MacLean et al. annexed external rings to adjacent levels of intervertebral discs by inserting 0.5 mm pins transfixing the vertebral bodies percutaneously (74). Stokes et al. modified the method by installing rings either parallel to each other or with an angle of 15-degree (75). Their results showed that 15-degree angulation plus compression yielded greater disc space loss. Hirata et al. exerted temporary static compression using an Ilizarov-type apparatus with springs between Co8 and Co10 (76). An axial force of 1.3 MPa was exerted and subsequent analysis found that the compression reproduced different stages of degeneration. The same compression pressure was adopted by other studies (77, 78), suggesting this pressure may be the appropriate pressure for constructing model. In a recent study, Ji et al. developed a novel device by inserting Kirschner wire into Co8 and Co10 vertebral bodies (79). Then the tail was bent for 40° and springs are used to exert 1.8N and 4.5N of force on Co8/9 and Co9/10 intervertebral disc. Pfirrmann grades and histological examinations revealed the occurrence of IDD two weeks after surgery. The severity of degeneration correlates positively with the force exerted (79).

In addition to constructing the IDD model on a histological and radiographic level, the axial-compressing external fixation devices can simulate pain caused by IDD. Miyagi et al. used both the compression model and needle puncture model to establish IDD in rats and found that the pro-inflammatory factors were elevated (80). Moreover, the positive labeling of calcitonin gene-related peptide (CGRP) neurons increased, suggesting a potential mechanism IDD leads to low back pain (80). Since many studies have shown neurogenic factors like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and CGRP and closely related to discogenic pain of IDD (81, 82), the compression model is applicable in pain-related phenomenon.

2.2.4. Vibration model

High-frequency, low-amplitude whole-body vibration (WBV) is a common physical therapy in some disorders. Notably, WBV has been used as an adjuvant treatment for osteoporosis, muscle weakness, and low back pain (83, 84). However, it remains controversial whether WBV retarded the progression of IDD. Clinical observations found that workers exposed to occupational vibration are susceptible to IDD (85). Studies have linked vibration exposure with increased matrix metalloproteinase and decreased ECM (86), suggesting vibration is a potential risk for IDD progression. In a study by McCann et al., they applied clinically used vibration frequency (45 Hz with peak acceleration at 0.3 g for 30 min per day and 5 days per week) on mice for four weeks (87). The morphologic grade was analyzed and confirmed the IDD occurrence, especially characterized by AF degeneration. Furthermore, they found that 4-week WBV followed by 4-week cessation did not reverse the IDD in mice, suggesting the damage is permanent (88). Zeeman et al. demonstrated that 8 Hz and 15 Hz WBV is associated with long-lasting cervical and lumbar pain in rats (89), indicating the WBV model may also be useful in pain-related research. Although it is now known that WBV contributes to the development of IDD and IDD-related pain, the ideal vibration mode (time, frequency, orientation) to induce IDD still needs more investigation (90).

2.2.5. Bipedal animal model

The bipedal animal model was established by forelimb amputation in rodents. After forelimb amputation, a forced bipedal stance mimics the bipedal gait of human(91). Liang et al. performed amputation surgery on 1-month-old male rats and the rats were kept in custom-made cages to force them to stand in an upright position (92). The rat was kept for 5 months and 7 months before histological analysis. Loss of cervical disc height was observed in the amputation surgery group five months after surgery, and the height loss was more severe seven months after surgery. The down-regulation of Col2a1 and aggrecan was also observed and may decrease anti-compression capacity (92). Using the bipedal rat model, Liu et al. discovered ligustrazine attenuate cartilage EP hypertrophy, a characteristic of IDD, within an observation period of 9 months (93). Kong et al. Found the myocardin-related transcription factor A (MRTF-A) inhibitor CCG-1423 attenuated IDD progression over six months (94). Although the bipedal animal model mimics the upright posture similar to human beings, this model may take as long as six months to gain a histologically observable degeneration. Another concern that hampers the application of this model is animal welfare since amputation surgery causes trauma and alters the feeding habits of animals (91).

In addition to forelimb amputation, bipedal models are modified to yield better potency. Liang et al. performed both brachial plexus rhizotomy and tail amputation on 4-weeks-old female rats (95). The rats were euthanized six weeks post-surgery and lumbar discs were dissected (L1–S1) and subjected to qPCR analysis. Data showed the loss of ECM matrix in six weeks post-surgery, suggesting the efficacy of this model (95). Recently, Ao et al. developed a novel bipedal model utilizing the water-escape nature of rodents without amputation surgery (96). The mice were kept in a chamber with a 5 mm depth of water on the bottom of the chamber. The mice were kept in the chamber for 6 h each day and were allowed to access water and food freely for 2 h. Because of the water-escape nature, the mice are more likely to keep an upright position in the chamber. Degeneration of the facet joint and the intervertebral disc was observed 6-week after treatment (96). Lao et al. developed a hot plate cage to exert accumulated spinal axial force on mice's spine (97). The mice were placed on the 50 °C hot plate for 15 min per day and were forced to jump before returning to the regular cage. IDD was observed one-month post-modeling and progressed more severely in 3-months of observation (97).

2.3. Spontaneous model

2.3.1. Genetically modified mice model

Certain gene deficiency impairs intervertebral disc metabolic homeostasis and structural integrity. Secreted protein acidic and rich in cysteine (SPARC) is a matricellular protein involved in the pathogenesis of IDD (98). The expression level of SPARC decreased with aging and intervertebral disc degeneration. Moreover, it has been demonstrated that SPARC deletion accelerates IDD in mice (98, 99). Histological analysis revealed that

herniations of lower lumbar discs in SPARC-null mice occur as early as 14-month-old. Millecamps et al. discovered that in addition to typical IDD pathologic features, the SPARC-null mice also developed the feature of chronic back pain (100). The chronic back pain was characterized by hind paw sensitivity to mechanical and cold stimuli, intolerance to axial stretching, and motor impairment, which all implied nerve root impairment. More studies confirmed the association between low back pain and IDD in the SPARC-null mice (101). In a study by Lee et al., the SPARC-null mice developed IDD and low back pain at 14 months (98). Krock et al. found that the SPARC-null mice presented with low back pain at a relatively young age of 7–9 months (102).

SM/J mice is a strain characterized by lacking cartilage regeneration ability (103). It is reasonable to propose the hypothesis that intervertebral disc homeostasis in SM/J mice may be disrupted. Choi et al. found that the cellularity and matrix components of SM/J mice are altered at a young age (104). Severe IDD was observed in 17-week-old SM/J mice, marked by increased apoptosis and collagen degradation. Moreover, the intervertebral disc of SM/J mice showed increased stiffness and the vertebral bone showed decreased bone quality (104). Zhang et al. compared LG/J mice, a mice strain characterized by a remarkable ability to heal after cartilage injury, with SM/J mice in spontaneous IDD (105). Their result suggested the potential use of combining LG/J mice and SM/J mice in the genetic and biological study of IDD. Study by Novais et al., demonstrated that SM/J mice have increased susceptibility to IDD. However, the same study found that the LG/J mice showed increased disc calcification and degeneration compared with the BL6 strain, which is inconsistent with research mentioned above (106).

