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Optimization of spine surgery outcomes in the pre-, peri-, and postoperative settings

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Optimization of spine surgery outcomes in the pre-, peri-, and postoperative settings

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Editorial: Optimization of spine surgery outcomes in the pre-, peri-, and postoperative settings

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KEYWORDS

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Editorial on the Research Topic
Optimization of spine surgery outcomes in the pre-, peri-, and postoperative settings

Patient optimization is one of the strongest predictive indicators to improve outcomes and mitigate complications after spinal surgery. While we have collectively known that optimizing a patient's cardiopulmonary and metabolic status are essential prior to any surgical procedure, it has been challenging to develop a set of clinical decision rules to help guide spine patients. Hence, the development of enhanced recovery after surgery (ERAS) protocols to standardize optimization across surgeons and healthcare systems (1).

The importance of pre-operative optimization was recently highlighted by Maitra et al. who demonstrated patients who medically optimized prior to spine surgery demonstrate improvements in satisfaction scores, decreased complications, and decreased length of stay (2). The results of this study were further supported with several reviews demonstrating reduction in the risk of surgical site infection with the implementation of pre-operative optimization protcols (3, 4). Patient-specific modifiable risk-factors that are potential areas for focused intervention include strict blood glucose control, weight loss, smoking cessation, optimization of bone quality in patients with osteoporosis, opioid weaning, and optimizing mental health disorders (5). Identifying and treating these pre-operative co-morbidities can directly improve outcomes after spinal surgery.

Interventions aimed at enhancing intra- and post-operative optimization are essential, as well. For example, the use of intravenous tranexamic acid to mitigate blood loss, patient positioning to reduce intra-orbital pressure while prone, the use of intraoperative cell salvage, and blood pressure control when operating on or near the spinal cord have been shown to improve outcomes after spinal surgery (6–8). While intra-operative optimization is generally heterogenous and can significantly vary among surgeons, post-operative protocols such as early ambulation, physical therapy, blood glucose monitoring, and reduced opioid use have been shown to clearly correlate with improved outcomes in patients undergoing lumbar fusion surgery (9). Of note, these protocols guiding pre-, intra-, and post-operative optimization are

interconnected and focusing on all phases of the surgical process is critical to optimize outcomes.

Clinicians should make every effort to "optimize" our patients before, during, and after spinal surgery. While more prospective and larger population studies are required, there is a strong consensus that optimization is as important as patient selection, decision-making, and surgical technique in guiding post-operative outcomes (10).

Author contributions

JS and JR conceived of the presented idea and wrote and edited the manuscript together. 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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SYSTEMATIC REVIEW
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Comparison of Laminoplasty vs. Laminectomy for Cervical Spondylotic Myelopathy: A Systematic Review and Meta-Analysis

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Objectives: Laminoplasty (LP) and laminectomy (LC) with or without fusion are recommended as treatment procedures for cervical spondylotic myelopathy (CSM). The purpose of this study is to conduct a meta-analysis to analyze the results of CSM patients undergoing LP or LC surgery.

Methods: We systematically and comprehensively searched Web of Science, Cochrane Library, PubMed, EMBASE, OVID, VIP database, Google Scholar, Chinese Bio-medicine Literature database, and China Scientific Journal Full-text database to July 2021 for randomized controlled trials (RCTs) and observational case series that compared LP and LC in patients with CSM. The main endpoints were the surgical process, radiographic outcomes, clinical outcomes, and surgical complications.

Results: A total of 19 were included the inclusion criteria in this meta-analysis ($n = 4,348$ patients). There was no significant difference in range of motion (ROM), sagittal vertical axis (SVA), Japanese Orthopedic Association (JOA), Cobb angle, visual analog scale (VAS), cervical curvature index (CCI), Nurick score, Neck Dysfunction Index (NDI), and complications. LP was found to be superior than LC in terms of complications of C5 radiculopathy and surperficial infection.

Conclusion: Our results indicate that LP can achieve better results in C5 radiculopathy and superficial infection in surgical treatment of CSM compared with LC. Further high-quality research is warranted to further verify our findings.

Systematic Review Registration: PRISMA: CRD42018107070.

Keywords: cervical myelopathy, laminoplasty, laminectomy, meta-analysis, systematic review

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BACKGROUND

Cervical spondylotic myelopathy (CSM) refers to a clinical chronic disorder that is usually releated with degenerative disease of intervertebral disk (1). Cervical spondylotic myelopathy is the most common spinal cord degeneration in older sufferers, caused by the progressive spinal canal stenosis and subsequent nerve root compression (2). Surgical management is generally indicated for

patients with CSM when conservative treatments are ineffective. Anterior cervical decompression and fusion for multilevel CSM is a complex procedure and may be associated with a long operative time, as well as complications, such as dysphagia, internal graft dislocation, and trigeminal nerve palsy (2). Laminoplasty (LP) and laminectomy (LC) with or without fusion are the primary posterior cervical surgical strategies for treating CSM to remove compressive elements, providing enough space for the cord, and decompressing the spinal cord (3).

Laminectomy, which is usually supplemented by additional fusion, was initially viewed as the gold standard practice for CSM (4). However, this technique is associated with many disadvantages, such as post-LC kyphosis, segmental instability, and subsequent neurological deterioration, which lead to a shorted indication. Laminoplasty was first reported by Tsuji et al. (5) in 1982, and is regarded as an effective way of maintaining anatomical cervical reduction. Laminoplasty retains a covering of the ligamentum flavum over the spinal cord and posterior laminar bone. Laminoplasty has the advantages of minimizing instability, limiting constriction of the dura from extradural scar formation, preserving motion, and avoiding complications related to fusion. However, LP is contraindicated in patients with CSM and $>13^{\circ}$ of kyphosis and severe neck pain (6). Although there are several disadvantages of LP, including vertebral canal reclosed problems, hinge fracture, higher technical requirements, and possible injuries to the cervical cord, LP has been gradually accepted by an increasing number of surgeons. At present, both surgical procedures decompress the spinal cord by enlarging the spinal canal and are regularly thought to be effective in treating CSM.

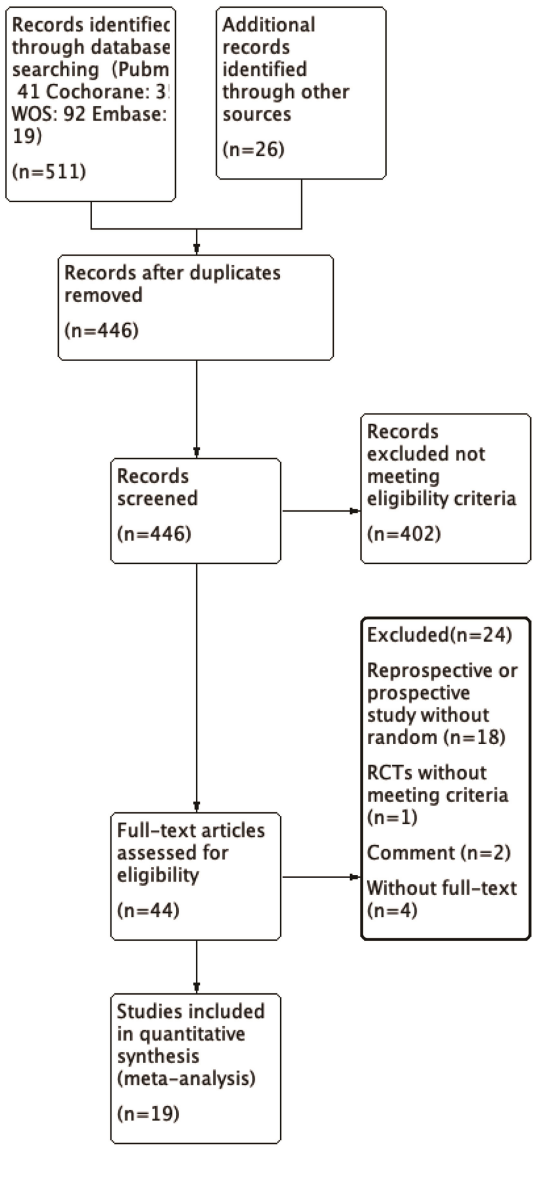

FIGURE 1 | Flowchart of study search and inclusion criteria.

Although several meta-analyses or systematic reviews have been conducted to compare LC with LP in treating CSM, the results of these studies were not consistent. In a systematic review, Chen et al. (7) reported that LC with fusion had a higher rate of reoperation, non-union, and infection compared with LP. However, Fehlings et al. (8) suggested that LP and LC with fusion had similar effectiveness. Laminoplasty and LC with fusion may result in clinical recovery and a similar loss of lordosis. Similar to LC followed by fusion, expansive LP has a shorter operative time and less C5 palsy. In this study, we aimed to provide some references for clinical surgical treatment of CSM by systematically comparing the safety and efficacy of LP and LC regarding surgical outcomes, radiographic outcomes, clinical outcomes, and surgical complications.

METHODS

Literature Search

International prospective register of systematic reviews (CRD42018107070) was prospectively registered in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (9) for this meta-analysis. Potentially relevant papers that were published in the Web of Science, Cochrane Library, PubMed, EMBASE, OVID, VIP database, Google Scholar, Chinese Bio-medicine Literature database, and China Scientific Journal Full-text database to July 2021 were retrieved and read. Additionally, we also screened the list of references included in publications and related reviews. All included literature only considers English or Chinese language. The following MeSH terms associated with text words were used: cervical vertebrae, spinal cord compression, LP, and LC.

Selection Criteria

Two researchers independently judged the eligibility of all studies retrieved from the database. Any disagreements between two independent researchers are resolved through discussion or consultation with a third researcher. This meta-analysis is included in the study based on the following criteria: (1) randomized controlled trial (RCTs) or observational studies; (2) studies that compared clinical outcomes between LP and

LC with or without fusion; (3) studies that included patients with CSM caused by spinal stenosis; and (4) studies that included outcome measurements, such as surgical outcomes, radiographic outcomes, clinical outcomes, and surgical complications. The exclusion criteria are as follows: (1) The randomized study did not conduct a control group study; (2) The data in the paper or research report was incomplete, resulting in unclear research results; (3) Incomplete papers, including abstracts, conference reports, case reports, and comments And expert opinions; (4) There is no data in the research results to estimate the relative risk (RR) and mean difference (MD).

According to the Cochrane risk-of-bias criteria, the risk of bias and methodological quality of the involved included studies was evaluated by two researchers independently. The methodological quality of each studies was assessed as unclear risk, low risk, or high risk.

Data Extraction

All revelant data were extracted independently by two researchers from article texts, tables, and figures. The extracted data includes: the first author, the time of publication, the origin country of the study, the type of experimental design, the sample size of the study, demographics, methods, length of post-operative follow-up and clinical results. The clinical results included length of operation, loss of blood, length of hospital stay, range of motion (ROM), sagittal vertical axis (SVA), Cobb angle, Japanese Orthopedic Association (JOA), mJOA, visual analog scale (VAS), cervical curvature index (CCI), SF-36 MCS, SF-36 PCS, Nurick score, NDI (neck disability index), and C5 radiculopathy.

Statistical Analysis

Relative risk with a 95% CI was computed for binary data, and the MD with a 95% CI was computed for continuous data. The heterogeneity between studies was assessed by the χ^2 test and the I^2 statistic. $I^2 \leq 50\%$ indicates acceptable heterogeneity, while $x\, I^2 > 50\%$ means significant heterogeneity. A fixed effects model was applied, if $P > 0.10$ and I^2 <50%. If not, a random effects model was chosen. Publication bias is evaluated by the symmetrical construction of the funnel chart. Review Manager (RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark) was performed for statistical analysis.

RESULTS

Search Results

We identified a total of 511 probably related articles from the database. An additional 26 possible publications were identified through other sources, primarily through manual search of the reference list. Of the 537 articles, 443 articles were excluded due to duplication or the exclusion criteria. Finally, a total of 19 articles (4, 6–8, 10–24), which were published between 1988 and 2019, were considered for inclusion in this meta-analysis. The detailed search strategy based on database is provided in **Figure 1**. A total of 1,724 patients (896 treated with LP and 828 treated with LC), were included, and the follow-up period ranged between 8.8 and 72 months. As shown in **Figures 2**, **3**, the results of methodological quality are presented in the risk of bias. Only three studies (12, 17, 25) were RCTs that compared LP with LC. The Adetailed overview of study characteristics can be consulted in **Table 1**.

Clinical Outcomes

Length of Operation, Loss of Blood, Length of Hospital Stays

In seven studies (8, 10, 16, 18, 19, 22, 24) that reported the length of operation, there was no significant difference observed between the length of operation of the LP and LC groups (MD = −16.41, 95% CI: −39.95 to 7.13, I^2 = 96%, P = 0.17) (**Figure 4A**; **Table 2**). Intraoperative blood loss was evaluated in six studies (10, 19, 21, 22, 24). No significant differences were demonstrated between the volume of blood loss of the two groups (MD = −17.11, 95% CI: −71.40 to 37.18, I^2 = 90%, P = 0.54) (**Figure 4B**; **Table 2**). The length of hospital stay was evaluated in four studies (4, 8, 14, 21), and there was no significant difference observed between the LP and LC groups (MD = 0.36, 95% CI −1.90 to 2.61, I^2 = 84%, P = 0.76) (**Figure 4C**; **Table 2**).

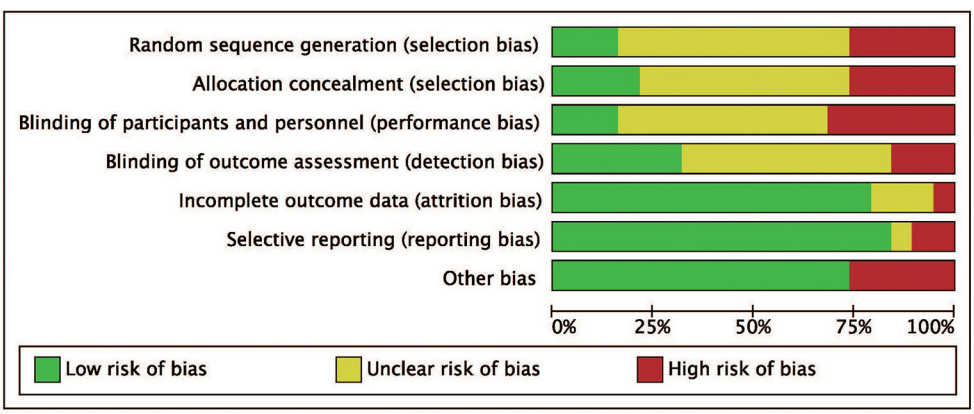

FIGURE 2 | Risk of bias graph. Review authors' judgments for each risk of bias item are presented as percentages across all included studies.

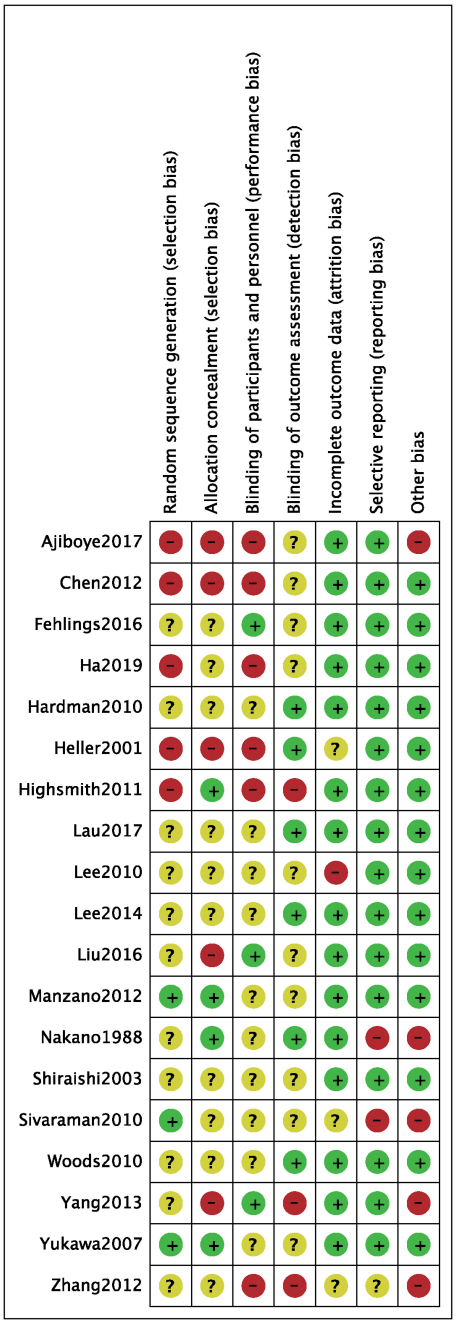

FIGURE 3 | Risk of bias of included randomized controlled trials. +, no bias; –, bias; ?, bias unknown.