Studies have identified many genes associated with IDD, and knockout of these genes may also replicate the phenotype of spontaneous IDD. For example, collagen type II, encoded by the Col2a1 gene, has been identified as the critical regulator in intervertebral discs embryonic development (107). Col2a1 knockout showed the feature of AF glycosaminoglycans loss and EP degeneration in 9-month-old mice (108). Deletion in other collagen encoding genes, including Col9a2 (109), and Col9a1 (110), also exhibited the feature of spontaneous IDD. Besides the extracellular matrix components, loss in other genes (e.g,. Smad3 (111), IL-1rn (112), Hif-1a (113), Apoe 114) may also contribute to IDD's pathogenesis (**Table 1**). However, because IDD has long been considered a heterogeneous disease with different etiology, the use of the gene-specific knockout mice model may be limited.

2.3.2. Aging-induced IDD model

In 1988, Silberberg demonstrated that the sand rat (*Psammomys obesus*), a small desert rodent, is susceptible to age-related IDD (127). The severity of IDD was correlated with greater age. Helen et al. examined the age-related IDD of sand rats in a more detailed manner. The intervertebral discs of younger (2–11.9 months) and older (12–25 months) animals were collected and subjected to histological analysis. Their results suggested that the cervical spine of both younger and older sand rats is more likely to develop osteophytes than the lumbar spine. Moreover, the occurrence of osteophytes correlates with the extrusion of the intervertebral disc (128).

Some previous studies have demonstrated that mice are less susceptible to age-related IDD, which may limit the application of this model to some extent. For example, Marfia et al. showed that half of the mice did not exhibit IDD *via* MRI analysis in 19 months (129). Ohnishi et al.explored the availability of age-related IDD model in mice by MRI analysis followed by Pfirrmann classification and histological analysis followed by classification proposed in this research (130). They analyzed the mice aged 6 months, 14 months, and 22 months with both Pfirrmann classification and histological classification and found the feature of IDD progressed with increased age. The 14-months-old mice exhibited mild IDD while the 22-months-old mice developed moderate to severe IDD, which suggested that at least a 14-month follow-up is required for age-related IDD in C57BL/6 mice (130). Aging alters IDD's metabolism in many aspects, such as elevated chondrocyte hypertrophy and loss of notochordal markers (131).

The age-related IDD mice model is also widely used in investigating factors associated with senescence and longevity. Lin et al. found that tenomodulin (Tnmd), an anti-angiogenic transmembrane glycoprotein, maintained the structural integrity and matrix gene expression in outer AF and NP (132). Loss of *Tnmd* gene leads to early-onset IDD in 6-month-old mice and the IDD progressed more severely in 18-month-old mice compared with wild-type mice. Novais et al. investigated the role of senolytic drugs in ameliorating age-related IDD and defined different age groups, namely healthy adult (6-month-old), middle-aged (14-month-old), aged (18-month-old), and old-aged (23-month-old) (133). The mice started senolysis treatment at 6,14 and 18 months and IDD was harvested at 23 months.

3. Discussions

Intervertebral disc degeneration is a disease with complex etiology and clinical heterogeneity. Therefore, it is hard to find an ideal animal model that mimics all the inherent pathophysiology of IDD. Among these pathophysiology changes, some features are considered extra important, including loss of extracellular matrix and proteoglycans, biomechanical property alternations, and increased cell death. Discogenic pain is not necessarily associated with the severity of IDD (134), but the pain is the most disturbing symptom and chief complaint in IDD cases. Lack of early signs impairs the ability of early identification of IDD. Thus the disease is commonly irreversible at a later stage. These remind us that more in-detail studies into the common pattern of human IDD development are needed. Encouragingly, some recent studies combined new technology, including single-cell RNA-sequencing, with human specimens to discover the disease's very nature. Recent studies by Gan et al. (135), Gao et al. (136), Han et al. (137) and Zhang et al. (138) made delightful exploration into the possible reason for IDD initiation. Subsequent studies are needed to determine the similarities and differences between patients with different natural disease histories.

In developing appropriate animal models, some important considerations need extensive attention. Firstly, the upright position determined the unique mechanical property of the human spine and intervertebral disc. Secondly, the notochordal cells

TABLE 1 Genetically modified or certain strain mice that exhibits features of early IDD.

Strain	Method of analysis	Observed onset of degeneration	Year
SPARC-null mice (99)	Histological analysis Radiographic analysis	14-month-old	2005
SPARC-null (100)	Behavioral assays Histological analysis	78-week-old	2015
SPARC-null mice (102)	Behavioral assays Radiographic analysis Biochemical tests: ELISA	7-month-old	2019
SPARC-null mice (115)	Biomechanical test	18-month-old	2020
SPARC-null mice (98)	Behavioral assays Biochemical tests: qPCR	14-month-old	2022
SM/J mice (104)	Histological analysis Biomechanical test	17-week-old	2018
SM/J mice (105)	Histological analysis Biochemical tests: proteomes	8-week-old	2018
SM/J mice (106)	Histological analysis Radiographic analysis: μCT	6-month-old and 23-month-old	2020
LG/J mice (106)	Histological analysis Radiographic analysis: µCT	6-month-old and 23-month-old	2020
Bmal1 CKO ($Col2a1^{Cre}Bmal^{fl/fl}$) (116)	Histological analysis Radiographic analysis: x-ray	6-month-old and 12-month-old	2017
$Skt^{Gt/Gt}$ (117)	Histological analysis	8-week-old	2006
Col IX KO (118)	Histological analysis Radiographic analysis: µCT	6-month-old and 10-month-old	2016
TonEBP-deficient (119)	Histological analysis Radiographic analysis: µCT	22-month-old	2020
ERCC1-deficient (120)	Histological analysis	20-week-old	2010
Il1rn KO (125)	Histological analysis Biochemical tests: qPCR	55-day-old and 155-day-old	2013
IL-1 KO (112)	Histological analysis Radiographic analysis: µCT	12-month-old and 20month-old	2019
MCT4 KO (122)	Histological analysis Radiographic analysis: µCT	8-month-old	2020
Sox9 CKO ($Acan^{CreERT2}Sox9^{fl/fl}$) (123)	Histological analysis Radiographic analysis: µCT	12-month-old	2020
Mkx KO (71)	Histological analysis Biochemical tests: qPCR & Western Blotting	12-month-old	2016
Tgfbr2 CKO ($Acan^{CreERT2}$;$Tgfbr2^{fl/fl}$) (124)	Histological analysis Radiographic analysis: x-ray	6-month-old and 12-month-old	2018
CCN2 CKO ($Noto^{Cre}$; $CCN2^{fl/fl}$) (125)	Histological analysis	12-month-old and 17-month-old	2013
FOXO1/3/4 CKO ($Col2a1^{Cre}$; $Foxo1^{fl/fl}$; $Foxo3^{fl/fl}$; $Foxo4^{fl/fl}$) (126)	Histological analysis	4-month-old and 6-month-old	2018
FOXO1/3/4 CKO ($Acan^{Cre}$; $Foxo1^{fl/fl}$; $Foxo3^{fl/fl}$; $Foxo4^{fl/fl}$) (126)	Histological analysis	6-month-old and 12-month-old	2018
Smad3 KO (111)	Histological analysis	30-day-old and 60-day-old	2009
Hif1α KO (Shh^{Cre}; $HIF1\alpha^{fl/fl}$) (113)	Histological analysis	6-week-old and 12-week-old	2013
Kindlin2 CKO ($Acan^{CreERT2}$;$Kindlin\text{-}2^{fl/fl}$) (78)	Histological analysis Radiographic analysis: µCT	18-week-old	2022

(*continued*)

undergo apoptosis and differentiation after birth and are absent in the adult human spine. But notochordal cells may remain in the intervertebral discs in certain specimens, which may promote the regeneration ability of damaged discs. Thirdly, the duration between modeling and detectable degeneration should be taken into consideration. If the degeneration occurs too soon, it is unlikely to replicate the actual circumstances in IDD. Severe structural destruction will conceal the effectiveness of certain therapy. Lastly, the ethical and cost issue should also be taken into consideration.

In this review, we elaborated on the commonly used method to construct IDD models, which mainly fall into three categories: damage-induced, mechanical, and spontaneous. Damage-induced models make punctures or incisions into the intervertebral discs and impair the integrity of the disc structure, while mechanical models exert external force into the disc and accelerate the degeneration process. The spontaneous models focus on common IDD causes, such as aging and collagen loss, which spontaneously lead to IDD development. Each category replicates a certain stage

of IDD to some extent. Therefore, in searching for possible treatments for IDD, we should emphasize the importance of selecting correct animal models. For example, SPARC-null mice develop significant chronic back pain, making it suitable for researching IDD-related pain. The discectomy model mimiked the clinical situation of disc resection and seemed ideal for developing disc regeneration therapy. Integrating more than one IDD animal model into one study is becoming more common (139). Combining these models is a helpful approach to gaining solid evidence for the efficacy of specific interventions.

4. Conclusions

In conclusion, animal models are indispensable for understanding, characterizing, and treating disc degeneration. However, despite the methods listed in this review, there is still no consensus on which model best mimics IDD. More importantly, there is still some gap between model-induced IDD and actual clinical features. Further studies are needed to determine the fidelity of these models and eventually contribute to developing new IDD therapeutic strategies.

Author contributions

TL, BG, and JZ: performed literature search and summarized related literature. XQ, TC, YL, and JQ: prepared the manuscript draft. TL, XQ, YL, JZ and WG: revised and finalized the manuscript. XQ and YL provided the idea for this study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9

2. Tucker HR, Scaff K, McCloud T, Carlomagno K, Daly K, Garcia A, et al. Harms and benefits of opioids for management of non-surgical acute and chronic low back pain: a systematic review. *Br J Sports Med*. (2020) 54:664. doi: 10.1136/bjsports-2018-099805

3. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J*. (2008) 8:8–20. doi: 10.1016/j.spinee.2007.10.005

4. Miyamoto GC, Lin CC, Cabral C, van Dongen JM, van Tulder MW. Cost-effectiveness of exercise therapy in the treatment of non-specific neck pain and low back pain: a systematic review with meta-analysis. *Br J Sports Med*. (2019) 53:172–81. doi: 10.1136/bjsports-2017-098765

5. Risbud MV, Shapiro IM. Role of cytokines in intervertebral disc degeneration: pain and disc content. *Nat Rev Rheumatol*. (2014) 10:44–56. doi: 10.1038/nrrheum.2013.160

6. Simon J, McAuliffe M, Shamim F, Vuong N, Tahaei A. Discogenic low back pain. *Phys Med Rehabil Clin N Am*. (2014) 25:305–17. doi: 10.1016/j.pmr.2014.01.006

7. Bonnheim NB, Wang L, Lazar AA, Zhou J, Chachad R, Sollmann N, et al. The contributions of cartilage endplate composition and vertebral bone marrow fat to intervertebral disc degeneration in patients with chronic low back pain. *Eur Spine J*. (2022) 31:1866–72. doi: 10.1007/s00586-022-07206-x

8. Cheung KM, Karppinen J, Chan D, Ho DW, Song YQ, Sham P, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine*. (2009) 34:934–40. doi: 10.1097/BRS.0b013e3181a01b3f

9. Fu F, Bao R, Yao S, Zhou C, Luo H, Zhang Z, et al. Aberrant spinal mechanical loading stress triggers intervertebral disc degeneration by inducing pyroptosis and nerve ingrowth. *Sci Rep*. (2021) 11:772. doi: 10.1038/s41598-020-80756-6

10. Samartzis D, Karppinen J, Chan D, Luk KD, Cheung KM. The association of lumbar intervertebral disc degeneration on magnetic resonance imaging with body mass index in overweight and obese adults: a population-based study. *Arthritis Rheum*. (2012) 64:1488–96. doi: 10.1002/art.33462

11. Alpantaki K, Kampouroglou A, Koutserimpas C, Effraimidis G, Hadjipavlou A. Diabetes mellitus as a risk factor for intervertebral disc degeneration: a critical review. *Eur Spine J*. (2019) 28:2129–44. doi: 10.1007/s00586-019-06029-7

12. Wong E, Altaf F, Oh LJ, Gray RJ. Adult degenerative lumbar scoliosis. *Orthopedics*. (2017) 40:e930–9. doi: 10.3928/01477447-20170606-02

13. Takeda K, Kou I, Hosogane N, Otomo N, Yagi M, Kaneko S, et al. Association of susceptibility genes for adolescent idiopathic scoliosis and intervertebral disc degeneration with adult spinal deformity. *Spine*. (2019) 44:1623–9. doi: 10.1097/BRS.0000000000003179

14. Li Y, Zhang T, Tian W, Hu H, Xin Z, Ma X, et al. Loss of TIMP3 expression induces inflammation, matrix degradation, and vascular ingrowth in nucleus pulposus: a new mechanism of intervertebral disc degeneration. *Faseb J*. (2020) 34:5483–98. doi: 10.1096/fj.201902364RR

15. Francisco V, Pino J, Gonzalez-Gay MA, Lago F, Karppinen J, Tervonen O, et al. A new immunometabolic perspective of intervertebral disc degeneration. *Nat Rev Rheumatol*. (2022) 18:47–60. doi: 10.1038/s41584-021-00713-z

16. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? *Spine*. (2006) 31:2151–61. doi: 10.1097/01.brs.0000231761.73859.2c

17. Vergroesen PA, Emanuel KS, Peeters M, Kingma I, Smit TH. Are axial intervertebral disc biomechanics determined by osmosis? *J. Biomech*. (2018) 70:4–9. doi: 10.1016/j.jbiomech.2017.04.027

18. Fields AJ, Berg-Johansen B, Metz LN, Miller S, La B, Liebenberg EC, et al. Alterations in intervertebral disc composition, matrix homeostasis and biomechanical behavior in the UCD-T2DM rat model of type 2 diabetes. *J Orthop Res*. (2015) 33:738–46. doi: 10.1002/jor.22807

19. Tellegen AR, Rudnik-Jansen I, Beukers M, Miranda-Bedate A, Bach FC, de Jong W, et al. Intradiscal delivery of celecoxib-loaded microspheres restores intervertebral disc integrity in a preclinical canine model. *J Control Release*. (2018) 286:439–50. doi: 10.1016/j.jconrel.2018.08.019

20. Vadala G, Russo F, Pattappa G, Schiuma D, Peroglio M, Benneker LM, et al. The transpedicular approach as an alternative route for intervertebral disc regeneration. *Spine*. (2013) 38:E319–24. doi: 10.1097/BRS.0b013e318285bc4a