Radiographic Outcomes

Radiographic parameters of the ROM, SVA, and the Cobb angle were evaluated in four studies (12, 18, 19, 24). No obvious difference was observed in ROM between the two groups the LP group compared with the LC (MD = 3.50, 95% CI: −3.74 to10.73, $I^2 = 94\%$, $P = 0.34$) (**Figure 5A**; **Table 2**). There was no significant difference observed in SVA between the two groups (MD = −0.78, 95% CI: −6.34 to 4.79, $I^2 = 75\%$, $P = 0.78$) (**Figure 5B**; **Table 2**). There was also no significant difference in the Cobb angle observed between the LP and LC (MD = −1.44, 95% CI: −6.57 to 3.68, $I^2 = 91\%$, $P = 0.58$) (**Figure 5C**; **Table 2**).

Functional Outcomes

Eight studies (4, 7, 8, 15, 17, 19, 22, 24) used the JOA to assess the clinical outcome. No significant difference was observed of JOA score in the LP group compared with the LC group (MD = 0.49, 95% CI: −0.01 to 0.98, $I^2 = 71\%$, $P = 0.06$) (**Figure 6A**; **Table 2**). There were no significant differences in the VAS, CCI, Nurick, and NDI scores between the two groups (**Figures 6B–E**; **Table 2**).

Surgical Complications

Eight studies (4, 7, 8, 13, 18, 19, 22, 24) evaluated the rate of C5 radiculopathy. A significantly higher complication rate of C5 radiculopathy was observed in the LC gcompared with the LP (RR = 0.35, 95% CI: 0.20 to 0.61, $I^2 = 0\%$, $P < 0.01$) (**Figure 7A**). C5 radiculopathy occurred in 17 (3.51%) of 485 patients who were treated with LP and in 40 (8.20%) of 488 patients who were treated with LC. Moreover, the complication of superficial infection occurred significantly less in the LP compared with the LP frequently (RR = 0.65, 95% CI: 0.20 to 0.98, $I^2 = 0\%$, $P = 0.04$) (**Figure 7B**). Additionally, other complications, such as hardware failure, adjacent segment degeneration, dural tear, deep infection, dysphagia, non-C5 radiculopathy, postoperative kyphosis, neck/arm pain, and pseudarthrosis, were not significantly different between the two groups (**Figures 7C–K**).

DISCUSSION

Our study showed that patients receiving LP for CSM had less frequent occurrence of C5 radiculopathy and superficial infection than those who underwent LP. Length of operation, loss of blood, length of hospital stays, Cobb angle, SVA, VAS score, CCI score, Nurick score, NDI score, and other surgical complications were not different observed between these two groups. These results suggest that LP is a useful therapeutic procedure promoting management of CSM.

Several previous systematic reviews and meta-analyses that analyzed LP and LC with or without fusion for CSM have been published and showed different results compared with our study (26, 27). A meta-analysis by Lee et al. (28) compared LP with LC for treating CSM. In this article, a total of seven studies were included in the meta-analysis (six English papers and one Chinese paper). The authors focused on the clinical and radiological outcomes between these two different methods. The two groups did not show significant differences in JOA grade, VAS score, and CCI at the baseline state. The authors suggest that both methods may obtain clinical improvement and lead to a similar loss of lordosis, but definitive conclusion could not be reached regarding which surgical approach is more effective for the treatment of CSM. Liu et al. (29) presented a meta-analysis of 23 studies comparing LP with LC for treating CSM. They focused on clinical outcome (JOA, CCI, VAS, and cervical lordosis), complication (C5 palsy and axial pain), blood loss, and operation time. The LP group showed shorter operation time and

TABLE 1 | Clinical characteristic of included studies.

Study	Year	Study design	Simple size		Mean age(years)		Gender (M/F)		Follow-up months	
			LP	LC	LP	LC	LP	LC	LP	LC
Ajiboye et al. (23)	2017	PRO	25	45	54.88 ± 9.05	65.36 ± 10.08	19/6	30/15	10.08 ± 12.87	10.67 ± 13.4
Chen et al. (7)	2012	RET	41	32	46.3 ± 2.5	52.6 ± 1.7	33/8	19/13	48–72	48–72
Fehlings et al. (8)	2016	PRO	100	166	60.68 ± 11.32	61.36 ± 10.59	33/67	53/113	24	24
Ha and Shin (24)	2019	RET	49	42	59.12 ± 8.53	62.21 ± 7.81	33/16	36/6	39.61	37.51
Hardman et al. (14)	2010	RET	72	49	59.7	57.3	29/48	14/35	NA	NA
Heller et al. (11)	2001	RET	13	13	56	55	NA	NA	26.2	25.5
Highsmith et al. (4)	2011	RET	30	26	61	58	NA	NA	42.3	41.3
Lau et al. (21)	2017	RET	101	44	63.9 ± 11.9	60.9 ± 9.0	74/27	21/23	17.4 ± 12.3	16.8 ± 8.4
Lee et al. (15)	2010	RET	30	28	52.4	58.6	18/12	19/9	26.2	25.6
Lee et al. (20)	2016	RET	21	15[a]/21[b]	54.2 ± 10.3	63.7 ± 6.6[a] /63.7 ± 7.7[b]	15/6	13/21[a] 9/2[b]	8.8 ± 8.4	16.8 ± 3.1[a] 13.8 ± 11.2[b]
Liu et al. (22)	2016	RET	32	35	59 ± 10	60 ± 8	26/6	25/10	38 ± 13	42 ± 9
Manzano et al. (17)	2012	RCT	9	7	59	61	5/4	2/5	59	61
Nakano et al. (10)	1988	RET	75	14	55.0	59.2	NA	NA	54	128
Shiraishi et al. (13)	2003	RET	51	43	67	69	NA	NA	43	30
Sivaraman et al. (25)	2010	RCT	25	25	62.4	69.6	11/14	13/12	NA	NA
Woods et al. (6)	2010	RET	39	81	60	64	14/25	32/49	23.99 ± 9.91	23.81 ± 5.98
Yang et al. (19)	2013	RET	75	66	57.19 ± 7.33	56.98 ± 8.34	56/19	49/17	NA	NA
Yukawa et al. (12)	2007	RCT	21	20	62.3 ± 11.4	66.1 ± 10.8	13/8	15/5	NA	NA
Zhang et al. (18)	2012	RET	87	56	55.5	58.0	36/51	24/32	NA	NA

LP, laminoplasty; LC, laminectomy with or without fusion; M, male; F, female; NA, not available; PRO, prospective study; RET, retrospective; RCT, randomized controlled trial; a, laminectomy alone; b, laminectomy with fusion.

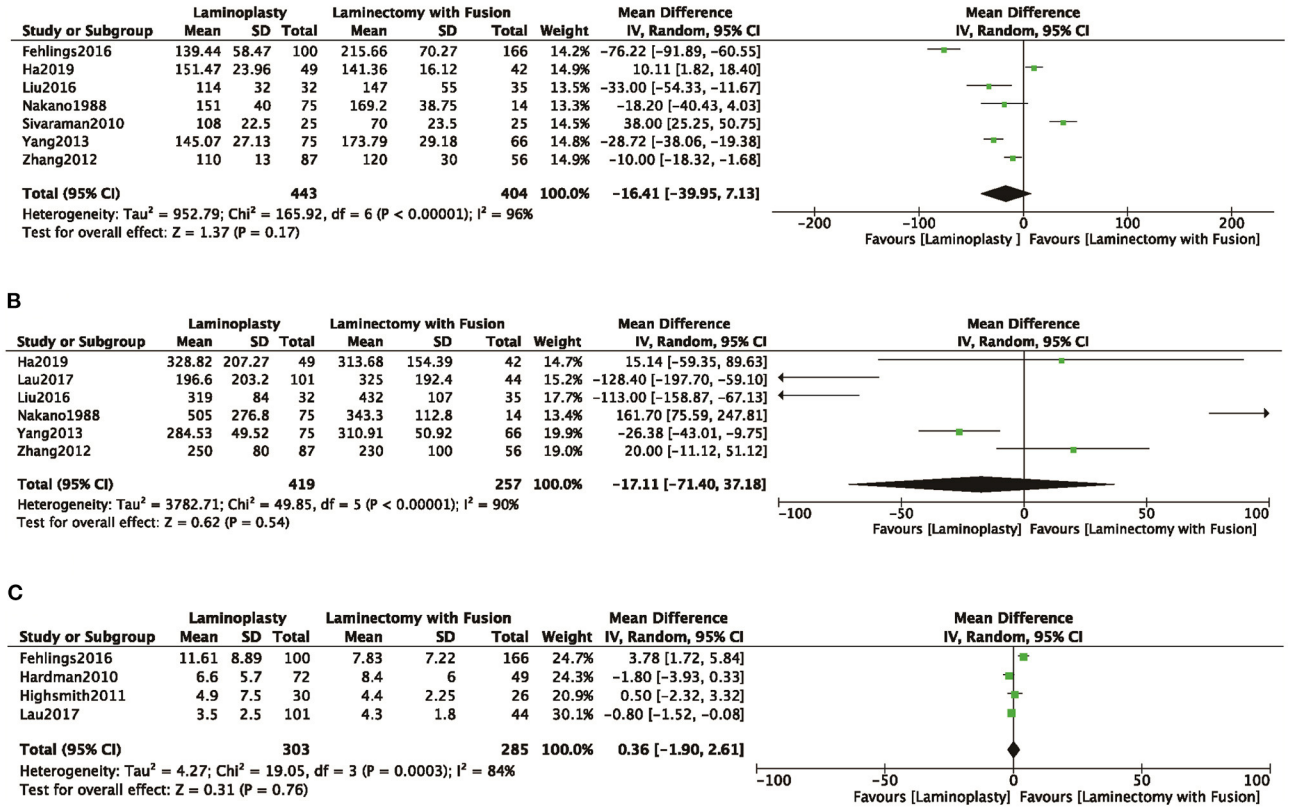

FIGURE 4 | Comparison of **(A)** operative time; **(B)** intraoperative blood loss; **(C)** the time of hospital stay; between the LP group and the LC group.

fewer C5 palsy. Others had may achieve clinical improvement and a similar result. Phan and Scherman et al. (30) compared LP with LC for treating CSM in 10 studies when treating patients with CSM. They focused on the Postoperative JOA, postoperative VAS neck pain, postoperative CCI, postoperative Nurich grade, complication (reoperation rate and nerve palsy), operative time, and intraoperative blood loss. They found that there was no difference in terms of clinical improvement. However, a higher complication of nerve palsy was found in the LC than in the LC. Otherwise, results of others studies showed that LP and LC fusion methods were similarly useful (31).

Patients were matched and both groups had a similar length of operation, blood loss, and hospital stay. These characteristics were not examined in other relevant meta-analyses. Heterogeneity in our meta-analysis was high (I^2 > 75%), those personal difference and surgical processes had multivariate analyses and reports for them are speculative. Pooled results from three studies (21, 22) showed that the Cobb angle was more acceptable in the LP than in the LC. The reason why the Cobb angle was more acceptable in the LP group may be that the muscles and ligamentous structures of the cervical spine are dissected minimally and restored maximally in the LP group. In our study, clinical measurements, such as VAS, CCI, SF-36 MCS, SF-36 PCS, Nurick, and neck disability index scores, were not significantly different in two groups. However, the LP procedure was superior to the LC procedure in evaluation of the JOA score for patients with CSM. These findings indicated that the effect of LP was more favorable than that for LC, which suggested that LP could be considered as the method of surgery for patients with CSM. Most importantly, these results are supportive of a significant improvement in the management of CSM. Specifically, LP as a treatment strategy for CSM can obtain better results in the surgical process, radiographic outcomes, and clinical outcomes (Cobb angle, JOA score, and risk of C5 radiculopathy) than LC.

Several limitations must be considered when interpreting the results. First, the quality of the studies included 3 RCTs and 16 observational studies was low. Most of the RCTs did not provide any insufficient information on the exact methods of randomization to determine if credibility analysis was present. Allocation concealment was performed in three studied using sealed envelopes. Based on the selection criteria, we could not make further deletions or additions to the included papers. Second, the number of individuals in these studies were relatively small and therefore statistical power might be limited. Third, we guess that the research heterogeneity is mainly caused by the low quality of the included articles, which is mainly reflected in the high heterogeneity of the articles. The heterogeneity among the

TABLE 2 | Detail characteristic of included studies.

Analysis item	Studies	Patients	Heterogeneity		Statistical method	Effect estimate	*P*-value
			I^2 (%)	*P*			
Clinical outcomes							
Operative time	7	847	96	0.00	MD (IV, random, 95% CI)	−16.41(−39.95, 7.13)	0.17
Blood loss	6	676	90	0.00	MD (IV, random, 95% CI)	−17.11 (−71.40, 37.18)	0.54
Hospital stay	4	588	84	0.00	MD (IV, random, 95% CI)	0.36 (−1.90, 2.61)	0.76
Radiographic outcomes							
ROM	4	416	94	0.00	MD (IV, random, 95% CI)	3.50 (−3.74, 10.73)	0.34
SVA	4	345	75	0.00	MD (IV, random, 95% CI)	−0.78 (−6.34, 4.79)	0.78
Cobb angle	4	345	91	0.00	MD (IV, random, 95% CI)	−1.44 (−6.57, 3.68)	0.58
Functional outcomes							
JOA	8	766	71	0.00	MD (IV, random, 95% CI)	0.49 (−0.01, 0.98)	0.06
VAS	8	616	90	0.00	MD (IV, random, 95% CI)	−0.62 (−1.39, −0.15)	0.12
CCI	4	293	86	0.00	MD (IV, random, 95% CI)	−0.17(−2.08, 1.73)	0.86
Nurick score	4	345	91	0.00	MD (IV, random, 95% CI)	−1.44 (−6.57, 3.68)	0.58
NDI	4	605	70	0.00	MD (IV, random, 95% CI)	−1.35 (−3.66, 0.95)	0.25
Complications							
Hardware failure	3	348	0	0.71	RR (M-H, fixed, 95% CI)	0.52 (0.13, 2.03)	0.34
C5 radiculopathy	9	931	0	0.52	RR (M-H, fixed, 95% CI)	0.35(0.20, 0.61)	0.00
Adjacent segment degeneration	2	292	0	0.78	RR (M-H, fixed, 95% CI)	0.23 (0.03, 1.95)	0.18
Dural tear	6	701	0	0.51	RR (M-H, fixed, 95% CI)	0.68 (0.27, 1.69)	0.41
Deep infection	2	292	0	1.00	RR (M-H, fixed, 95% CI)	0.33 (0.04, 2.93)	0.32
Superficial infection	7	792	0	0.65	RR (M-H, fixed, 95% CI)	0.45 (0.20, 0.98)	0.04
Dysphagia	2	386	0	0.74	RR (M-H, fixed, 95% CI)	0.45 (0.05, 3.94)	0.47
New radiculopathy (not C5)	2	322	0	0.74	RR (M-H, fixed, 95% CI)	0.44 (0.07, 2.72)	0.38
Postoperative kyphosis	5	720	15	0.32	RR (M-H, fixed, 95% CI)	1.24 (0.51, 3.01)	0.63
Neck/arm pain	5	674	52	0.08	RR (M-H, random, 95% CI)	0.77 (0.48, 1.23)	0.28
Pseudarthrosis	3	291	0	0.34	RR (M-H, fixed, 95% CI)	0.18 (0.03, 1.24)	0.08

ROM, range of move; SVA, postoperative C2–7 sagittal vertical axis; JOA, Japanese Orthopedic Association; NDI, neck dysfunction index; CCI, cervical curvature index; MD, mean difference; RR, risk ratio; IV, inverse variance; M-H, Mantel-Haenszel; CI, confidence interval.