21. Yang JJ, Li F, Hung KC, Hsu SH, Wang JL. Intervertebral disc needle puncture injury can be repaired using a gelatin-poly (gamma-glutamic acid) hydrogel: an in vitro bovine biomechanical validation. *Eur Spine J*. (2018) 27:2631–8. doi: 10.1007/s00586-018-5727-5

22. Xi Y, Kong J, Liu Y, Wang Z, Ren S, Diao Z, et al. Minimally invasive induction of an early lumbar disc degeneration model in rhesus monkeys. *Spine*. (2013) 38:E579–86. doi: 10.1097/BRS.0b013e31828b695b

23. Guo Q, Zhu D, Wang Y, Miao Z, Chen Z, Lin Z, et al. Targeting STING attenuates ROS induced intervertebral disc degeneration. *Osteoarthritis Cartilage*. (2021) 29:1213–24. doi: 10.1016/j.joca.2021.04.017

24. Xiao L, Xu SJ, Liu C, Wang J, Hu B, Xu HG. Sod2 and catalase improve pathological conditions of intervertebral disc degeneration by modifying human adipose-derived mesenchymal stem cells. *Life Sci*. (2021) 267:118929. doi: 10.1016/j.lfs.2020.118929

25. Lei M, Zhao K, Hua W, Wang K, Li S, Wu X, et al. An in vivo study of the effect of c-jun on intervertebral disc degeneration in rats. *Bioengineered*. (2021) 12:4320–30. doi: 10.1080/21655979.2021.1946459

26. Xu D, Jin H, Wen J, Chen J, Chen D, Cai N, et al. Hydrogen sulfide protects against endoplasmic reticulum stress and mitochondrial injury in nucleus pulposus cells and ameliorates intervertebral disc degeneration. *Pharmacol Res*. (2017) 117:357–69. doi: 10.1016/j.phrs.2017.01.005

27. Chen F, Jiang G, Liu H, Li Z, Pei Y, Wang H, et al. Melatonin alleviates intervertebral disc degeneration by disrupting the IL-1beta/NF-kappaB-NLRP3 inflammasome positive feedback loop. *Bone Res*. (2020) 8:10. doi: 10.1038/s41413-020-0087-2

28. Qiu X, Liang T, Wu Z, Zhu Y, Gao W, Gao B, et al. Melatonin reverses tumor necrosis factor-alpha-induced metabolic disturbance of human nucleus pulposus cells via MTNR1B/Galphai2/YAP signaling. *Int J Biol Sci*. (2022) 18:2202–19. doi: 10.7150/ijbs.65973

29. Issy AC, Castania V, Silveira JW, Nogueira-Barbosa MH, Salmon CE, Del-Bel E, et al. Does a small size needle puncture cause intervertebral disc changes? *Acta Cir Bras*. (2015) 30:574–9. doi: 10.1590/S0102-865020150080000009

30. Matta A, Karim MZ, Gerami H, Jun P, Funabashi M, Kawchuk G, et al. NTG-101: a novel molecular therapy that halts the progression of degenerative disc disease. *Sci Rep*. (2018) 8:16809. doi: 10.1038/s41598-018-35011-4

31. Issy AC, Castania V, Castania M, Salmon CE, Nogueira-Barbosa MH, Bel ED, et al. Experimental model of intervertebral disc degeneration by needle puncture in wistar rats. *Braz J Med Biol Res*. (2013) 46:235–44. doi: 10.1590/1414-431X20122429

32. Han B, Zhu K, Li FC, Xiao YX, Feng J, Shi ZL, et al. A simple disc degeneration model induced by percutaneous needle puncture in the rat tail. *Spine*. (2008) 33:1925–34. doi: 10.1097/BRS.0b013e31817c64a9

33. Masuda K, Aota Y, Muehleman C, Imai Y, Okuma M, Thonar EJ, et al. A novel rabbit model of mild, reproducible disc degeneration by an anulus needle puncture: correlation between the degree of disc injury and radiological and histological appearances of disc degeneration. *Spine*. (2005) 30:5–14. doi: 10.1097/01.brs.0000148152.04401.20

34. Kim H, Hong JY, Lee J, Jeon WJ, Ha IH. IL-1beta promotes disc degeneration and inflammation through direct injection of intervertebral disc in a rat lumbar disc herniation model. *Spine J*. (2021) 21:1031–41. doi: 10.1016/j.spinee.2021.01.014

35. Chen D, Xia D, Pan Z, Xu D, Zhou Y, Wu Y, et al. Metformin protects against apoptosis and senescence in nucleus pulposus cells and ameliorates disc degeneration in vivo. *Cell Death Dis*. (2016) 7:e2441. doi: 10.1038/cddis.2016.334

36. Tang Z, Hu B, Zang F, Wang J, Zhang X, Chen H. Nrf2 drives oxidative stress-induced autophagy in nucleus pulposus cells via a Keap1/Nrf2/p62 feedback loop to protect intervertebral disc from degeneration. *Cell Death Dis*. (2019) 10:510. doi: 10.1038/s41419-019-1701-3

37. Kobori S, Miyagi M, Orita S, Gemba T, Ishikawa T, Kamoda H, et al. Inhibiting IkappaB kinase-beta downregulates inflammatory cytokines in injured discs and neuropeptides in dorsal root ganglia innervating injured discs in rats. *Spine*. (2014) 39:1171–7. doi: 10.1097/BRS.0000000000000374

38. Liu Y, Lin J, Wu X, Guo X, Sun H, Yu B, et al. Aspirin-mediated attenuation of intervertebral disc degeneration by ameliorating reactive oxygen Species in vivo and in vitro. *Oxid Med Cell Longev*. (2019) 2019:7189854. doi: 10.1155/2019/7189854

39. Mohd II, Abbah SA, Kilcoyne M, Sakai D, Dockery P, Finn DP, et al. Implantation of hyaluronic acid hydrogel prevents the pain phenotype in a rat model of intervertebral disc injury. *Sci Adv*. (2018) 4:q597. doi: 10.1126/sciadv.aav0295

40. Kang R, Li H, Rickers K, Ringgaard S, Xie L, Bunger C. Intervertebral disc degenerative changes after intradiscal injection of TNF-alpha in a porcine model. *Eur Spine J*. (2015) 24:2010–6. doi: 10.1007/s00586-015-3926-x

41. Li Z, Liu H, Yang H, Wang J, Wang H, Zhang K, et al. Both expression of cytokines and posterior annulus fibrosus rupture are essential for pain behavior changes induced by degenerative intervertebral disc: an experimental study in rats. *J Orthop Res*. (2014) 32:262–72. doi: 10.1002/jor.22494

42. Norcross JP, Lester GE, Weinhold P, Dahners LE. An in vivo model of degenerative disc disease. *J Orthop Res*. (2003) 21:183–8. doi: 10.1016/S0736-0266(02)00098-0

43. Jiang H, Wang J, Xu B, Yang Q, Liu Y. Study on the expression of nerve growth associated protein-43 in rat model of intervertebral disc degeneration. *J Musculoskelet Neuronal Interact*. (2017) 17:104–7. PMCID: PMC5492325

44. Jung WW, Kim HS, Shon JR, Lee M, Lee SH, Sul D, et al. Intervertebral disc degeneration-induced expression of pain-related molecules: glial cell-derived neurotropic factor as a key factor. *J Neurosurg Anesthesiol*. (2011) 23:329–34. doi: 10.1097/ANA.0b013e318220f033

45. Wei F, Zhong R, Wang L, Zhou Z, Pan X, Cui S, et al. Pingyangmycin-induced in vivo lumbar disc degeneration model of rhesus monkeys. *Spine*. (2015) 40:E199–210. doi: 10.1097/BRS.0000000000000736

46. Wei F, Zhong R, Zhou Z, Wang L, Pan X, Cui S, et al. In vivo experimental intervertebral disc degeneration induced by bleomycin in the rhesus monkey. *BMC Musculoskelet Disord*. (2014) 15:340. doi: 10.1186/1471-2474-15-340

47. Alvi MA, Kerezoudis P, Wahood W, Goyal A, Bydon M. Operative approaches for lumbar disc herniation: a systematic review and multiple treatment meta-analysis of conventional and minimally invasive surgeries. *World Neurosurg*. (2018) 114:391–407. doi: 10.1016/j.wneu.2018.02.156

48. Hudson KD, Alimi M, Grunert P, Hartl R, Bonassar LJ. Recent advances in biological therapies for disc degeneration: tissue engineering of the annulus fibrosus, nucleus pulposus and whole intervertebral discs. *Curr Opin Biotechnol*. (2013) 24:872–9. doi: 10.1016/j.copbio.2013.04.012

49. Liu Y, Du J, Peng P, Cheng R, Lin J, Xu C, et al. Regulation of the inflammatory cycle by a controllable release hydrogel for eliminating postoperative inflammation after discectomy. *Bioact Mater*. (2021) 6:146–57. doi: 10.1016/j.bioactmat.2020.07.008

50. Ukeba D, Yamada K, Tsujimoto T, Ura K, Nonoyama T, Iwasaki N, et al. Bone marrow aspirate concentrate combined with in situ forming bioresorbable gel enhances intervertebral disc regeneration in rabbits. *J Bone Joint Surg Am*. (2021) 103:e31. doi: 10.2106/JBJS.20.00606

51. Sloan SJ, Wipplinger C, Kirnaz S, Delgado R, Huang S, Shvets G, et al. Imaging the local biochemical content of native and injured intervertebral disc using Fourier transform infrared microscopy. *JOR Spine*. (2020) 3:e1121. doi: 10.1002/jsp2.1121

52. Chiang CJ, Cheng CK, Sun JS, Liao CJ, Wang YH, Tsuang YH. The effect of a new anular repair after discectomy in intervertebral disc degeneration: an experimental study using a porcine spine model. *Spine*. (2011) 36:761–9. doi: 10.1097/BRS.0b013e3181e08f01

53. Varma DM, Lin HA, Long RG, Gold GT, Hecht AC, Iatridis JC, et al. Thermoresponsive, redox-polymerized cellulosic hydrogels undergo in situ gelation and restore intervertebral disc biomechanics post discectomy. *Eur Cell Mater*. (2018) 35:300–17. doi: 10.22203/eCM.v035a21

54. Alini M, Eisenstein SM, Ito K, Little C, Kettler AA, Masuda K, et al. Are animal models useful for studying human disc disorders/degeneration? *Eur Spine J*. (2008) 17:2–19. doi: 10.1007/s00586-007-0414-y

55. Sheng SR, Wang XY, Xu HZ, Zhu GQ, Zhou YF. Anatomy of large animal spines and its comparison to the human spine: a systematic review. *Eur Spine J*. (2010) 19:46–56. doi: 10.1007/s00586-009-1192-5

56. Sloan SJ, Wipplinger C, Kirnaz S, Navarro-Ramirez R, Schmidt F, McCloskey D, et al. Combined nucleus pulposus augmentation and annulus fibrosus repair prevents acute intervertebral disc degeneration after discectomy. *Sci Transl Med*. (2020) 58:12(534):eaay2380. doi: 10.1126/scitranslmed.aay2380

57. Oehme D, Ghosh P, Shimmon S, Wu J, McDonald C, Troupis JM, et al. Mesenchymal progenitor cells combined with pentosan polysulfate mediating disc regeneration at the time of microdiscectomy: a preliminary study in an ovine model. *J Neurosurg Spine*. (2014) 20:657–69. doi: 10.3171/2014.2.SPINE13760

58. Yang B, Klineberg E, O'Connell GD. Intervertebral disc mechanics with nucleotomy: differences between simple and dual loading. *J Biomech Eng*. (2021) 60:143(8):081002. doi: 10.1115/1.4050538

59. Schwan S, Ludtka C, Wiesner I, Baerthel A, Friedmann A, Gohre F. Percutaneous posterolateral approach for the simulation of a far-lateral disc herniation in an ovine model. *Eur Spine J*. (2018) 27:222–30. doi: 10.1007/s00586-017-5362-6

60. Schwan S, Ludtka C, Friedmann A, Heilmann A, Baerthel A, Brehm W, et al. Long-term pathology of ovine lumbar spine degeneration following injury via percutaneous minimally invasive partial nucleotomy. *J Orthop Res*. (2019) 37:2376–88. doi: 10.1002/jor.24402

61. Nishimura K, Mochida J. Percutaneous reinsertion of the nucleus pulposus. An experimental study. *Spine*. (1998) 23:1531–1538; 1539. doi: 10.1097/00007632-199807150-00006

62. Miyamoto S, Yonenobu K, Ono K. Experimental cervical spondylosis in the mouse. *Spine*. (1991) 16:S495–500. doi: 10.1097/00007632-199110001-00008

63. Zheng L, Cao Y, Ni S, Qi H, Ling Z, Xu X, et al. Ciliary parathyroid hormone signaling activates transforming growth factor-beta to maintain intervertebral disc homeostasis during aging. *Bone Res*. (2018) 6:21. doi: 10.1038/s41413-018-0022-y

64. Xue P, Wang S, Lyu X, Wan M, Li X, Ma L, et al. PGE2/EP4 skeleton interoception activity reduces vertebral endplate porosity and spinal pain with low-dose celecoxib. *Bone Res*. (2021) 9:36. doi: 10.1038/s41413-021-00155-z

65. Liu S, Wang Q, Li Z, Ma L, Li T, Li Y, et al. TRPV1 Channel activated by the PGE2/EP4 pathway mediates spinal hypersensitivity in a mouse model of vertebral endplate degeneration. *Oxid Med Cell Longev*. (2021) 2021:9965737. doi: 10.1155/2021/9965737

66. Bian Q, Ma L, Jain A, Crane JL, Kebaish K, Wan M, et al. Mechanosignaling activation of TGFbeta maintains intervertebral disc homeostasis. *Bone Res*. (2017) 5:17008. doi: 10.1038/boneres.2017.8

67. Bian Q, Jain A, Xu X, Kebaish K, Crane JL, Zhang Z, et al. Excessive activation of TGFbeta by spinal instability causes vertebral endplate sclerosis. *Sci Rep*. (2016) 6:27093. doi: 10.1038/srep27093

68. Lonner BS, Toombs CS, Mechlin M, Ciavarra G, Shah SA, Samdani AF, et al. MRI Screening in operative scheuermann kyphosis: is it necessary? *Spine Deform*. (2017) 5:124–33. doi: 10.1016/j.jspd.2016.10.008