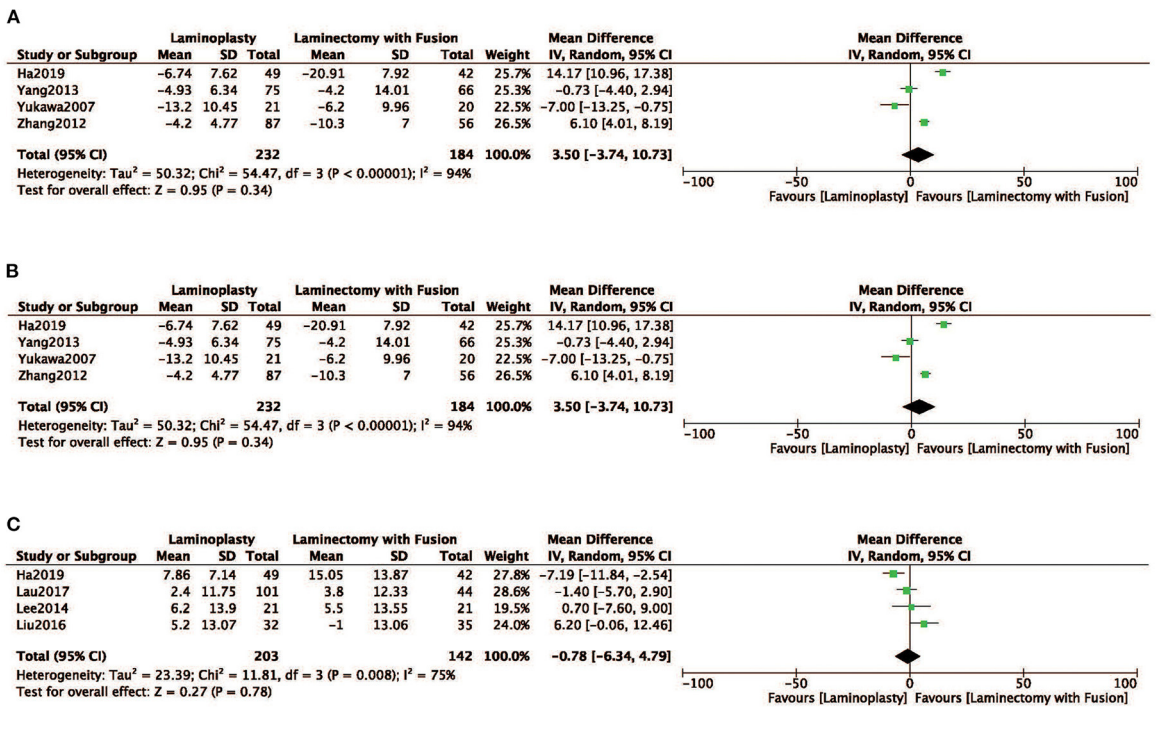

FIGURE 5 | Comparison of **(A)** ROM; **(B)** SVA; **(C)** Cobb angle; between the LP group and the LC group.

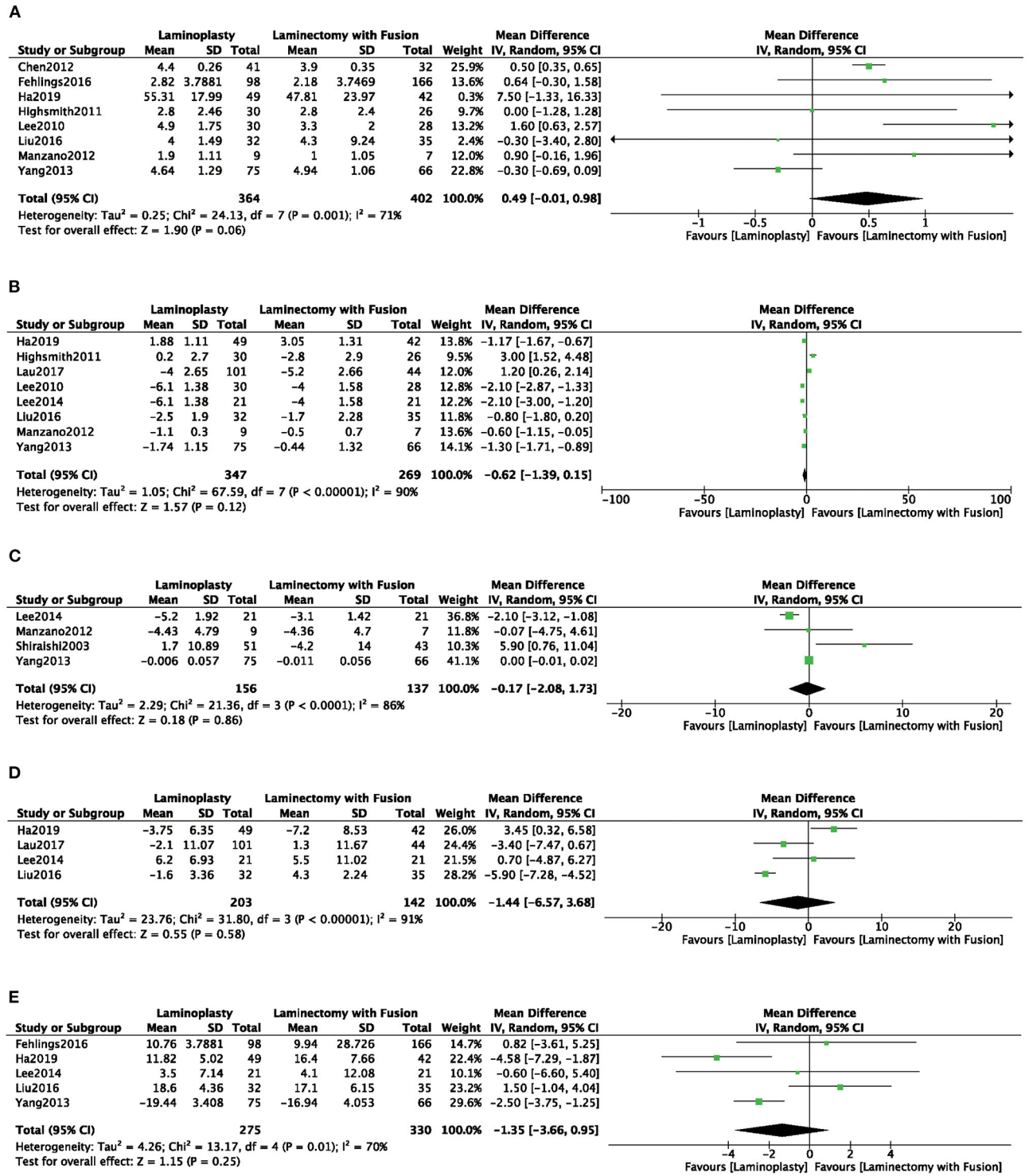

FIGURE 6 | Comparison of **(A)** JOA; **(B)** VAS; **(C)** CCI; **(D)** Nurick; **(E)** NDI; between the LP group and the LC group.

indicators included in our meta-analysis was mainly reflected in the time of operative, intraoperative blood loss, the time of hospital stay, ROM, SVA, Cobb angle, JOA, VAS, CCI, Nurick NDI, and Pseudarthrosis, and for the above heterogeneity, we used a random effects model for treatment statistics, while rate of C5 radiculopathy, Superficial infection, Hardware failure, Adjacent segment degeneration, Dural tea, Deep infection, Dysphagia, New radiculopathy (not C5), Postoperative kyphosis,

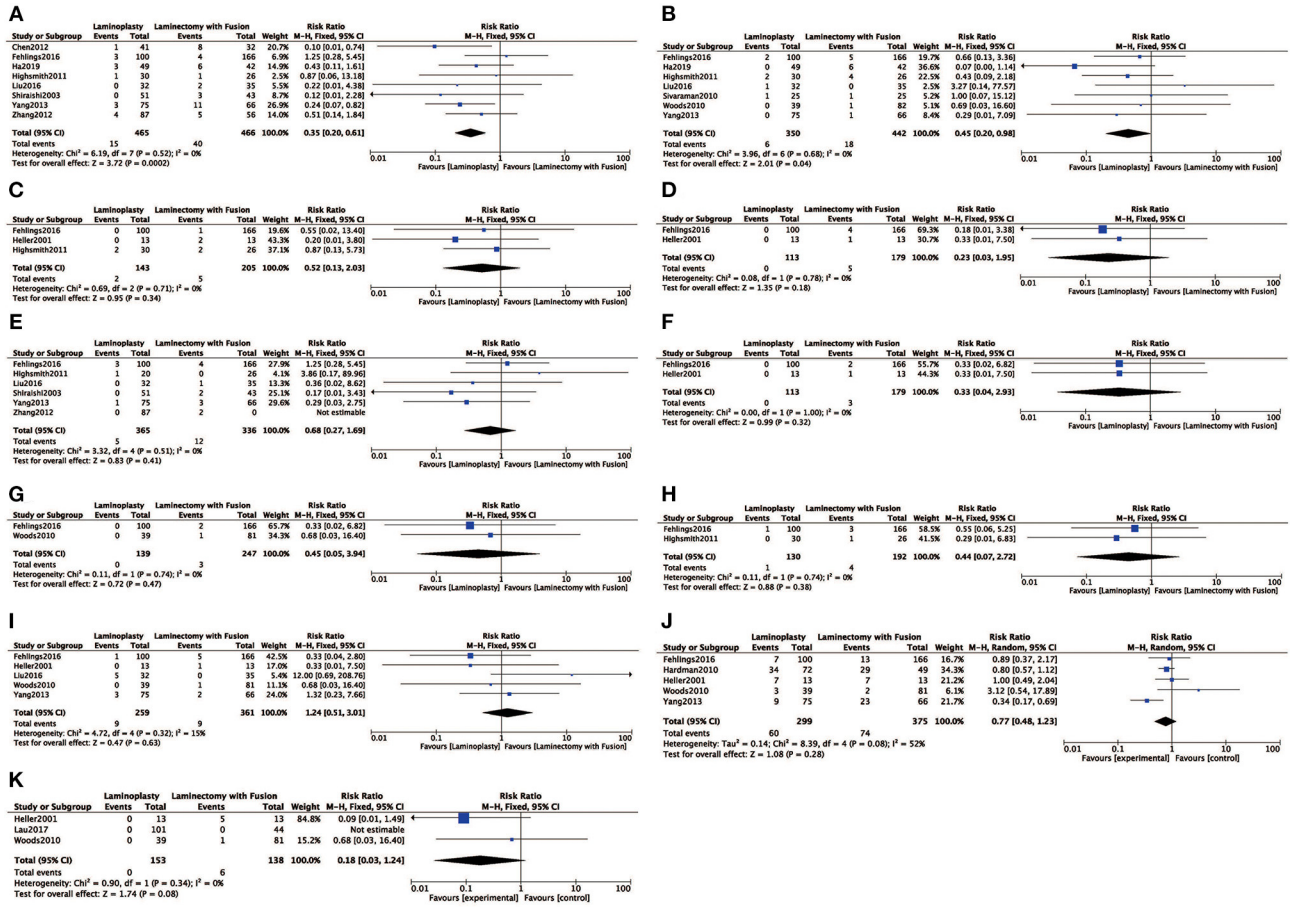

FIGURE 7 | Comparison of **(A)** complication rate of C5 radiculopathy; **(B)** superficial infection; **(C)** hardware failure; **(D)** adjacent segment degeneration; **(E)** dural tear; **(F)** deep infection; **(G)** dysphagia; **(H)** new radiculopathy (not C5); **(I)** postoperative kyphosis; **(J)** neck/arm pain; **(K)** pseudarthrosis; between the LP group and the LC group.

and Neck/arm pain had lower heterogeneity and we used a fixed effects model for the treatment statistics. In addition, this general clinical heterogeneity may be caused by individual differences in patients, technical differences in the surgeon team, differences in medical equipment, and follow-up time. We considered whether our results might be affected by confounding factors. Therefore, high-quality RCTs are required to examine the long-term effects of these two surgical procedures on patients with CSM.

CONCLUSION

Our study shows that LP can achieve better results in C5 radiculopathy and superficial infection in surgical treatment of CSM compared with LC. These results suggest that LP is a therapeutic procedure for promoting management of CSM. Furthermore, high-quality research, adequately powered randomized studies are required to provide more evidence for the optimal surgical treatment of CSM for definite conclusions.

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

ZZ and YZ: protocol and project development. LP: data collection or management. WM and SX: data analysis. HZ and RR: manuscript writing and editing. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Diagnosis of Primary *Klebsiella pneumoniae* in Cervical Spine by Metagenomic Next-Generation Sequencing

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Introduction: Spinal infection is a disease that affects the intervertebral disks or adjacent paravertebral tissue in the vertebral body. There are few reports of spinal infections caused by *Klebsiella pneumoniae*. Cervical spine infection by *K. pneumoniae* especially preoperative is extremely rare. Nowadays, metagenomic next-generation sequencing (mNGS) has led to the accurate and timely diagnoses of numerous infectious diseases.

Case Presentation: We described a case of a 64-year-old woman, with a chief complaint of neck, shoulder, and upper limb pain for 10 days. The patient had symptoms of abscess compression before surgery, and inflammatory indicators such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT) were significantly elevated. The patient's imaging suggested cervical infectious lesions, and the patient had no symptoms of tuberculosis poisoning, and the blood samples associated with tuberculosis were negative. The patient was diagnosed with cervical suppurative infection before surgery. For the patient who failed conservative treatment and had abscess compression, we performed anterior cervical surgery to remove the lesion at an early stage and collected intraoperative specimens for culture and mNGS. Postoperative antibiotic treatment was adjusted according to the etiology and drug sensitivity.

Conclusion: This case suggests that the clinical symptoms of *K. pneumoniae* infection are not typical and the imaging examination lacks specificity. When the clinical diagnosis of etiology is not clear or there are symptoms such as abscess compression, early surgical specimens can be collected for culture and mNGS to identify the pathogen, and postoperative sensitive antibiotics can be used to continue treatment. This helps to identify the cause as early as possible, treat it effectively early, relieve symptoms, prevent complications, and keep the spine stable.

Keywords: *K. pneumoniae*, cervical infection, metagenomic next-generation sequencing (mNGS), operation, diagnosis

INTRODUCTION

Spinal infection is a disease that affects the intervertebral disks or adjacent paravertebral tissue in the vertebral body (1). It is usually caused by bacterial microorganisms and requires a high level of diagnosis and treatment, in most cases requiring a multidisciplinary approach by spinal surgeons, radiologists, and infectious disease specialists (2). The most common pathogen of spinal infection is *Staphylococcus aureus*, followed by *Streptococcus* and *Enterococcus* (3). *Klebsiella pneumoniae* is a common pathogen of nosocomial infections, yet there are few reports of spinal infections caused by *K. pneumoniae* (4, 5). Cervical infection by *K. pneumoniae* especially preoperative is extremely rare. We recently admitted a patient with primary cervical *K. pneumoniae* infection, whose pathogens were first identified by metagenomic next-generation sequencing (mNGS) and treated surgically.

CASE PRESENTATION

The patient was a 64-year-old woman, with a chief complaint of neck, shoulder, and upper limb pain for 10 days. On February 19, 2021, the patient was admitted to our spinal surgery ward. Furthermore, the patient had painful difficulty in swallowing, neck and upper limbs pain which were not relieved by rest or sleep. This made the patient take painkillers daily before sleep. The patient denies any history of night sweats, tiredness, cough, loss of power in the upper limbs, tingling, numbness, and loss of appetite. The examination showed clear breathing sounds on both lungs, and no fistula or subcutaneous mass on the neck. Furthermore, the patient had the following specific signs: diminished cervical lordosis, painful palpation at C4–6 supraspinous and paravertebral muscle, pain radiating in both upper limbs and at the back, and moderate limitation on both flexion and extension of the neck. On the other hand, the patient exhibited muscle strength in the upper limbs grades 4 and normal muscle strength in the lower limbs, as well as normal sensation and muscle tone on both limbs. Laboratory investigation showed amounts of white blood cells (WBC) at 10.3×10^9/L, neutrophil count percent (NEUT%) at 82.7%, procalcitonin (PCT) at 0.135 ng/ml, erythrocyte sedimentation rate (ESR) at 104 mm/h, and C-reactive protein (CRP) at 67.6 mg/L (**Table 1**). The patient had a maximum fever of 38.3°C, on hospitalization, but was normalized after 1 day of treatment. Tuberculin skin test (TST), anti-tuberculosis antibody test, and T cell antigen-specific (ESAT-6 and CFP-10) IFN-γ release assays (IGRAs) were normal. Continuity morning sputum direct smear for three times resulted negative, tuberculosis infection T cells result negative and three consecutive automatic acid-fast staining results negatives. Radiological examination showed that cervical spine X-ray reported degenerative changes at C5/6, as well as C6/7 intervertebral space (**Figure 1A**). Cervical and lung plain CT scan indicated soft tissue thickening at the anterior margin of the C4-T2 vertebra, narrowing of the C5/6 intervertebral space (**Figure 1B**). Cervical MRI plain scan revealed disc herniation at C3/4, C4/5, C5/6, C6/7, and showed the abscess was located in front of the C2-T2 vertebral body and also in the C5/6 intervertebral space. Moreover, the C5 and C6 vertebral bodies showed hypersignal changes (**Figures 1C,D**). We had a ward diagnosis of suppurative infection of the cervical spine with a differential of cervical tuberculosis. The patient was treated with intravenous piperacillin/tazobactam 4.5 g every 8 h for 3 days and was then planned for surgery.

Surgery was done under general endotracheal anesthesia; the patient was positioned supine and a standard Smith-Robinson approach for anterior exposure of cervical spine was done on the right side. After routine exposure, the anterior esophageal fascia was found inflamed and when the prevertebral fascia was cut open light-yellow pus was found around C5/6 intervertebral disc. The same intervertebral space was found necrotic with pus. The pus was drained and thorough debridement and decompression were done, all diseased tissues and necrotic disc were removed. The incision site was washed with hydrogen peroxide followed by normal saline. During the operation, the sample was taken for rapid histological examination and reported C5/6 inflammatory lesions. The titanium mesh filled with allograft was firmly inserted the C5/6 intervertebral space. A titanium plate of appropriate length was placed in front of C5 and C6 vertebral bodies, locked firmly with screws. C-arm fluoroscopy was used to confirm the proper positioning

TABLE 1 | Patient treatment timeline and relevant main clinical data.

	First 3 days after admission	Day 3 (Day of surgery)	One weeks after surgery	Seven weeks after surgery	3 month after surgery
Therapy method	Intravenous antibiotics	Surgical treatment	Intravenous antibiotics	Intravenous antibiotics	Oral antibiotics for 5 weeks
Clinical manifestations	Had painful difficulty in swallowing, neck and upper limbs pain	—	No fever, mild neck and upper limb pain	No special discomfort	No special discomfort
WBC ($\times 10^9$/L)	10.3	—	Normal	Normal	Normal
NEUT%	82.7%	—	78.2%	Normal	Normal
ESR (mm/h)	104	—	120	107	Normal
CRP (mg/L)	67.6	—	25.7	11.36	Normal
PCT (ng/mL)	0.135	—	Normal	Normal	Normal

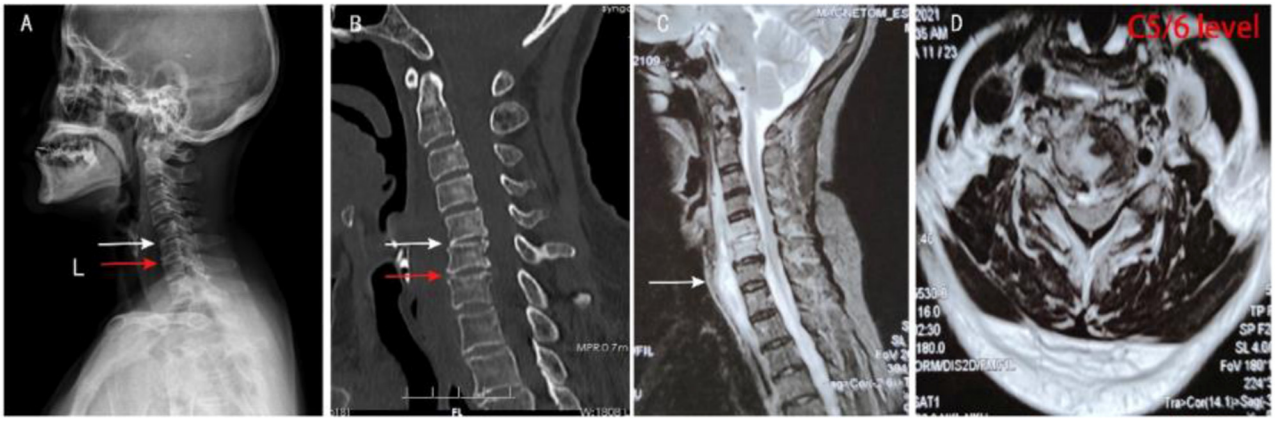

FIGURE 1 | Preoperative imaging results of the patient. **(A,B)** Preoperative cervical spine X-ray and CT showed narrowing of the C5/6 (white arrow) and C6/7 (red arrow) intervertebral space, poor bone structure at the upper and posterior edges of the C6 vertebral body, and thickened soft tissue at the anterior edge of the C4-T2 vertebral body. **(C,D)** Preoperative sagittal and transverse MRI of the cervical spine showed the abscess was located in front of the C2-T2 vertebral body (white arrow) and also in the C5/6 intervertebral space, both C5 and C6 vertebral bodies showed hypersignal changes.

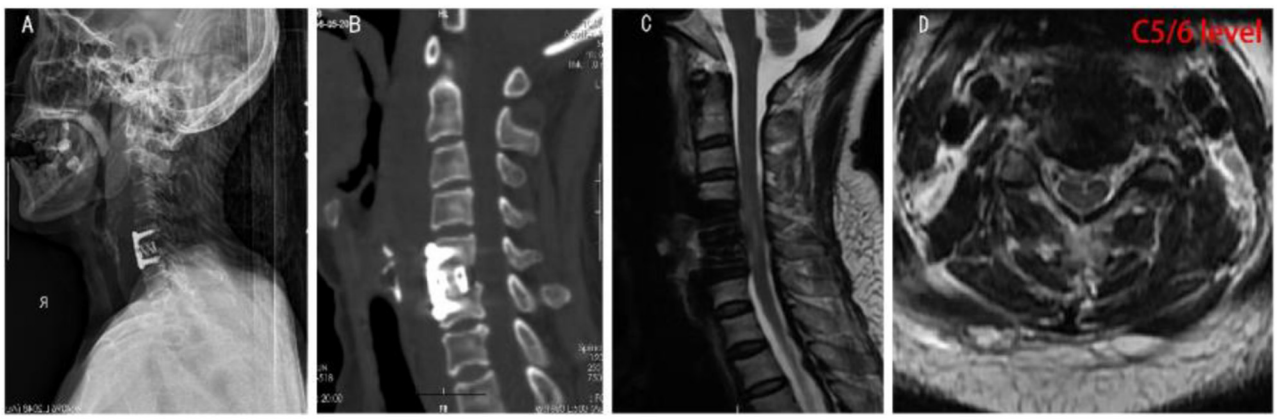

FIGURE 2 | Postoperative imaging results of the patient. **(A,B)** Postoperative X-ray and CT of the cervical spine showed changes in the C5-6 vertebral body after screw internal fixation, no slippage and fracture were observed, and cage shadow was observed in the C5/6 intervertebral space. **(C,D)** Postoperative sagittal and transverse MRI of the cervical spine showed internal fixation shadow in the C5-6 vertebrae, showing postoperative changes, with internal fixation in place. No obvious effusion was observed in the C2-T2 prevertebral space.

of the implants. Somatosensory evoked potential (SEP) and motor evoked potential (MEP) were used intraoperatively to check the occurrences of new neurological deficits. Intraoperative diseased lesions were collected and sent for culture and other pathological examinations. Twenty hours after surgery, mNGS detected *K. pneumoniae* (sequence number 3824), and the drug-resistant gene SHV-9 (sequence number 1), which implied resistance to β-lactam antibiotics. After consulting experts from the infectious department, the decision to treat the patient with intravenous piperacillin/tazobactam 4.5 g every 8 h. Blood culture results at the local hospital also showed *K. pneumoniae* 3 days after surgery, suggesting that *K. pneumoniae* is sensitive to piperacillin/tazobactam. The results of mNGS were confirmed by tissue bacterial culture 1 week after surgery.

The DNA test result for the Mycobacterium tuberculosis complex group was negative, but both anaerobic and aerobic cultures of bone tissues produced *K. pneumoniae*, which further confirmed the diagnosis of *K. pneumoniae* infection. To find the source of the pathogen, sputum smear and culture were performed again, but no *K. pneumoniae* was found. One week after surgery, imaging showed no loosening, fracture, prolapse, or displacement of the internal fixation devices, and the titanium cage was in a good position (**Figure 2**). Postoperative histopathology revealed a large number of inflammatory cells exudate, suggesting chronic suppurative inflammation of the C5/6 disc (**Supplementary Figure 1**).

One week postoperative the patient's, general condition improved, neck and shoulder pain alleviated, inflammatory markers PCT returned to normal value, NEUT% 78.2%, ESR 120 mm/h, CRP decreased from 67.6 to 25.7 mg/L, and the patient showed no symptoms of fever. The patient was discharged from our hospital and continued with the same antibiotic treatment

for 6 weeks in the nearby local hospital (7 weeks after surgery), wherein WBC and PCT returned to normal at re-examination, with CRP at 11.36 mg/L and ESR at 107 mm/h. Oral levofloxacin was continued for 5 weeks (3 months after surgery), wherein WBC, ESR, CRP, and PCT were normal (**Table 1**). During follow-up, there were no postoperative limb pain, decreased muscle strength, numbness, and other spinal cord and nerve injuries.

DISCUSSION

Klebsiella pneumoniae is among the opportunistic pathogens that mainly cause hospital-related infections as well as a risk factor for serious community-acquired infections (6, 7). The most common sites of infection are the urinary tract and respiratory tract, and rarely attack the vertebral column. In addition, it has been reported that some *K. pneumoniae* produce an extended-spectrum β-lactamase, which can develop resistance to β-lactamide antibiotics (8). The widespread use of broad-spectrum antibiotics weakened immunity and other factors that can easily cause spinal infections (9).

Culture is the gold standard for the identification of pathogenic agents. However, 2–3 days are typically required for initial results and up to 1 week for confirmation (10). In recent years, a large number of studies have reported that mNGS is a novel method to detect pathogens of infectious diseases with high speed, specificity, and sensitivity (11). mNGS only needs 24–48 h to give the final result after receiving the sample, which is determined by the sequencing technology, modes, and bioinformatics software used by the clinician (12). Therefore, mNGS can detect pathogens early and guide clinical treatment faster than traditional culture.

The treatment of spinal infection includes conservative treatment and surgical treatment. Conservative treatment mainly consists of a large dose of broad-spectrum antibiotics, which lasts for a long time. At present, some scholars advocate active surgical treatment, complete removal of lesions, prevention of complications such as infection spread, and postoperative adjustment of antibiotics according to culture and drug sensitivity tests (13, 14). The best treatment for infection with abscess formation involves surgical decompression and drainage, and antibiotic treatment for up to 12 weeks (15). Clinically, for patients with spinal infection complicated with bone destruction, the treatment principle is mainly supplemented by surgery and anti-tuberculosis chemotherapeutic drugs. The focus of spinal infection was removed by operation, the balance of the sagittal plane of the spine was reconstructed by the internal fixation system, and bone graft was grafted in the focus area in order to achieve long-term bony fusion and recovery of spinal stability (16). In this case, the abscess was located in front of the cervical vertebra and also in the C5/6 intervertebral space, and the intervertebral space infection was mainly located in the anterior column of the spine. Therefore, anterior surgery was more effective in removing the lesion completely, and a full course of antibiotics was given after surgery.

Extrapulmonary infection of *K. pneumoniae* is rare in clinical practice, and cervical *K. pneumoniae* infection is even rarer in clinical practice. The patient had obvious symptoms of abscess compression before surgery, and inflammatory indicators such as PCT and CRP were significantly increased. The patient's imaging suggested infectious lesions, and the patient had no symptoms of tuberculosis poisoning such as afternoon low fever, fatigue and night sweats.In addition, the blood samples associated with tuberculosis were negative, so tuberculosis infection was not considered before the operation, and anti-infection treatment was mainly applied. After the operation, mNGS found *K. pneumoniae* within 24 h, later, traditional culture confirmed the diagnosis of cervical *K. pneumoniae* infection. We need to consider that it was the hematogenous or transesophageal route, even if it is asymptomatic elsewhere. After a detailed examination of the medical history, the patient showed no high risk of infection, no *K. pneumoniae* was found in sputum smear and culture, and no infection was found in other parts of the body. Therefore, it is highly likely that *K. pneumoniae* originated in the cervical vertebra. In the case of cervical spine infection combined with prevertebral space effusion, the patient had symptoms caused by abscess compressing on adjacent organs, and these were the indications for early operation, so surgical treatment was used to remove the lesions and postoperative antibiotic treatment lasted for a long time according to the results of drug sensitivity. The standardized intravenous treatment of sensitive antibiotics greatly shortened the treatment course. During the postoperative follow-up of 3 months, the patient's discomfort symptoms such as neck and shoulder pain and dysphagia were disappeared, and the stability of the cervical spine was restored.

CONCLUSION

This case report implies that the clinical symptoms of *K. pneumoniae* infection are not typical, and the imaging examination lack specificity. When the disease is highly suspected clinically or there are symptoms of abscess compression, mNGS can be taken to identify the pathogen within hours, and sufficient treatment can be performed by intravenous treatment with sensitive antibiotics combined with surgical removal of the lesion. We found this beneficial to eradicate the disease, relieve the symptoms, and maintain the stability of the spine as early as possible.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Xiangya Hospital, Central South University. 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

TL wrote this case. QG proofread the text. CG and YL revised the report according to journal requirements. All authors have read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.800396/full#supplementary-material

Supplementary Figure 1 | Pathological results of the patient. **(A,B)** The pathological section of the C5/6 intervertebral disc showed a large number of inflammatory cells exudate, suggesting chronic suppurative inflammation.

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Perioperative Anesthesia and Acute Smell Alterations in Spine Surgery: A "Sniffing Impairment" Influencing Refeeding?

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Medications for general anesthesia can cause smell alterations after surgery, with inhalation anesthetics being the most acknowledged drugs. However, spine patients have been poorly studied in past investigations and whether these alterations could influence the refeeding remains unclear. This research aims to observe detectable dysosmias after spine surgery, to explore any amplified affection of halogenates (DESflurane and SEVoflurane) against total intravenous anesthesia (TIVA), and to spot potential repercussions on the refeeding. Fifty patients between 50 and 85 years old were recruited before elective spine procedure and tested for odor acuity and discrimination using the Sniffin' Sticks test. The odor abilities were re-assessed within the first 15 h after surgery together with the monitoring of food intakes. The threshold reduced from 4.92 ± 1.61 to 4.81 ± 1.64 ($p = 0.237$) and the discrimination ability reduced from 10.50 ± 1.83 to 9.52 ± 1.98 ($p = 0.0005$). Anesthetic-specific analysis showed a significant reduction of both threshold ($p = 0.004$) and discrimination ($p = 0.004$) in the SEV group, and a significant reduction of discrimination abilities ($p = 0.016$) in the DES group. No dysosmias were observed in TIVA patients after surgery. Food intakes were lower in the TIVA group compared to both DES ($p = 0.026$) and SEV ($p = 0.017$). The food consumed was not associated with the sniffing impairment but appeared to be inversely associated with the surgical time. These results confirmed the evidence on inhalation anesthetics to cause smell alterations in spine patients. Furthermore, the poor early oral intake after complex procedures suggests that spinal deformity surgery could be a practical challenge to early oral nutrition.

Keywords: smell disorder, anesthesia, inhalation exposures and halogens, fluorinated hydrocarbons, perioperative period and refeeding, critical care, orthopedic procedures, spine

INTRODUCTION

Thousands of spine patients worldwide are daily subjected to a controlled and reversible loss of consciousness with drugs administered by intravenous infusion or inhalation. General anesthesia is advantageous for the surgeon who operates a motionless body, for the anesthesiologist who has full control of the patient's intrinsic physiological mechanisms, and for the patient who has no pain or future reminiscence (from the Greek *anaisthisía*: ἀ ν- "without" and -αἴ σθησις "sensation"). However, some reports suggest that the patient may experience another shortage: a reduction of the sense of smell. Postoperative smell disorders were observed in different surgical populations, and they have been studied in relation to drugs used for general anesthesia, such as the inhaled DESflurane (DES) and SEVoflurane (SEV) or the intravenous anesthetics (TIVA) (1–3). The anesthetic-induced unconsciousness is known to derive from a general disconnection of higher-order brain centers (4), with connectivity networks being required for olfactory processing (5). Inhaled halogenates can nevertheless be the ones mostly affecting the sense of smell because they also collide with the posterodorsal olfactory epithelium of the nasal cavity that houses the odorant receptors (cranial nerve I). Importantly, these sensory neurons play a fundamental role in driving eating behaviors, and subjects with sniffing impairment can decide to alter their diet to compensate for the loss (6). In fact, the smelling of palatable food aromas promotes appetite, liking, and food intake (7, 8), especially in restrained eaters (9). Fasting patients undergoing surgery refrain from eating from the day before, making early oral food after surgery one of the cornerstones of the perioperative nutritional support program in spine surgery (10, 11). Whether the potential sniffing impairment after surgery could affect the refeeding in surgical patients has never been properly explored, with spine patients being scarcely included in past trials on acute anesthesia-derived decays of the sense of smell.