69. Lonner BS, Ren Y, Upasani VV, Marks MM, Newton PO, Samdani AF, et al. Disc degeneration in unfused caudal motion segments ten years following surgery for adolescent idiopathic scoliosis. *Spine Deform*. (2018) 6:684–90. doi: 10.1016/j.jspd.2018.03.013

70. Sakai D, Nishimura K, Tanaka M, Nakajima D, Grad S, Alini M, et al. Migration of bone marrow-derived cells for endogenous repair in a new tail-looping disc degeneration model in the mouse: a pilot study. *Spine J*. (2015) 15:1356–65. doi: 10.1016/j.spinee.2013.07.491

71. Nakamichi R, Ito Y, Inui M, Onizuka N, Kayama T, Kataoka K, et al. Mohawk promotes the maintenance and regeneration of the outer annulus fibrosus of intervertebral discs. *Nat Commun*. (2016) 7:12503. doi: 10.1038/ncomms12503

72. Huang Y, Zhang Z, Wang J, Shen S, Yao T, Xu Y, et al. circSPG21 protects against intervertebral disc disease by targeting miR-1197/ATP1B3. *Exp Mol Med*. (2021) 53:1547–58. doi: 10.1038/s12276-021-00674-z

73. Stokes IA, McBride C, Aronsson DD, Roughley PJ. Intervertebral disc changes with angulation, compression and reduced mobility simulating altered mechanical environment in scoliosis. *Eur Spine J*. (2011) 20:1735–44. doi: 10.1007/s00586-011-1868-5

74. MacLean JJ, Lee CR, Grad S, Ito K, Alini M, Iatridis JC. Effects of immobilization and dynamic compression on intervertebral disc cell gene expression in vivo. *Spine*. (2003) 28:973–81. doi: 10.1097/01.BRS.0000061985.15849.A9

75. Stokes IA, McBride CA, Aronsson DD, Roughley PJ. Metabolic effects of angulation, compression, and reduced mobility on Annulus fibrosis in a model of altered mechanical environment in scoliosis. *Spine Deform*. (2013) 1:161–70. doi: 10.1016/j.jspd.2013.02.001

76. Hirata H, Yurube T, Kakutani K, Maeno K, Takada T, Yamamoto J, et al. A rat tail temporary static compression model reproduces different stages of intervertebral disc degeneration with decreased notochordal cell phenotype. *J Orthop Res*. (2014) 32:455–63. doi: 10.1002/jor.22533

77. He R, Wang Z, Cui M, Liu S, Wu W, Chen M, et al. HIF1A Alleviates compression-induced apoptosis of nucleus pulposus derived stem cells via upregulating autophagy. *Autophagy*. (2021) 17:3338–60. doi: 10.1080/15548627.2021.1872227

78. Chen S, Wu X, Lai Y, Chen D, Bai X, Liu S, et al. Kindlin-2 inhibits Nlrp3 inflammasome activation in nucleus pulposus to maintain homeostasis of the intervertebral disc. *Bone Res*. (2022) 10:5. doi: 10.1038/s41413-021-00179-5

79. Ji Y, Zhu P, Zhang L, Yang H. A novel rat tail disc degeneration model induced by static bending and compression. *Animal Model Exp Med*. (2021) 4:261–7. doi: 10.1002/ame2.12178

80. Miyagi M, Ishikawa T, Kamoda H, Suzuki M, Murakami K, Shibayama M, et al. ISSLS Prize winner: disc dynamic compression in rats produces long-lasting increases in inflammatory mediators in discs and induces long-lasting nerve injury and regeneration of the afferent fibers innervating discs: a pathomechanism for chronic discogenic low back pain. *Spine*. (2012) 37:1810–8. doi: 10.1097/BRS.0b013e31824ffac6

81. Krock E, Rosenzweig DH, Chabot-Dore AJ, Jarzem P, Weber MH, Ouellet JA, et al. Painful, degenerating intervertebral discs up-regulate neurite sprouting and CGRP through nociceptive factors. *J Cell Mol Med*. (2014) 18:1213–25. doi: 10.1111/jcmm.12268

82. Ohtori S, Miyagi M, Inoue G. Sensory nerve ingrowth, cytokines, and instability of discogenic low back pain: a review. *Spine Surg Relat Res*. (2018) 2:11–7. doi: 10.22603/ssrr.2016-0018

83. Verschueren SM, Roelants M, Delecluse C, Swinnen S, Vanderschueren D, Boonen S. Effect of 6-month whole body vibration training on hip density, muscle strength, and postural control in postmenopausal women: a randomized controlled pilot study. *J Bone Miner Res*. (2004) 19:352–9. doi: 10.1359/JBMR.0301245

84. Wang XQ, Gu W, Chen BL, Wang X, Hu HY, Zheng YL, et al. Effects of whole-body vibration exercise for non-specific chronic low back pain: an assessor-blind, randomized controlled trial. *Clin Rehabil*. (2019) 33:1445–57. doi: 10.1177/0269215519848076

85. Kuisma M, Karppinen J, Haapea M, Niinimaki J, Ojala R, Heliovaara M, et al. Are the determinants of vertebral endplate changes and severe disc degeneration in the lumbar spine the same? A magnetic resonance imaging study in middle-aged male workers. *BMC Musculoskelet Disord*. (2008) 9:51. doi: 10.1186/1471-2474-9-51

86. Yamazaki S, Banes AJ, Weinhold PS, Tsuzaki M, Kawakami M, Minchew JT. Vibratory loading decreases extracellular matrix and matrix metalloproteinase gene expression in rabbit annulus cells. *Spine J*. (2002) 2:415–20. doi: 10.1016/S1529-9430(02)00427-8

87. McCann MR, Patel P, Pest MA, Ratneswaran A, Lalli G, Beaucage KL, et al. Repeated exposure to high-frequency low-amplitude vibration induces degeneration of murine intervertebral discs and knee joints. *Arthritis Rheumatol*. (2015) 67:2164–75. doi: 10.1002/art.39154

88. McCann MR, Veras MA, Yeung C, Lalli G, Patel P, Leitch KM, et al. Whole-body vibration of mice induces progressive degeneration of intervertebral discs associated with increased expression of il-1beta and multiple matrix degrading enzymes. *Osteoarthritis Cartilage*. (2017) 25:779–89. doi: 10.1016/j.joca.2017.01.004

89. Zeeman ME, Kartha S, Jaumard NV, Baig HA, Stablow AM, Lee J, et al. Whole-body vibration at thoracic resonance induces sustained pain and widespread cervical neuroinflammation in the rat. *Clin Orthop Relat Res*. (2015) 473:2936–47. doi: 10.1007/s11999-015-4315-9

90. Patterson F, Miralami R, Tansey KE, Prabhu RK, Priddy LB. Deleterious effects of whole-body vibration on the spine: a review of in vivo, ex vivo, and in vitro models. *Animal Model Exp Med*. (2021) 4:77–86. doi: 10.1002/ame2.12163

91. Yao W, Jee WS, Chen J, Liu H, Tam CS, Cui L, et al. Making rats rise to erect bipedal stance for feeding partially prevented orchidectomy-induced bone loss and added bone to intact rats. *J Bone Miner Res*. (2000) 15:1158–68. doi: 10.1359/jbmr.2000.15.6.1158