This observational trial aims at clarifying three research questions. (1) The existence of acute (early 15 h) dysosmias after spine surgery. (2) Any amplified affection of halogenates on the sense of smell vs. the subgroup of patients with halogen-free general anesthesia. (3) If the potential decrease in olfactory abilities could have clinical repercussions on the postoperative refeeding (early 15 h) in terms of energy intakes.

MATERIALS AND METHODS

Study Design and Participants

The study was conducted at IRCCS Orthopedic Institute Galeazzi of Milan, Italy. The research was planned as a prospective observational trial of 50 patients recruited from the population undergoing elective spine surgery. The study protocol was drafted in accordance with the Good Clinical Practice and the current revision of the Declaration of Helsinki. The competent Ethics Committee approved the study on April 11 2019 and the trial was registered on the online resource ClinicalTrials.gov (NCT04194788). The eligibility criteria included Caucasian race, male or female gender, age between 50 and 85, elective spine surgery, signature and acceptance of informed consent. Patients with one of the following characteristics were excluded: stage III–IV heart failure, stage III–V renal failure, cancer, neuropsychiatric diseases, smokers, olfactory, or taste disorders of any nature.

All cohort subjects followed the routine anesthesiology care with antibiotics, antiemetic, proton-pump inhibitors, neuromuscular blocker, antipyretics, anti-inflammatory, and analgesics. Patients underwent general anesthesia with endotracheal intubation. The groups with halogens received propofol IV bolus for induction followed by halogens for balanced general anesthesia maintenance while the TIVA group received continuous IV infusion of propofol. In all groups, analgesia was obtained with fentanyl IV bolus before intubation and maintained with remifentanil during surgery. Standard electrocardiography, non-invasive blood pressure monitoring, $SatO_2$ monitoring, end-tidal carbon dioxide ($ETCO_2$) monitoring, and urine output monitoring were performed. The depth of anesthesia in the TIVA group was controlled with a brain function monitor (SEDline® of Masimo Corporation, USA) and maintained in the range of 25–50 PSI (Patient State Index) (12). In the DES and SEV groups, anesthesia was maintained to achieve the desirable age-related minimum alveolar end-tidial concentration (MAC) (13). After the surgical procedure, patients were extubated and discharged with Aldrete's score $\geq$9.

In the first 15 h after surgery, food consumption from in-hospital diets was monitored through bedside examinations, which comprised the first lunch of the day and the first breakfast following surgery. The first meal of the hospital diet included a first course (e.g., pasta in broth), a second course (e.g., cooked ham), vegetables (e.g., boiled carrots), a fruit mousse, and bread at the patient's choice, with a total of 750–900 kcals. The standard breakfast included two rusks, jam, and tea (milk as an alternative), with a total of 100–150 kilocalories (kcal). Condiments during cooking or extra snacks were also considered during the evaluation. The study sample has been subjected to pre- and postoperative assessment of olfaction abilities, being performed within 15 h after surgery before or after the first meal of the day.

The Sniffing Tests

The olfaction abilities were evaluated by using the threshold and the discrimination tests from the "Sniffin' Sticks" (Burghart Messtechnik GmbH, Tinsdaler Weg 175, 22880 Wedel, Deutchland), which is composed of pen-like devices dispensing odors to evaluate the nasal chemosensory performance. Both tasks generate a score ranging from 1 to 16. Normative data of healthy subjects are available (14), and have been considered as a check of the correct execution of the tests. The two tests were performed according to the instructions for use. Briefly, non-lateralized measures were evaluated presenting a single pen about 2 cm under both patient's nostrils for 2–3 s. A single trained researcher wearing gloves carried out all tests, with the patients not consuming food, chewing, or eating sweets at least 3–4 h before since odor receptors are distinctly more responsive to food aromas in a fed state. The olfaction acuity

task determines the olfactory threshold of a subject by using graduated concentrations of *n*-butanol solution (16 triplets of pens, two containing deionized water and the third the odorant). The patient was first familiarized with the pen with the highest concentration. Then, a staircase procedure was started from the most diluted pen, with the patient being asked to identify the odor-containing pen twice in a row (i.e., staircase-reversal trials). The discrimination test evaluates the patient's ability to differentiate odors based on the comparison between three odors (16 triplets of pens, two containing the same non-target odor and the third the target odor). The patient had to choose the pen containing the odor that smells different in each triplet, with no given clue on the correctness of the statements.

Statistical Analyses

Descriptive statistics have been reported in the form of mean ± standard deviation (min; max) for normally distributed values (Shapiro–Wilk test >0.05) or in the form of median (Q1/Q3) for skewed data. Categorical variables were reported as frequencies or percentages. Sex-differentiation and presbyosmia were analyzed using Pearson correlation as a determinant of the linear association direction and strength. The three research questions have been subsequently investigated using 2-tailed tests. (1) Before-after surgery differences in olfaction abilities of the whole study cohort was investigated using paired sample *t*-test for normally distributed threshold data and Wilcoxon signed-rank test for the skewed discrimination data. (2) The analyses on the variations for each anesthesia group used paired samples *t*-test for normally distributed continuous values (threshold of DES, SEV, TIVA; discrimination of SEV, TIVA) and Wilcoxon signed-rank test for skewed continuous values (discrimination of DES). The variations of olfaction abilities between anesthesia groups have been investigated through the paralleling of delta (Δ) variations using Mann–Whitney *U*-test for DES vs. SEV or TIVA groups, and for SEV vs. TIVA. (3) Food intakes in the first 15 h after surgery have been compared between groups using independent sample *t*-test controlled for the homogeneity of variances (Levene's test > 0.05). The amount of food consumed has been analyzes as the percentage of energy ingested compared to the whole meal presented in the tray of the first breakfast and first lunch. Changes of threshold and discrimination abilities were analyzed against the percentage of food intakes after surgery in the first 15 h. The delta changes were skewed data. Therefore, Spearman correlation was used to observe the existence, strength, and direction of the association. Data analyses were performed by using the Statistical Package for the Social Sciences (SPSS Statistics 22). The locked database to support the findings is available as a **Supplementary Material**.

RESULTS

The study cohort comprised 50 consecutive patients (26 females and 24 males). The demographic and clinical characteristics were reported in the following **Table 1**.

Sex-differentiation of threshold and discrimination was observed at baseline: 5.00 ± 1.48 and 10.73 ± 1.93 in females vs. 4.83 ± 1.77 and 10.25 ± 1.73 in males. For what concerns baseline presbyosmia, baseline olfaction abilities negatively associated with the years of age (threshold: $r = -0.385$, $p = 0.006$; discrimination: $r = -0.068$, $p = 0.637$). No baseline differences were found between different anesthesia-specific groups for what concerned threshold (DES vs. SEV, $p = 0.381$; DES vs. TIVA, $p = 0.972$; SEV vs. TIVA, $p = 0.543$) or discrimination (DES vs. SEV, $p = 0.263$; DES vs. TIVA, $p = 0.442$; SEV vs. TIVA, $p = 0.294$).

TABLE 1 | Demographic and clinical characteristics of the study cohort.

	n = 50
Age (years)	65.37 ± 8.13 (50.06; 80.52)
Gender	24 males, 26 females
Weight (kilograms)	73.33 ± 17.44 (40.00; 117.00)
BMI	25.78 ± 4.51 (17.78; 36.75)
CCI	2 (1/3)
ASA	2 (2/2)
Surgical indication	
Intervertebral disc surgery	16
Spondylolisthesis	16
Lumbar stenosis	10
Deformity	8
Anesthesia	
TIVA-TCI (halogenates-free)	7
Halogenates (DES/SEV)	43 (36/7)
Induction-extubation (minutes)	123 (81/178)
Aldrete	10 (10/10)

BMI, body mass index; CCI, Charlson comorbidity index (scores 1–2, mild; scores 3–4, moderate; scores>5, severe); ASA, American society of anesthesiologists physical status classification system (I, healthy; II, mild; III, severe; IV, life threatening; V, moribund; VI, brain-dead); TIVA-TCI, total intravenous anesthesia-target controlled infusion; Aldrete, Aldrete's scoring system (a score≥9 is required for discharge).

After spine surgery, the threshold reduced from 4.92 ± 1.61 to 4.81 ± 1.64 [$t_{(49)} = 1.198$; 95% CI: −0.0745 to 0.2945, $p = 0.237$] and the discrimination ability reduced from 10.50 ± 1.83 to 9.52 ± 1.98 ($Z = -3.497$, $p = 0.0005$). Results are reported in the following **Figure 1**.

Patients undergoing anesthesia with halogens experienced a general reduction of threshold from 4.93 ± 1.62 to 4.73 ± 1.65 and of discrimination ability from 10.56 ± 1.71 to 9.47 ± 1.88. Specifically, in the DES group the threshold reduced from 4.83 ± 1.60 to 4.72 ± 1.66 [$t_{(35)} = 1.160$; 95% CI: −0.0833 to 0.3055, $p = 0.254$] and the discrimination reduced from 10.42 ± 1.61 to 9.61 ± 1.79 ($Z = -2.403$, $p = 0.016$). In the SEV group the threshold reduced from 5.43 ± 1.77 to 4.79 ± 1.73 [$t_{(6)} = 4.500$; 95% CI: 0.2933–0.9924, $p = 0.004$] and the discrimination reduced from 11.29 ± 2.14 to 8.71 ± 2.29 [$t_{(6)} = 4.500$; 95% CI: 1.173–3.970, $p = 0.004$]. In the TIVA group the threshold increased from 4.86 ± 1.65 to 5.29 ± 1.58 [$t_{(6)} = -1.353$; 95% CI: −1.2037 to 0.3465, $p = 0.225$] and the discrimination reduced from 10.14 ± 2.61 to 9.86 ± 2.67 [$t_{(6)} = 1.000$; 95% CI: −0.413 to 0.985, $p = 0.356$]. See **Figure 2** for the histogram. The analysis of inter-groups variations showed a difference of both Δthreshold ($U = 60.500$, $p = 0.025$) and Δdiscrimination ($U = 50.500$, $p = 0.011$) between DES and SEV. No difference was observed in Δthreshold ($U = 80.500$, $p = 0.122$) and Δdiscrimination between DES and TIVA ($U = 110.000$, $p = 0.587$). Both Δthreshold ($U = 4.000$, p

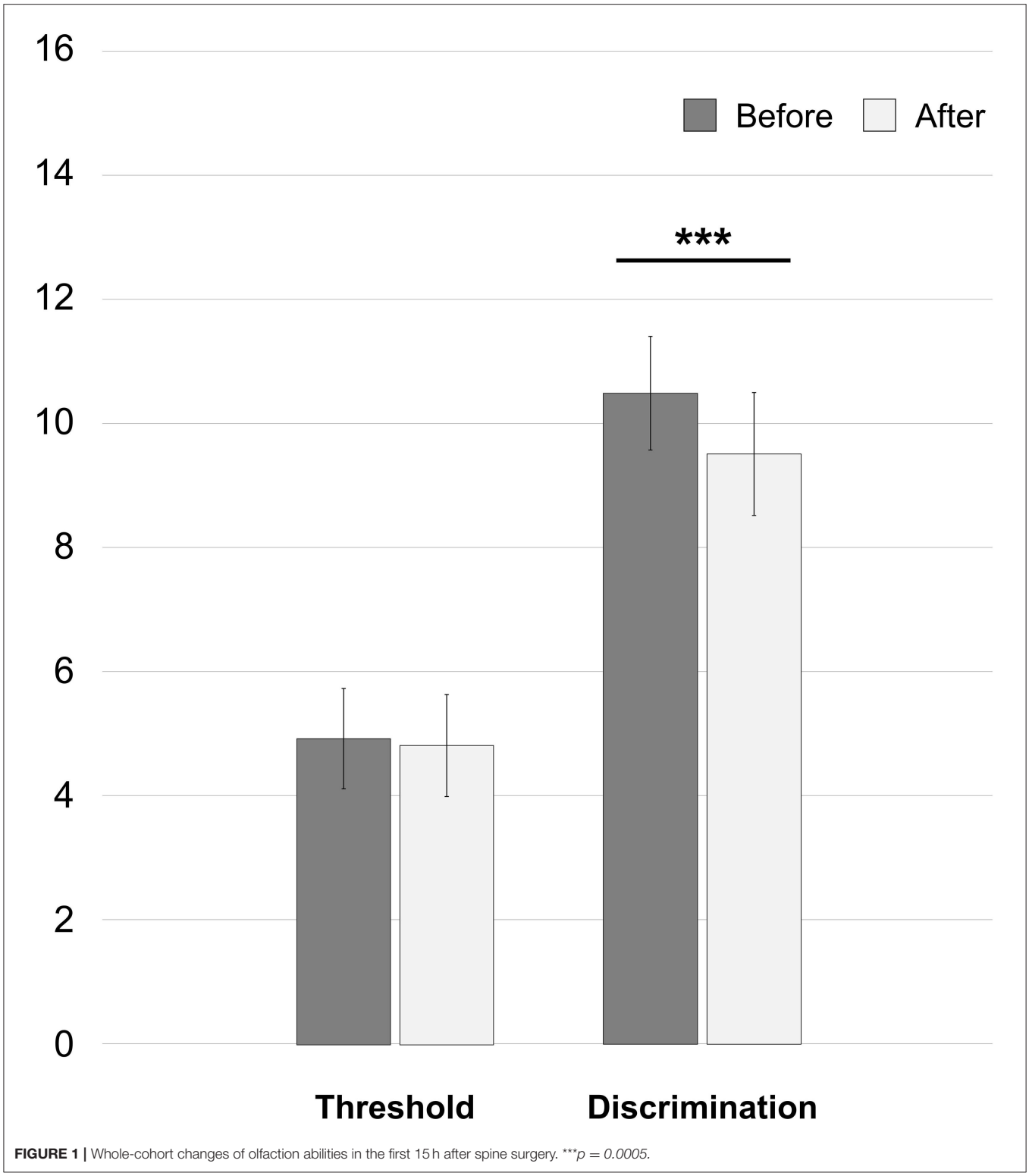

FIGURE 1 | Whole-cohort changes of olfaction abilities in the first 15 h after spine surgery. ****p = 0.0005.*

= 0.007) and Δdiscrimination ($U = 3.000$, $p = 0.005$) showed a difference in SEV vs. TIVA.