92. Liang QQ, Cui XJ, Xi ZJ, Bian Q, Hou W, Zhao YJ, et al. Prolonged upright posture induces degenerative changes in intervertebral discs of rat cervical spine. *Spine*. (2011) 36:E14–9. doi: 10.1097/BRS.0b013e3181d2dec2

93. Liu S, Zhao B, Shi H, Liang Q, Fu Y, Yang Z, et al. Ligustrazine inhibits cartilage endplate hypertrophy via suppression of TGF-beta1. *Evid Based Complement Alternat Med*. (2016) 2016:1042489. doi: 10.1155/2016/1042489

94. Kong M, Zhang Y, Song M, Cong W, Gao C, Zhang J, et al. Myocardinrelated transcription factor A nuclear translocation contributes to mechanical overloadinduced nucleus pulposus fibrosis in rats with intervertebral disc degeneration. *Int J Mol Med*. (2021) 96:48(1):123. doi: 10.3892/ijmm.2021.4956

95. Liang X, Shen H, Shi WD, Ren S, Jiang W, Liu H, et al. Effect of axial vertical vibration on degeneration of lumbar intervertebral discs in modified bipedal rats: an in-vivo study. *Asian Pac J Trop Med*. (2017) 10:714–7. doi: 10.1016/j.apjtm.2017.07.014

96. Ao X, Wang L, Shao Y, Chen X, Zhang J, Chu J, et al. Development and characterization of a novel bipedal standing mouse model of intervertebral disc and facet joint degeneration. *Clin Orthop Relat Res*. (2019) 477:1492–504. doi: 10.1097/CORR.0000000000000712

97. Lao YJ, Xu TT, Jin HT, Ruan HF, Wang JT, Zhou L, et al. Accumulated spinal axial biomechanical loading induces degeneration in intervertebral disc of mice lumbar spine. *Orthop Surg*. (2018) 10:56–63. doi: 10.1111/os.12365

98. Lee S, Jang SH, Suzuki-Narita M, Gregoire S, Millecamps M, Stone LS. Voluntary running attenuates behavioural signs of low back pain: dimorphic regulation of intervertebral disc inflammation in male and female SPARC-null mice. *Osteoarthritis Cartilage*. (2022) 30:110–23. doi: 10.1016/j.joca.2021.06.014

99. Gruber HE, Sage EH, Norton HJ, Funk S, Ingram J, Hanley EJ. Targeted deletion of the SPARC gene accelerates disc degeneration in the aging mouse. *J Histochem Cytochem*. (2005) 53:1131–8. doi: 10.1369/jhc.5A6687.2005

100. Millecamps M, Czerminski JT, Mathieu AP, Stone LS. Behavioral signs of axial low back pain and motor impairment correlate with the severity of intervertebral disc degeneration in a mouse model. *Spine J*. (2015) 15:2524–37. doi: 10.1016/j.spinee.2015.08.055

101. Millecamps M, Tajerian M, Naso L, Sage HE, Stone LS. Lumbar intervertebral disc degeneration associated with axial and radiating low back pain in ageing SPARC-null mice. *Pain*. (2012) 153:1167–79. doi: 10.1016/j.pain.2012.01.027

102. Krock E, Millecamps M, Anderson KM, Srivastava A, Reihsen TE, Hari P, et al. Interleukin-8 as a therapeutic target for chronic low back pain: upregulation in human cerebrospinal fluid and pre-clinical validation with chronic reparixin in the SPARC-null mouse model. *Ebiomedicine*. (2019) 43:487–500. doi: 10.1016/j.ebiom.2019.04.032

103. Rai MF, Hashimoto S, Johnson EE, Janiszak KL, Fitzgerald J, Heber-Katz E, et al. Heritability of articular cartilage regeneration and its association with ear wound healing in mice. *Arthritis Rheum*. (2012) 64:2300–10. doi: 10.1002/art.34396

104. Choi H, Tessier S, Silagi ES, Kyada R, Yousefi F, Pleshko N, et al. A novel mouse model of intervertebral disc degeneration shows altered cell fate and matrix homeostasis. *Matrix Biol*. (2018) 70:102–22. doi: 10.1016/j.matbio.2018.03.019

105. Zhang Y, Xiong C, Kudelko M, Li Y, Wang C, Wong YL, et al. Early onset of disc degeneration in SM/J mice is associated with changes in ion transport systems and fibrotic events. *Matrix Biol*. (2018) 70:123–39. doi: 10.1016/j.matbio.2018.03.024

106. Novais EJ, Tran VA, Miao J, Slaver K, Sinensky A, Dyment NA, et al. Comparison of inbred mouse strains shows diverse phenotypic outcomes of intervertebral disc aging. *Aging Cell*. (2020) 19:e13148. doi: 10.1111/acel.13148

107. Aszodi A, Chan D, Hunziker E, Bateman JF, Fassler R. Collagen II is essential for the removal of the notochord and the formation of intervertebral discs. *J Cell Biol*. (1998) 143:1399–412. doi: 10.1083/jcb.143.5.1399

108. Sahlman J, Inkinen R, Hirvonen T, Lammi MJ, Lammi PE, Nieminen J, et al. Premature vertebral endplate ossification and mild disc degeneration in mice after inactivation of one allele belonging to the Col2a1 gene for type II collagen. *Spine*. (2001) 26:2558–65. doi: 10.1097/00007632-200112010-00008

109. Xu H, Dong R, Zeng Q, Fang L, Ge Q, Xia C, et al. Col9a2 gene deletion accelerates the degeneration of intervertebral discs. *Exp Ther Med*. (2022) 23:207. doi: 10.3892/etm.2022.11130

110. Boyd LM, Richardson WJ, Allen KD, Flahiff C, Jing L, Li Y, et al. Early-onset degeneration of the intervertebral disc and vertebral end plate in mice deficient in type IX collagen. *Arthritis Rheum*. (2008) 58:164–71. doi: 10.1002/art.23231

111. Li CG, Liang QQ, Zhou Q, Menga E, Cui XJ, Shu B, et al. A continuous observation of the degenerative process in the intervertebral disc of Smad3 gene knock-out mice. *Spine*. (2009) 34:1363–9. doi: 10.1097/BRS.0b013e3181a3c7c7

112. Phillips KL, Jordan-Mahy N, Nicklin MJ, Le Maitre CL. Interleukin-1 receptor antagonist deficient mice provide insights into pathogenesis of human intervertebral disc degeneration. *Ann Rheum Dis*. (2013) 72:1860–7. doi: 10.1136/annrheumdis-2012-202266

113. Wu WJ, Zhang XK, Zheng XF, Yang YH, Jiang SD, Jiang LS. SHH-dependent knockout of HIF-1 alpha accelerates the degenerative process in mouse intervertebral disc. *Int J Immunopathol Pharmacol*. (2013) 26:601–9. doi: 10.1177/039463201302600304

114. Beierfuss A, Dietrich H, Kremser C, Hunjadi M, Ritsch A, Rulicke T, et al. Knockout of apolipoprotein E in rabbit promotes premature intervertebral disc degeneration: a new in vivo model for therapeutic approaches of spinal disc disorders. *Plos One*. (2017) 12:e187564. doi: 10.1371/journal.pone.0187564

115. Whittal MC, Molladavoodi S, Zwambag DP, Millecamps M, Stone LS, Gregory DE. Mechanical consequence of induced intervertebral disc degeneration in the SPARC-null mouse. *J Biomech Eng*. (2021) 143(2):024501. doi: 10.1115/1.4047995