Concerning the food ingested in the first 15 h, the DES group consumed 84.14 ± 56.77 kcal at breakfast and 486.22 ± 153.01 kcal at lunch. The SEV group consumed 99.57 ± 65.15 at breakfast and 541.43 ± 174.51 kcal at lunch. The TIVA group consumed 7.71 ± 20.41 kcal at breakfast and 239.14 ± 314.47 kcal at lunch. The energy taken from the food was converted

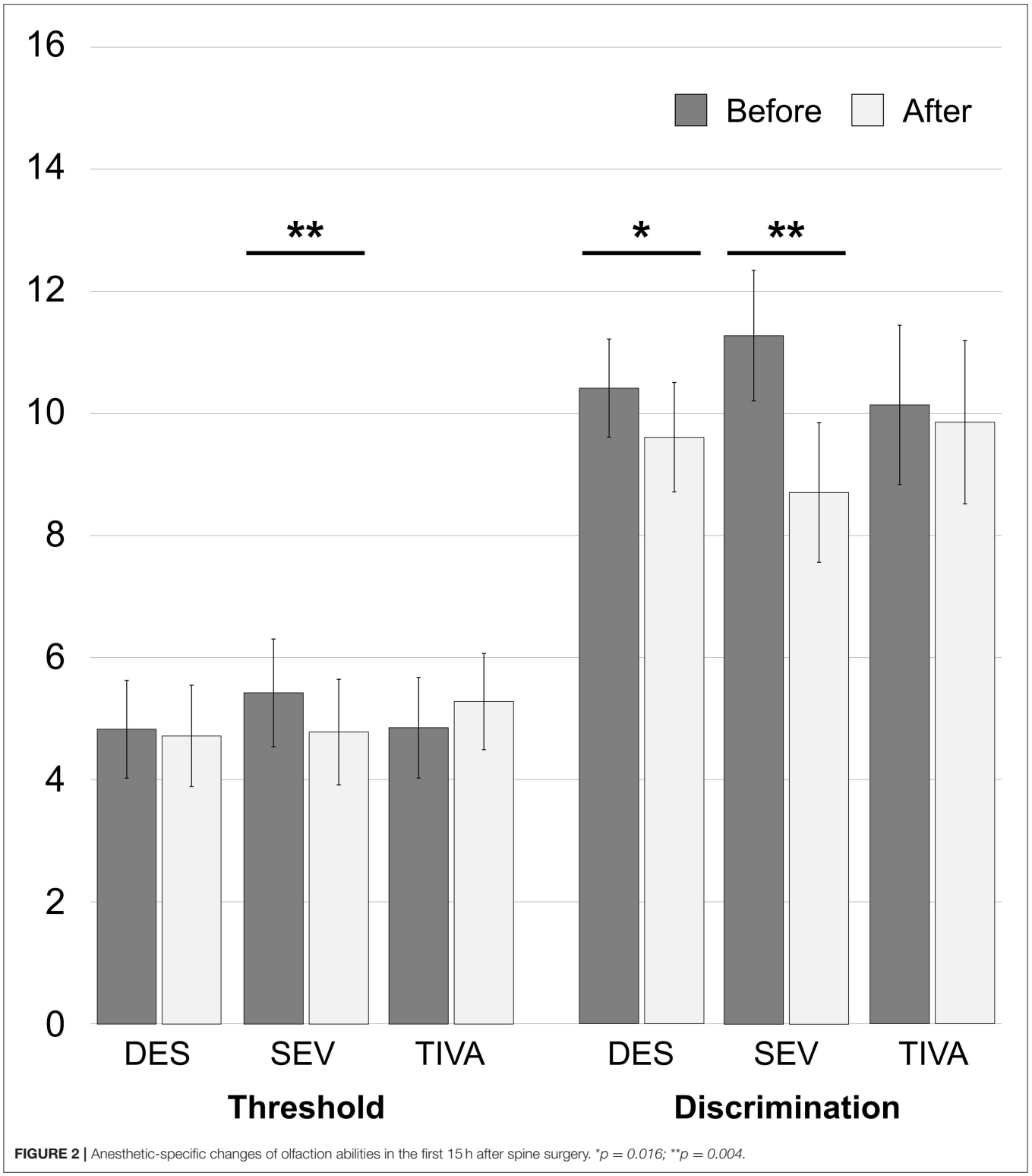

FIGURE 2 | Anesthetic-specific changes of olfaction abilities in the first 15 h after spine surgery. *$p = 0.016$; **$p = 0.004$.

into a percentage of the energy of the two meals consumed with respect to the total that was delivered in the tray to the patient's bed in order to decrease any variability in food quality. The percentage of food ingested in the first 15 h after surgery (breakfast plus lunch) in the TIVA group was 26.03 ± 33.11%, which was lower compared to 62.60 ± 18.88% for DES [unequal variance $t_{(6.778)} = 2.834$; 95% CI: −1.2037 to 0.3465, $p = 0.026$) and 69.27 ± 24.43% for the SEV group [equal variance $t_{(12)}$

= 2.780; 95% CI: 9.3529–77.1192, $p = 0.017$]. No differences were found between the DES and SEV groups [equal variance $t_{(41)} = -0.816$; 95% CI: −23.1816 to 9.8416, $p = 0.419$]. Results were reported in the following **Figure 3**. In order to observe a possible association between the reduction of olfaction abilities and the diverse food consumption of the whole cohort, the Δthreshold and Δdiscrimination have been correlated with the percentages of energy intakes. No correlation was found between the percentages of food intakes and Δthreshold [$r_s(48) = -0.205$, $p = 0.154$] or Δdiscrimination [$r_s(48) = -0.088$, $p = 0.545$].

Based on the observed absence of association between early food intakes and anesthesia-derived decays, the following *post-hoc* analysis on cofactors influencing food intakes has been conducted. The results of this enquiry are to be considered as hypothesis-generating. Delta changes in threshold and discrimination scores were reduced in a composite factor using the dimension reduction technique of Principal Component Analysis (PCA). DES and SEV groups have been clustered in a single HALO group, and analyzed against the TIVA group. The covariance analysis (ANCOVA) accounted for the following cofactors influencing food intakes: the composite reduction of olfaction abilities, old age (years), comorbid conditions (CCI), perioperative morphine (mg), postoperative numerical rating scale (NRS) for pain (early 15 h), postoperative NRS for nausea (early 15 h), and anesthesia induction-extubation time (minutes) as a measure of surgical complexity. No multiple-model effects have been observed on acute food intakes after controlling for smell affections ($p = 0.001$, adjusted), aging ($p = 0.0002$, adjusted), CCI ($p = 0.0001$, adjusted), morphine ($p = 0.0004$, adjusted), NRS for pain ($p = 0.0001$, adjusted), NRS for nausea ($p = 0.0002$, adjusted). Interestingly, the covariate induction-extubation time did not satisfied the assumption on the variance of the covariate values across the different levels of the independent variable (type of anesthesia) and it could not be included in the ANCOVA. This latter observation drew attention to the complexity of the surgery as a possible obstacle to the proper postoperative refeeding. In fact, The percentages of food intakes correlated with the minutes of induction-extubation [$r_s(48) = -0.378$, $p = 0.007$]. In the next **Figure 4**, the linear dependence between the two variables was reported (adjusted R Square = 0.230; unstandardized B = −0.144, 95% CI: −0.218 to −0.071; $p = 0.002$). Of note, no association was found between the minutes of induction-extubation and the composite reduction of olfaction abilities [$r_s(48) = 0.60$, $p = 0.678$].

Multiple regression analysis confirmed the predictor potential of the time between anesthesia induction-extubation (unstandardized B = −0.144, 95% CI: −0.243 to −0.045; $p = 0.005$) on the percentage of food intake after surgery, with no contribution observed from smell affections ($p = 0.117$), aging ($p = 0.725$), CCI ($p = 0.415$), morphine ($p = 0.936$), NRS for pain ($p = 0.904$), NRS for nausea ($p = 0.803$).

DISCUSSION

In this trial, we studied the smell function of spine patients before and after surgery, exploring the different effects on olfaction abilities of general anesthetics and the potential impact on the refeeding. After surgery, the patients of our cohort experienced a significant loss of discrimination ability of 9.33% from baseline. The patients undergoing general anesthesia with SEV encountered an amplified affection on their sense of smell compared to patients receiving DES or halogen-free general anesthesia (TIVA), with a significant postoperative reduction of 11.84% for odor acuity and 22.78% for discrimination from basal scores. Even if patients of the DES group experienced a decrease in discrimination abilities after surgery, the sniffing impairment in the SEV group had been significantly higher than the variations observed in both DES and TIVA patients. Importantly, the observed affections on the sense of smell showed no association with the amount of food consumed after surgery. Manifest differences in terms of early food intakes have been attributed to the complexity of the surgery, meaning the time between anesthesia induction and extubation. Unlike what might have been supposed, advanced age, the presence of comorbidities, the use of morphine, pain, or nausea did not seem to influence the early feeding in our cohort.

Spine surgery is an operation that involves no anatomical locations at potential risk for smell disturbances, and the early onset of sniffing impairments would suggest general anesthetics as a causative factor (15). Olfaction threshold is considered a test assessing dysfunctions at the level of peripheral structures, whereas odor discrimination reflects more the sensineural function of central olfactory processes (16). Odor discrimination testing requires the patient to memorize the suprathreshold smell-containing pens before completing the three-alternative task, and memorizing odors requires, at least to some degree, a differential role of memory. Higher-order brain centers seem to be disconnected from the specificity of the odor stimulus, thus focusing more on hedonic and behavioral values (17). Therefore, we may assume that a peripheral type of dysfunction involved patients of the SEV group whereas a hypo-function of central olfactory processes concerned patients of both halogen groups. The few studies investigating the postoperative effects of general anesthetics on the sense of smell agreed with our results on the superiority of SEV in causing affections of the central olfactory system compared to DES (3) or TIVA (1, 2).

Conversely, to the authors' knowledge this is the first time that early nutrition has been investigated in relation to postoperative sniffing impairment as a mean to contribute with a clinical significance to the research scope. In fact, quantitative olfactory dysfunctions are known to be strongly related to qualitative therefore hedonic misperception of odors (i.e., parosmia) (18), presumably influencing the patients' perceived pleasantness of hospital food (19). In the whole cohort, a considerable portion of the food served was left on the plate, with halogenated and TIVA patients consuming <70 and <30% of the energy served, respectively. Despite the fact that the TIVA patients did not experience any postoperative sniffing impairment, they had been those with the lowest intakes. Regardless of the type of anesthesia, the ingestion of food in the first 15 h has been negatively associated with the length of surgical time, deducing that patients undergoing spinal deformity procedures might be the most at risk of early malnutrition giving that these complex

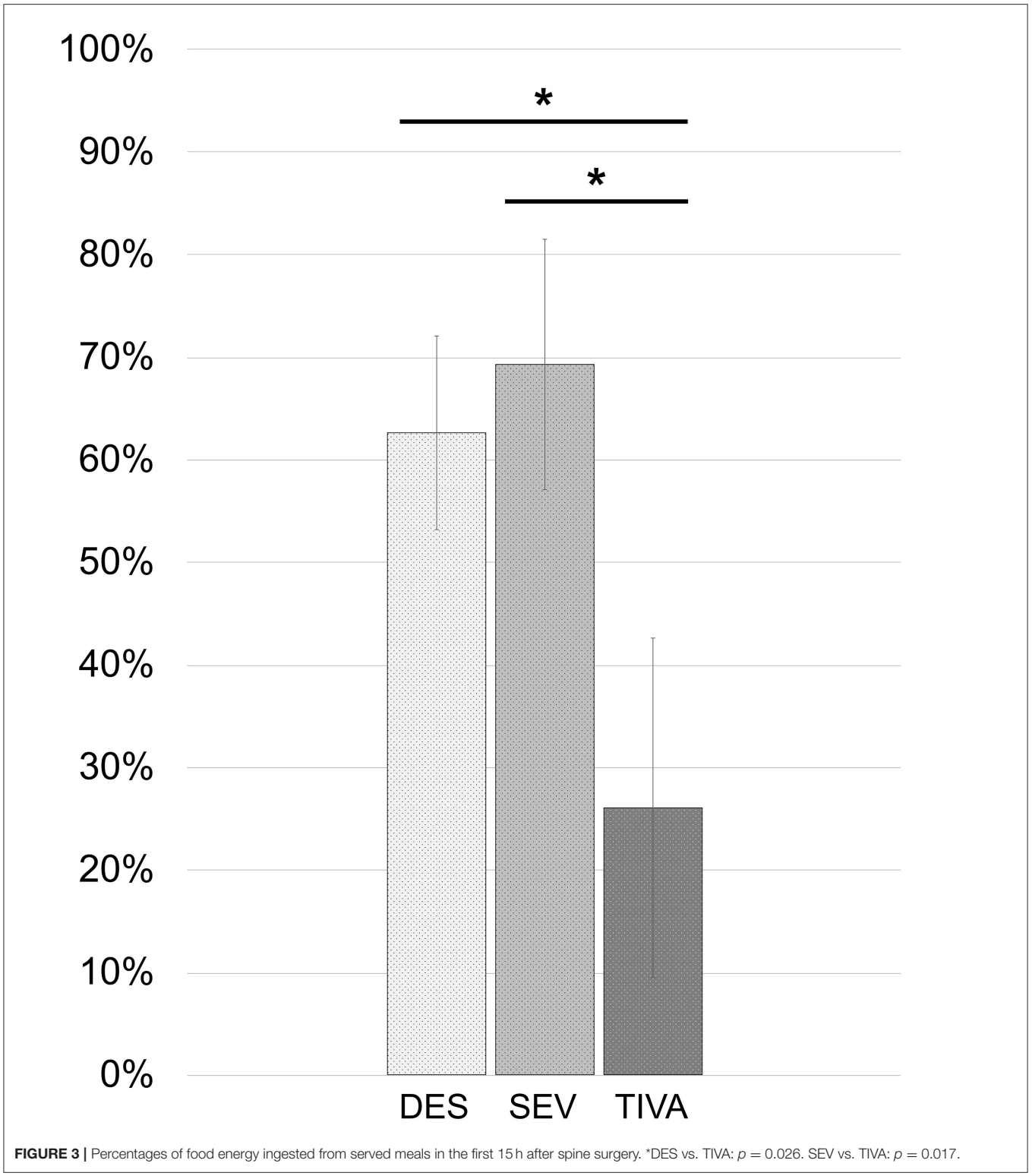

FIGURE 3 | Percentages of food energy ingested from served meals in the first 15 h after spine surgery. *DES vs. TIVA: $p = 0.026$. SEV vs. TIVA: $p = 0.017$.

surgeries are usually associated with long operation times. In the subgroup of TIVA patients, in fact, four patients had deformity as primary surgical indication (with two patients having a fusion of 9 or more vertebrae) and represented half of the patients with the same surgical indication in the entire study cohort (see **Table 1**).

Inhalation of volatile organic compounds has not always occurred for medical purposes. Diethyl ether has long been used

FIGURE 4 | Percentages of early energy intakes after spine surgery depending on the complexity of surgery. $R^2 = 0.230$ ($p = 0.002$).

for recreational activities from eleventh to the nineteenth century (20). Hydrocarbons in glue, cleaners, or paints were smelled by teenagers who turned on in twentieth-century America, giving birth to the "sniffing syndrome" (21). Glue-sniffing is still widespread in the young population of many countries where any kind of solvent abuse by inhalation is considered an immediate and affordable recreation (22). The *ad libitum* abuse of these ethers is likely to have caused nose irritation (23), contrary to the current halogenated ethers for medical purposes that are known to have a high safety profile and nimbler titratability. It cannot be excluded with certainty a causative role in provoking a mucosal swelling or vasodilation of nasal capillaries that impedes the physical access of odors to the olfactory region, or toxicity damaging of olfactory receptors (24). However, it is reasonable to disregard the possibility of nasal blockage, as the patients would have reported poor nasal breathing. Concerning the existing hypotheses about the pharmacodynamics of general anesthetics, direct interaction with membrane proteins other than indirect lipid bilayer fluidization seem to be the most plausible (25, 26). DES, SEV, and other inhalation anesthetics are known to modulate both synaptic and extrasynaptic $GABA_A$ receptors (27, 28), and this implication could substantiate the observed sniffing impairment given the role of GABAergic neuromodulation in olfactory bulb activity (29). Moreover, the anesthesia-derived corruption of higher-order network-level interactions, while leaving local network functions intact (20), could have played a role in disrupting the proper combination of the spatiotemporal pattern of glomerular activation and the corresponding olfactory features, which is necessary for odor discrimination (30). Nonetheless, the loss

of consciousness from propofol is also produced by a positive modulation on GABA neurotransmission (31), supporting the prospect either of a propofol interference or of a dissimilar mediator involved in the herein observed sniffing impairment. Of note, individual volatile anesthetics showed some degrees of binding site selectivity in the olfactory epithelium of rats (32).

We can list some limitations of this research. First, the observational nature of the study acquired an uneven allocation of patients between groups, and both SEV and TIVA counted a number of individuals far fewer than the DES group. However, this aspect does not seem to have influenced our research since the current results are arguably similar to those reported by other clinical trials. Second, it cannot be ruled out that the alteration of olfactory discrimination could have been derived from a generalized postoperative cognitive dysfunction (1), though no differences regarding the cognitive status appeared to interest patients emerging either from halogen or TIVA anesthesia (33). Third, the interference from drugs other than morphine in causing the observed effects has not been investigated. For instance, some intraoperative non-steroidal anti-inflammatory drugs may have interfered with the trigeminal activation (34), whose proper *sensitivity* is known to be part of the dynamic interaction with the olfactory system that underlies the perception (35). Besides, the continuous IV infusion of propofol in the TIVA group could have accounted for the difference in non-nutritional calorie burdens that are known to derive from the lipid content of refined soybean oil and purified egg phosphatide (36), thus possibly playing a role in the observed postoperative low food intakes of TIVA patients.

Future studies addressing the anesthesia-derived decays of the sense of smell should consider the use of non-invasive recordings from the olfactory bulb able to detect altered signals and avoid odor habituation, like the electrobulbogram (37). Moreover, there should be the inclusion of tests assessing qualitative olfactory perception, such as the Sniffin' sticks parosmia test (18), in order to observe changes in the odor valence. In conclusion, our study reinforces the evidence on inhalation anesthetics to cause a sniffing impairment after spine surgery. Furthermore, the complexity of these procedures that preclude the prospect of early mobilization to maintain the ideal alignment of the spine could represent a practical challenge also to early oral nutrition. A prudent integration with dietary supplements should be considered to compensate for the lack of nutrition until the complete recovery of the ability to feed on the in-hospital diets (38, 39).

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

The studies involving human participants were reviewed and approved by the Ethics Committee of IRCCS San Raffaele Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MB formulated the conception and design of the work, analyzed and interpreted the patient data, and wrote the first draft of the manuscript. MB and TC contributed to the acquisition of data. TC, FL, PR, MP, LS, RB, MB-B, and PB substantively revised the first draft of the manuscript. All authors read and approved the final manuscript. All authors have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.785676/full#supplementary-material

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CASE REPORT
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Multiple Spinal Tuberculosis with Severe Kyphosis: A Case Report

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Background: The purpose of this study was to analyze the clinical efficacy of a patient with multiple tuberculosis of the spine combined with severe kyphosis.

Case Summary: A 56-year-old male patient presented with low back pain with numbness and fatigue in both lower extremities for 5 months. Chest and back showed intermittent acid pain. The patient had not a history of constitutional symptoms. Preoperative X-ray and CT examination revealed multiple vertebral segmental bone destruction, multiple abscess calcification, and severe kyphosis. Preoperative MRI examination showed that the tuberculous abscess broke through the spinal canal and compressed the spinal cord and nerve roots. The patient underwent posterior lumbar abscess debridement, expanded decompression of the spinal canal, and nerve lysis in our hospital. The operation time was 70 min, and the intraoperative blood loss was 200 ml. The postoperative drainage volume was 250 ml. The patient was hospitalized for a total of 13 days, and the patient's vital signs were stable before and after surgery. The patient was satisfied with the treatment.

Conclusion: For the patient with multiple spinal tuberculosis complicated with severe kyphosis and multiple calcified abscesses in this study, we considered performing abscess debridement to relieve the symptoms of back pain and achieved good clinical efficacy.

Keywords: spinal tuberculosis, abscess, debridement, orthopedic, kyphosis

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INTRODUCTION

According to the Global Tuberculosis Report 2020, global TB in China accounted for 8.4% (1). Spinal tuberculosis is the most common form of extrapulmonary tuberculosis (2). Although patients with spinal tuberculosis usually have chest and back pain (3), scoliosis is also common (4, 5). Scoliosis due to spinal tuberculosis is usually associated with cumulative sagittal and coronal plane imbalance (4). Thoracolumbar kyphosis could be surgically treated with a 66% corrective effect (6). The effect of sagittal correction was still the same after a long follow-up (7). However, for patients with severe scoliosis, the incidence of the failure rate of internal fixation was 7.15% (8). Whether patients with severe kyphosis caused by spinal tuberculosis should be treated with orthopedic surgery is still worthy of further consideration.

Although abscess debridement and orthopedic surgery for patients with spinal tuberculosis combined with scoliosis had been reported in the literature, the kyphosis angle of tuberculous scoliosis was not more than 100° (9). In this study, we reported for the first time a patient with multiple spinal tuberculosis complicated with severe kyphosis and multiple calcified abscesses underwent abscess debridement.

CASE PRESENTATION

A 56-year-old male patient presented with low back pain with numbness and fatigue in both lower extremities for 5 months. Chest and back showed intermittent acid pain. The patient had radiating pain in both lower extremities. The patient's visual analog scale (VAS) for back pain was as high as 9 points. The Oswestry disability index (ODI) of patient quality of life was 78 points. The patient's neurological status was diagnosed as grade C on the American Spinal Injury Association (ASIA) scale. The patient had not a history of constitutional symptoms, such as loss of appetite, night sweats, fever, or weight loss. In addition, the patient had no history of pulmonary tuberculosis and AIDS. The patient's spinal tuberculosis was initially diagnosed through clinical symptoms, imaging examinations and anti-tuberculosis treatment. The patient agreed to be admitted for further treatment to undergo surgery. Patient was routinely prescribed anti-tuberculosis therapy with drugs including isoniazid, rifampicin, ethambutol, and pyrazinamide for 3–4 weeks prior to surgery. The patient underwent electrocardiogram and echocardiography to assess cardiac function, and lung function was assessed according to lung CT and pulmonary function tests.

Physical Check

The physiological curvature of the cervical spine was straightened. Thoracic vertebra presents kyphosis deformity, with the 10th thoracic spinous process as the apex of backward deformity, local tenderness, and local percussion pain. The physiological curvature of the lumbar spine disappeared and the lumbar spine presented kyphosis deformity, with tenderness and percussion pain in lumbar 2,3,4 spinous processes. The patient had no sensory impairment. The muscle strength of the left lower limb was grade III, and the muscle strength of the right lower limb was normal. There was no abnormality in the examination of extremities muscle tension. The right knee reflex is hyperactive and the left is normal. The left Achilles tendon reflex was weakened and the right side was normal. Tomas's sign was positive. Hoffmann sign was negative, as well as Babinsky sign, Chaddock sign, Oppenheim sign, Gordon sign, patellar clonus, and condyle clonus.

Laboratory Examination

A blood test was performed after admission (**Table 1**). Blood routine: white blood cells 5.84*10^9/L, hemoglobin 145.8 g/L, platelet count 244.9*10^9/L. Inflammatory markers were examined, C-reactive protein <10.00 mg/L, erythrocyte sedimentation rate 8 mm. Liver function examination showed aspartate aminotransferase 48 U/L, alanine aminotransferase 47 U/L, albumin 42.1 g/L. Renal function examination showed urea 5.66 mmol/L, creatinine 73 μmol/L, and uric acid 294 μmol/L. Tumor markers test results showed CA199 18.08 U/ml, CA193 19.75 U/ml, CA125 9.87 U/ml, AFP 1.68 ng/ml and CEA 1.5 ng/ml.

TABLE 1 | A blood test was performed in our hospital.

Blood project	Measured value
White blood cells (*10^9/L)	5.84
Hemoglobin (g/L)	145.80
Platelet (*10^9/L)	244.90
C-reactive protein (mg/L)	<10
Erythrocyte sedimentation rate (mm)	8.00
Aspartate aminotransferase (U/L)	48.00
Alanine aminotransferase (U/L)	47.00
Albumin (g/L)	42.10
Urea (mmol/L)	5.66
Creatinine (μmol/L)	73.00
Uric acid (μmol/L)	294.00
CA199 (U/ml)	18.08
CA193 (U/ml)	19.75
CA125 (U/ml)	9.87
AFP (ng/ml)	1.68
CEA (ng/ml)	1.50

Imaging Examination

All the imaging data of the patients were taken in our hospital. Preoperative Cobb angle could not be measured from the X-ray coronal sequence due to interference with calcified abscesses (**Figure 1A**). The kyphosis angle was measured at 117.3° from the X-ray sagittal sequence (**Figure 1B**). Pelvic parameters were measured as follows, SS 38.7°, PT32.8°, PI71.5° (**Figure 1B**). Chest radiographs showed no obvious lung abnormalities (**Figure 1C**). Pathological examination results showed caseous necrosis and inflammatory fibrous tissue (**Figures 1D,E**). Combined with clinical data, it was consistent with spinal tuberculosis. CT scan revealed calcification of the abscess and destruction of the vertebral body in various locations (**Figures 1F–Q**). MRI showed many calcified abscesses in the sagittal plane, coronal plane, and cross-section (**Figure 2**).

Surgical Procedures

After successful anesthesia, the patient was placed in the prone position, with routine skin disinfection and towel laying. The posterior median longitudinal incision was made with the lumbar spinous process as the center. The skin, subcutaneous fascia, and ligaments were cut layer by layer, The

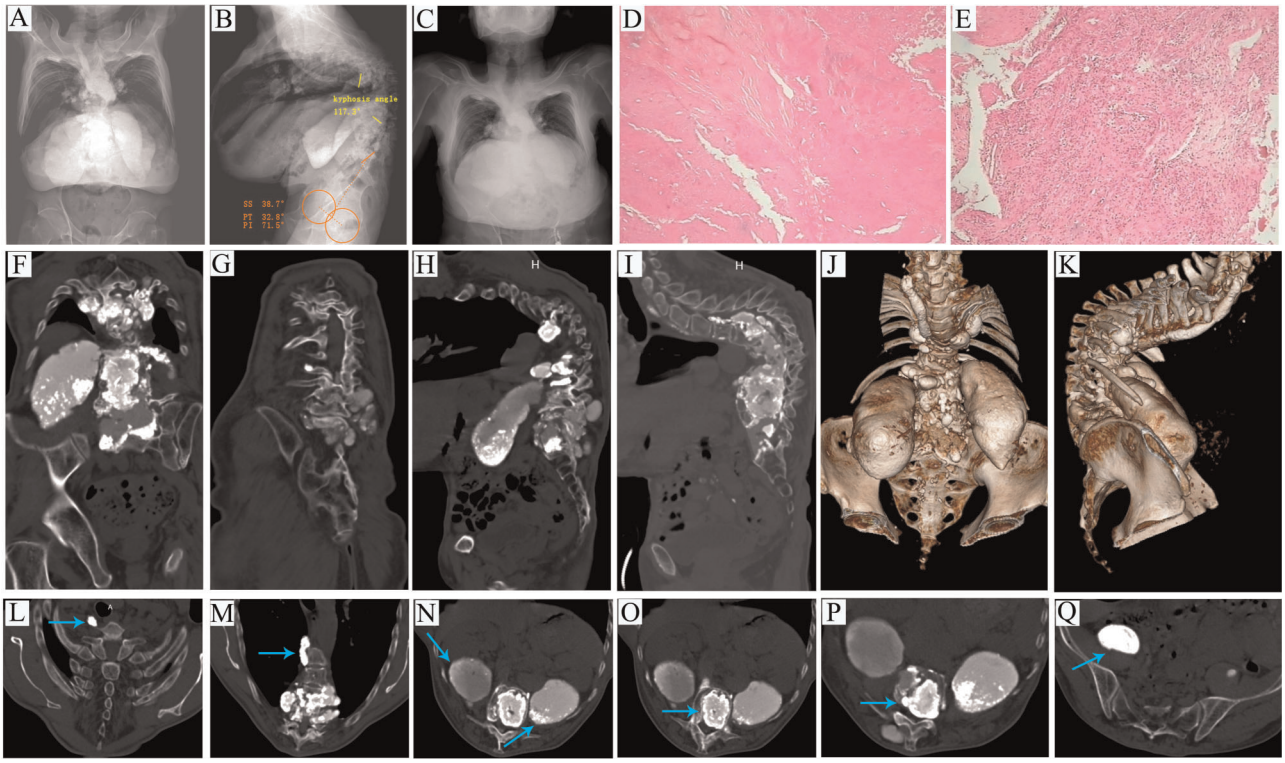

FIGURE 1 | (**A–C**) Preoperative X-ray examination. (**A**) Coronal Cobb angle cannot be measured due to interference with multiple calcified abscesses. (**B**) The kyphosis angle was measured at 117.3° in the sagittal plane. Pelvic parameters were measured as follows, SS 38.7°, PT32.8°, PI71.5°. (**C**) Chest radiographs showed no obvious lung abnormalities. (**D** and **E**) Postoperative pathological examination. (**D**) This image shows caseous necrosis. (**E**) This image shows inflammatory fibrous tissue. (**F–Q**) Preoperative CT examination. (**F**), Multiple calcified abscesses in the coronal plane. (**G**) Bone destruction in the coronal plane. (**H**) Multiple calcified abscesses in the sagittal plane. (**I**) Bone destruction in the sagittal plane. (**J**) CT 3D reconstruction in the coronal plane. (**K**) CT 3D reconstruction in the sagittal plane. (**L**) The arrow points to a cervical paravertebral calcified abscess in the cross-section. (**M**) The arrow points to a thoracic paraspinal calcified abscess in the cross-section. (**N**) The arrow points to bilateral psoas calcified abscess in the cross-section. (**O**) The arrow points to the vertebral calcified abscess in the cross-section. (**P**) The arrow points to the intervertebral calcified abscess in the cross-section. (**Q**) The arrow points to the pelvic calcified abscess in the cross-section.

paravertebral muscles were removed along the spinous process and the lamina. A hemilamina retractor was placed to retract the muscles. After full exposure of the operating field, the spinous process of the lumbar 2–3 vertebral body and simultaneous lumbar 2–3 level laminectomy was performed. The ligament flavum and the dura mater were incised to expose the caseous abscess in the spinal canal, and the caseous necrotic tissue was completely removed. Spinal cord compression and nerve root adhesion were relieved during the operation. After the wound was thoroughly rinsed and no active bleeding was detected, streptomycin powder was placed around the lesion. After placing the drainage tube, the incision was sutured layer by layer, and the operation was finished.

RESULTS

The patient underwent posterior lumbar abscess debridement, expanded decompression of the spinal canal, and nerve lysis under general anesthesia in our hospital. Patients and their families refuse to perform internal fixation implantation reconstruction orthopaedics because they could not afford huge economic and surgical risks. The operation time was 70 min, and the intraoperative blood loss was 200 ml. The patient returned to the ward after surgery. The postoperative drainage volume was 250 ml. There was no redness and swelling in the incision of the back, and no obvious flushing and swelling of the surrounding skin. The patient continued anti-tuberculosis treatment postoperatively, including isoniazid, rifampicin, ethambutol, and pyrazinamide. During postoperative follow-up, the patient's condition improved and anti-tuberculosis treatment was effective. Multiple drug resistance was not observed. The patient was hospitalized for a total of 13 days, and the patient's vital signs were stable before and after surgery (**Figure 3**). The patient was discharged from the hospital 8 days after surgery with no obvious low back pain, and the numbness and fatigue of both lower limbs were significantly relieved compared with that before surgery. The

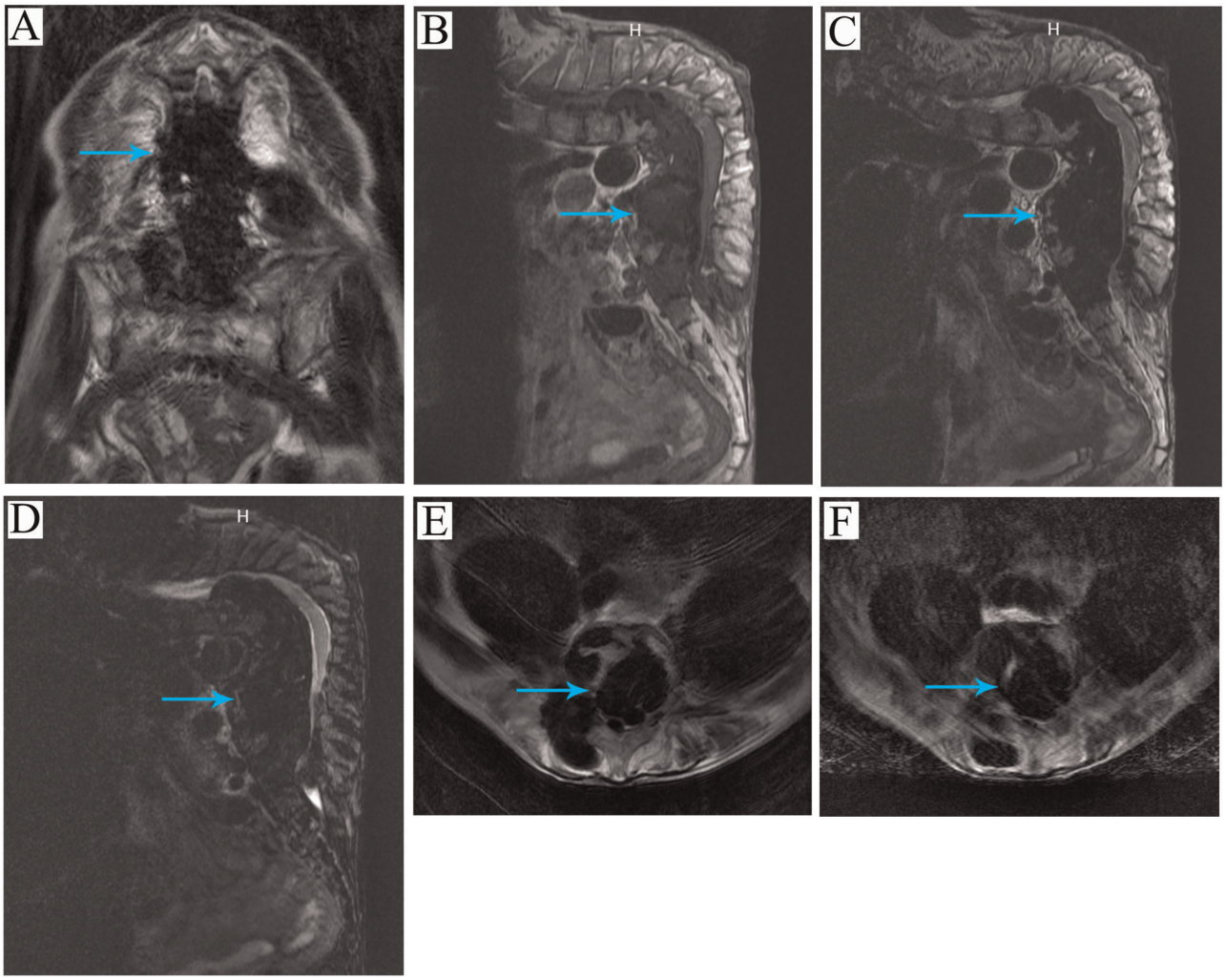

FIGURE 2 | Preoperative MRI examination. (**A**) The arrow points to the calcified abscess in the T1 coronal sequence. (**B**) The arrow points to the calcified abscess in the T1 sagittal sequence. (**C**) The arrow points to the calcified abscess in the T2 sagittal sequence. (**D**) The arrow points to the calcified abscess in the T2 lipid pressing sagittal sequence. (**E**) The arrow points to the calcified abscess in the T2 lipid pressing cross-section sequence. (**F**) The arrow points to the calcified abscess in the T2 cross-section sequence.

patient was satisfied with the treatment. We did not find any recurrence of spinal tuberculosis in our follow-up for up to 2 years after surgery. The patients were satisfied with the treatment effect.