116. Dudek M, Yang N, Ruckshanthi JP, Williams J, Borysiewicz E, Wang P, et al. The intervertebral disc contains intrinsic circadian clocks that are regulated by age and cytokines and linked to degeneration. *Ann Rheum Dis*. (2017) 76:576–84. doi: 10.1136/annrheumdis-2016-209428

117. Semba K, Araki K, Li Z, Matsumoto K, Suzuki M, Nakagata N, et al. A novel murine gene, sickle tail, linked to the Danforth's Short tail locus, is required for normal development of the intervertebral disc. *Genetics*. (2006) 172:445–56. doi: 10.1534/genetics.105.048934

118. Kamper M, Hamann N, Prein C, Clausen-Schaumann H, Farkas Z, Aszodi A, et al. Early changes in morphology, bone mineral density and matrix composition of vertebrae lead to disc degeneration in aged collagen IX -/- mice. *Matrix Biol*. (2016) 49:132–43. doi: 10.1016/j.matbio.2015.09.005

119. Tessier S, Tran VA, Ottone OK, Novais EJ, Doolittle A, DiMuzio MJ, et al. TonEBP-deficiency accelerates intervertebral disc degeneration underscored by matrix remodeling, cytoskeletal rearrangements, and changes in proinflammatory gene expression. *Matrix Biol*. (2020) 87:94–111. doi: 10.1016/j.matbio.2019.10.007

120. Vo N, Seo HY, Robinson A, Sowa G, Bentley D, Taylor L, et al. Accelerated aging of intervertebral discs in a mouse model of progeria. *J Orthop Res*. (2010) 28:1600–7. doi: 10.1002/jor.21153

121. Gorth DJ, Shapiro IM, Risbud MV. A new understanding of the role of IL-1 in age-related intervertebral disc degeneration in a murine model. *J Bone Miner Res*. (2019) 34:1531–42. doi: 10.1002/jbmr.3714

122. Silagi ES, Novais EJ, Bisetto S, Telonis AG, Snuggs J, Le Maitre CL, et al. Lactate efflux from intervertebral disc cells is required for maintenance of spine health. *J Bone Miner Res*. (2020) 35:550–70. doi: 10.1002/jbmr.3908

123. Tsingas M, Ottone OK, Haseeb A, Barve RA, Shapiro IM, Lefebvre V, et al. Sox9 deletion causes severe intervertebral disc degeneration characterized by apoptosis, matrix remodeling, and compartment-specific transcriptomic changes. *Matrix Biol*. (2020) 94:110–33. doi: 10.1016/j.matbio.2020.09.003

124. Alkhatib B, Liu C, Serra R. Tgfbr2 is required in acan-expressing cells for maintenance of the intervertebral and sternocostal joints. *JOR Spine*. (2018) 1(2):e1025. doi: 10.1002/jsp2.1025

125. Bedore J, Sha W, McCann MR, Liu S, Leask A, Seguin CA. Impaired intervertebral disc development and premature disc degeneration in mice with notochord-specific deletion of CCN2. *Arthritis Rheum*. (2013) 65:2634–44. doi: 10.1002/art.38075

126. Alvarez-Garcia O, Matsuzaki T, Olmer M, Miyata K, Mokuda S, Sakai D, et al. FOXO Are required for intervertebral disk homeostasis during aging and their deficiency promotes disk degeneration. *Aging Cell*. (2018) 17:e12800. doi: 10.1111/acel.12800

127. Silberberg R. Histologic and morphometric observations on vertebral bone of aging sand rats. *Spine*. (1988) 13:202–8. doi: 10.1097/00007632-198802000-00013

128. Gruber HE, Phillips R, Ingram JA, Norton HJ, Hanley EJ. Spontaneous age-related cervical disc degeneration in the sand rat. *Clin Orthop Relat Res*. (2014) 472:1936–42. doi: 10.1007/s11999-014-3497-x

129. Marfia G, Campanella R, Navone SE, Zucca I, Scotti A, Figini M, et al. Potential use of human adipose mesenchymal stromal cells for intervertebral disc regeneration: a preliminary study on biglycan-deficient murine model of chronic disc degeneration. *Arthritis Res Ther*. (2014) 16:457. doi: 10.1186/s13075-014-0457-5

130. Ohnishi T, Sudo H, Tsujimoto T, Iwasaki N. Age-related spontaneous lumbar intervertebral disc degeneration in a mouse model. *J Orthop Res*. (2018) 36:224–32. doi: 10.1002/jor.23634

131. Silva MJ, Holguin N. Aging aggravates intervertebral disc degeneration by regulating transcription factors toward chondrogenesis. *Faseb J*. (2020) 34:1970–82. doi: 10.1096/fj.201902109R

132. Lin D, Alberton P, Delgado CM, Prein C, Clausen-Schaumann H, Dong J, et al. Loss of tenomodulin expression is a risk factor for age-related intervertebral disc degeneration. *Aging Cell*. (2020) 19:e13091. doi: 10.1111/acel.13091

133. Novais EJ, Tran VA, Johnston SN, Darris KR, Roupas AJ, Sessions GA, et al. Long-term treatment with senolytic drugs dasatinib and quercetin ameliorates age-dependent intervertebral disc degeneration in mice. *Nat Commun*. (2021) 12:5213. doi: 10.1038/s41467-021-25453-2

134. Brinjikji W, Diehn FE, Jarvik JG, Carr CM, Kallmes DF, Murad MH, et al. MRI Findings of disc degeneration are more prevalent in adults with low back pain than in asymptomatic controls: a systematic review and meta-analysis. *AJNR Am J Neuroradiol*. (2015) 36:2394–9. doi: 10.3174/ajnr.A4498

135. Gan Y, He J, Zhu J, Xu Z, Wang Z, Yan J, et al. Spatially defined single-cell transcriptional profiling characterizes diverse chondrocyte subtypes and nucleus pulposus progenitors in human intervertebral discs. *Bone Res*. (2021) 9:37. doi: 10.1038/s41413-021-00163-z

136. Gao B, Jiang B, Xing W, Xie Z, Luo Z, Zou W. Discovery and application of postnatal nucleus Pulposus progenitors essential for intervertebral disc homeostasis and degeneration. *Adv Sci (Weinh)*. (2022) 9(13):e2104888. doi: 10.1002/advs.202104888

137. Han S, Zhang Y, Zhang X, Zhang H, Meng S, Kong M, et al. Single-cell RNA sequencing of the nucleus pulposus reveals chondrocyte differentiation and regulation in intervertebral disc degeneration. *Front Cell Dev Biol*. (2022) 10:824771. doi: 10.3389/fcell.2022.824771

138. Zhang Y, Han S, Kong M, Tu Q, Zhang L, Ma X. Single-cell RNA-seq analysis identifies unique chondrocyte subsets and reveals involvement of ferroptosis in human intervertebral disc degeneration. *Osteoarthritis Cartilage*. (2021) 29:1324–34. doi: 10.1016/j.joca.2021.06.010

139. Wang Z, Chen H, Tan Q, Huang J, Zhou S, Luo F, et al. Inhibition of aberrant Hif1alpha activation delays intervertebral disc degeneration in adult mice. *Bone Res*. (2022) 10(1):2. doi: 10.1038/s41413-021-00165-x

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