DISCUSSION

Tuberculosis placed a huge burden on developing countries (1). Spinal tuberculosis usually presents as back pain, but in severe cases, it also caused neurological impairment (5, 10). In this case, treatment of the patient usually required surgical intervention (11). Anterior or posterior approach treatment of lumbar tuberculosis could achieve satisfaction. In this study, the patient's severe kyphosis was considered unsuitable for a long operation. We considered posterior approach surgery to reduce operative time and intraoperative blood loss, which was consistent with the advantages of posterior approach surgery reported in the literature (11).

Spinal tuberculosis destroyed the vertebrae severely and was usually accompanied by kyphosis, which caused the severe imbalance of the spine in the sagittal plane (12). The kyphosis deformity angle reached 47.7° and could be treated surgically (12). Although Alexander et al. studied 42 patients with spinal tuberculosis and kyphosis who underwent surgical treatment for kyphosis improvement, the mean kyphosis angle did not exceed 50° (49.2° ± 14.3° in average) (13). However, when the kyphosis angle was more than 80°, long-term follow-up is needed to determine whether surgery could improve sagittal plane balance and lung function (14).

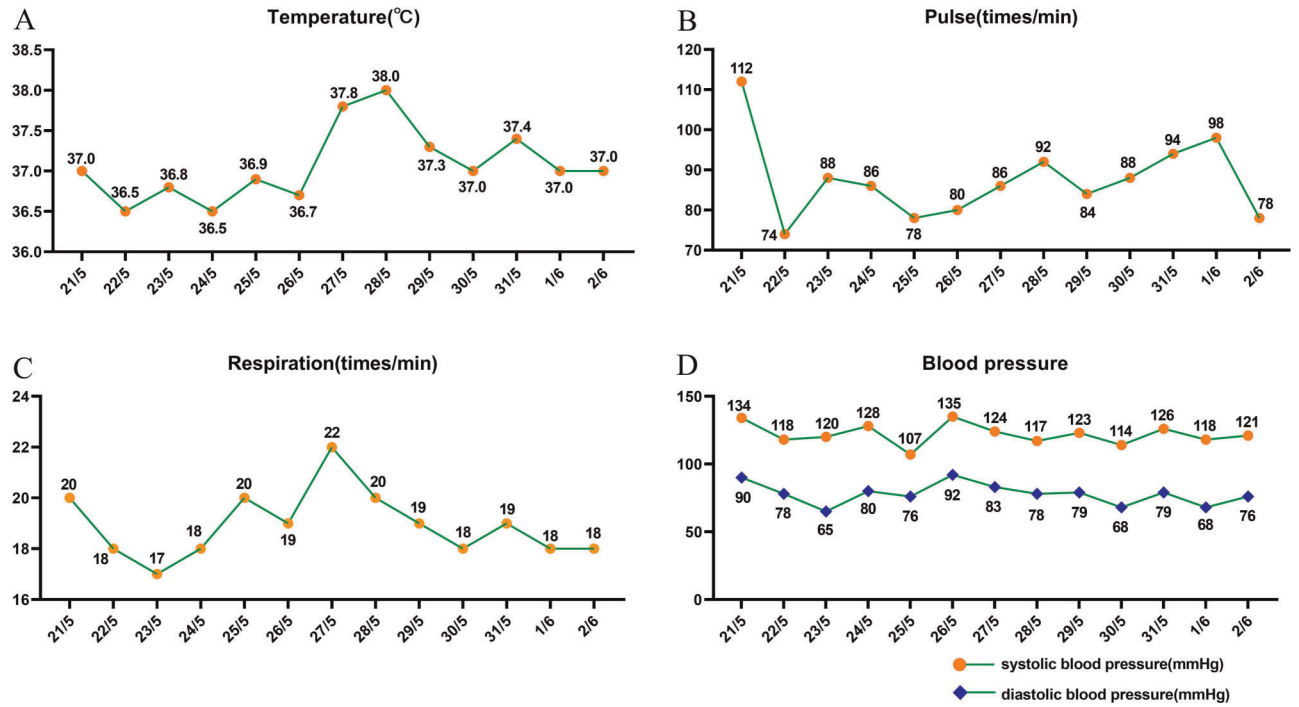

FIGURE 3 | Patient's vital signs were measured daily in the hospital. (**A**) The results of temperature examination. (**B**) The results of pulse examination. (**C**) The results of respiration examination. (**D**) The results of blood pressure examination.

Although Wong et al.'s 34-year follow-up study recommended early surgical intervention, Frankel grades worsened in 3 patients and did not improve in 5 patients after surgery in 16 patients (15). In this study, the kyphosis angle of the patient was as high as 117.3°, and due to patient refusal of kyphosis orthopaedic surgery, we did not perform orthopedic surgery. For patients with severe kyphosis (kyphosis angle 92.5°), the outcome of orthopedic surgery treatment was satisfactory after halo traction for 3–7 weeks (16). In this study, the patient's tuberculosis foci compressed the spinal cord and nerves, requiring timely surgery to relieve the compression. Halo traction was not available, and the patient did not agree to perform orthopedic surgery due to economic considerations. we did not consider orthopedic surgery, which was consistent with the treatment methods reported before (17).

In addition to the symptoms of tuberculosis poisoning, the common manifestation of spinal tuberculosis was a paraspinal abscess, which damaged the vertebral body and aggravated kyphosis deformity, and even damaged the neurological function (18). Abscess debridement and nerve decompression was an effective treatment for patients' back pain (19). Recent literature had reported that abscess drainage could also achieve good clinical outcomes (20, 21). In this paper, the patient had multiple abscess calcification, so drainage was not suitable for this case. Routine abscess debridement surgery achieved the same clinical effect (11). The case of bilateral calcified psoas abscess was rarely reported in the literature (17). However, bilateral calcified psoas abscess combined with multiple calcified abscesses in the cervical spine, thoracic spine, lumbar spine, and the pelvic cavity was reported for the first time in this paper.

The patient underwent posterior lumbar abscess debridement, expanded decompression of the spinal canal, and nerve lysis in our hospital. The operation time was short and the amount of blood loss was less. Postoperative vital signs were stable and there were no operative complications. This paper had reported for the first time a case of multiple spinal tuberculosis with severe kyphosis and multiple calcified abscesses involving the cervical spine, thoracic spine, lumbar spine, bilateral psoas major muscle, and pelvic cavity. The patient was satisfied with the treatment.

However, there were some limitations in the article. The article was a single case report, and the treatment effect need to be verified by multiple cases.

CONCLUSION

For the patient with multiple spinal tuberculosis complicated with severe kyphosis and multiple calcified abscesses in this study, we considered performing abscess debridement to relieve the symptoms of back pain and achieved good clinical efficacy. Whether orthopedic surgery was necessary for such a patient should be fully considered.

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 Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LyC wrote the article and prepared **Figures 1–3** and **Table 1**. CL, this author contributed equally to this work and should be considered co-first authors. All authors reviewed the article and All authors have read and approved the manuscript.

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Spinous Process Combined With a Titanium Mesh Cage as a Bone Graft in the Stability Reconstruction of Lumbar or Lumbosacral Spinal Tuberculosis

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Background: Autogenous bone grafts, such as iliac bone or rib struts, have been used in the anterior reconstruction of spinal tuberculosis (STB) and have their own benefits and limitations. Here, we introduced a new method, the spinous process (SP), combined with a titanium mesh cage (TMC) as a bone graft in the stability reconstruction of lumbar or lumbosacral STBs. By retrospectively comparing patients who received SP+TMC to traditional TMC bone grafts or allogeneic bone grafts in terms of safety, efficacy and cost-effectiveness, we aimed to evaluate whether SP+TMC could be a possible alternative method.

Methods: From 2010 to 2018, 69 patients who underwent one-stage posterior debridement with grafts and internal fixation within a single lumbar or lumbosacral segment were included in this study. Twelve patients who received SP combined with a TMC (SP+TMC, group A), 30 patients who received a TMC only (group B), and 27 patients who received allografts (group C) were included. Measurements including operative time, blood loss, length of hospital stay, visual analog scale (VAS) score, Oswestry Disability Index (ODI), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), American Spinal Injury Association Impairment (ASIA) grade, final follow-up (FFU) duration and postoperative complications were recorded. Radiological measurements, including the number of segments fixated, the number of pedicle screws used, the Cobb angle, pelvic parameters, and the bony fusion time, were reviewed. All outcomes were analyzed using SPSS 25.

Results: We found that the SP+TMC group had fewer fixation segments, fewer pedicle screws implanted, a shorter operative time, reduced blood loss, and a considerably lower hospital cost than allografts. In addition, the TMC group had a comparable clinical outcome with the TMC group regarding lower economic cost.

Conclusion: Our study demonstrates that compared to a TMC or allograft, the use of SP combined with a TMC as a bone graft is an effective and reliable approach for

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the surgical management of one-level lumbar or lumbosacral spinal tuberculosis, leading to effective restoration of spinal stability. Furthermore, this approach is a cost-effective structural bone grafting method, especially for patients in developing countries.

Keywords: titanium mesh cage, spinous process bone graft, spinal tuberculosis, posterior-only approach, intervertebral bone grafting

INTRODUCTION

Tuberculosis is a major health problem worldwide, with an estimated 10.0 million new cases each year (1). Bone tuberculosis is the most common type of extrapulmonary tuberculosis, and spine tuberculosis (STB) accounts for 50% of all bone tuberculosis cases, with no age or sex exempt from spinal TB (2). Among all spinal regions, the lumbar and lumbosacral segments support the majority of body weight and exhibit the greatest mobility, resulting in chronic damage and thus increasing susceptibility. Hence, the lumbar region is the most frequently affected site in 38.2–59.57% cases of STBs, while 8.0–8.48% cases of STBs involve lumbosacral segments (3, 4). As the onset of disease can be insidious and difficult to diagnose early, patients' initial symptoms can include minor back pain and the development of kyphotic deformities with/without neurological complications. With limited health care resources, a large number of patients from developing countries are seen for the first time at an advanced stage of disease (1). The kyphotic deformity ranges from mild knuckle-shaped deformation to angular or rounded kyphotic deformity. Paraplegia, the most dreaded complication, occurs in 10% to 30% of those patients (4).

Surgical treatment plays a key role in the management of patients with STB who present with spinal deformity, severe or progressive neurologic dysfunction, spinal instability, extensive paravertebral, and epidural abscess (5). With the introduction of the spinal pedicle screw system, a one-stage posterior approach has been increasingly adopted by surgeons to treat lumbar and lumbosacral STBs (6–8). However, the spinal pedicle screw system only provides temporary stability, with long-term stability primarily relying on bony fusion of the vertebral defect. At present, the most commonly used bone grafts for STB surgery are allogeneic bone grafts (allografts), autogenous iliac bone grafts, and titanium mesh cages (TMCs) filled with allogeneic or autogenous bone (9, 10), each of which has benefits and limitations. The autogenous iliac bone graft is considered the gold standard due to its high bone fusion rate, but it may result in additional surgical trauma and complications at the donor site (10, 11). Other autogenous bone methods, such as rib strut or spinous process (SP) and transverse process (TP) bone, have also been applied in one-level thoracic or lumbar tuberculosis (12–14). For surgery using the posterior approach, the SP is spontaneously exposed during this process, reducing operative time, bleeding, and trauma. Additionally, SP as an autogenous bone graft benefits osteogenesis, bone healing, bone conduction, and osteoinduction since it effectively fills the defect space. However, regarding structural strength and stability, the SP is not as effective as a TMC. Considering this, we decided to use SP combined with a TMC (filled with autogenous cancellous bone granules) for anterior reconstruction.

To date, no study has reported the use of SP combined with a TMC as a bone graft in the surgical treatment of lumbosacral STB. By retrospectively comparing patients who received SP+TMC to those who received traditional TMC bone grafts or allogeneic bone grafts in terms of safety and efficacy, we aimed to evaluate whether SP+TMC could be a possible alternative method for surgeons. Moreover, since patients in less developed areas are more likely to be affected by STB, individual hospital costs were also reviewed.

MATERIALS AND METHODS

Patients

Patients with lumbar and lumbosacral STB who were hospitalized and underwent one-stage posterior focus debridement, interbody graft, posterior instrumentation, and fusion surgery in our department from January 2010 to February 2018 were included in this study. The patients were required to meet all of the following inclusion criteria: (1) the level involved was limited from L1 to S1; (2) only one segment was involved, or multiple segments were involved, but only one level needed surgical intervention; (3) no evidence of extensive TB abscess was observed; (4) the focal tissue was expected to be completely debrided via the posterior approach only; and (5) syndromes including spinal instability, vertebral collapse, kyphosis deformity, bone destruction, spinal cord compression, or progressive neurological impairment were observed. Patients presenting with any of the following conditions were excluded: (1) multilevel lesions needing surgical intervention; (2) deep multiple cold abscesses or an abscess that was primarily localized in the anterior column, which might be beyond the ability of debridement via the posterior approach; (3) other types of spinal disease or a history of spine surgery; and (4) active TB or other contraindications. This study was approved by our hospital and was conducted following the Declaration of Helsinki. All participants signed the informed consent. The benefits and limitations of each method were fully explained to the patients and their relatives before surgery to allow the patients to decide their preferred method of treatment.

Preoperative Management

All patients enrolled in this study received routine anti-tuberculosis chemotherapy (HREZ4) for 2–4 weeks. Supportive nutritional therapy was administered to rectify hypoproteinaemia and anemia. Related indexes, such as ESR and CRP, were closely monitored. In all patients, ESR was strictly controlled below 40 mm/h, except for

one patient who experienced progressive paralysis during presurgical chemotherapy.

Surgical Procedure

The patients were in the prone position after administration of general endotracheal anesthesia. A midline incision was made to expose posterior spinal elements of vertebrae that were 1–2 levels superior and inferior to the infected segment. After locating the infected vertebrae using C-arm fluoroscopy, the entire SP was cut off using spinal scissors and then preserved in clean wet gauze for future use. Posterior pedicle screws were allowed to be used in the affected vertebrae when necessary. A temporary rod on the mild side of the focus was installed to stabilize the spine. Unilateral facetectomy and a laminectomy were performed on the focal side. The nerve root and the dura mater were pulled to expose the infected intervertebral space under the protection of the nerve root retractor. Debridement was performed via a posterolateral approach to vertically remove the collapsed vertebrae and necrotic intervertebral disk. Focal lesions were removed under direct visualization, while contralateral lesions were scraped until the surface of the sclerotic bone turned into bleeding subhealthy bone tissue using a long curette at multiple

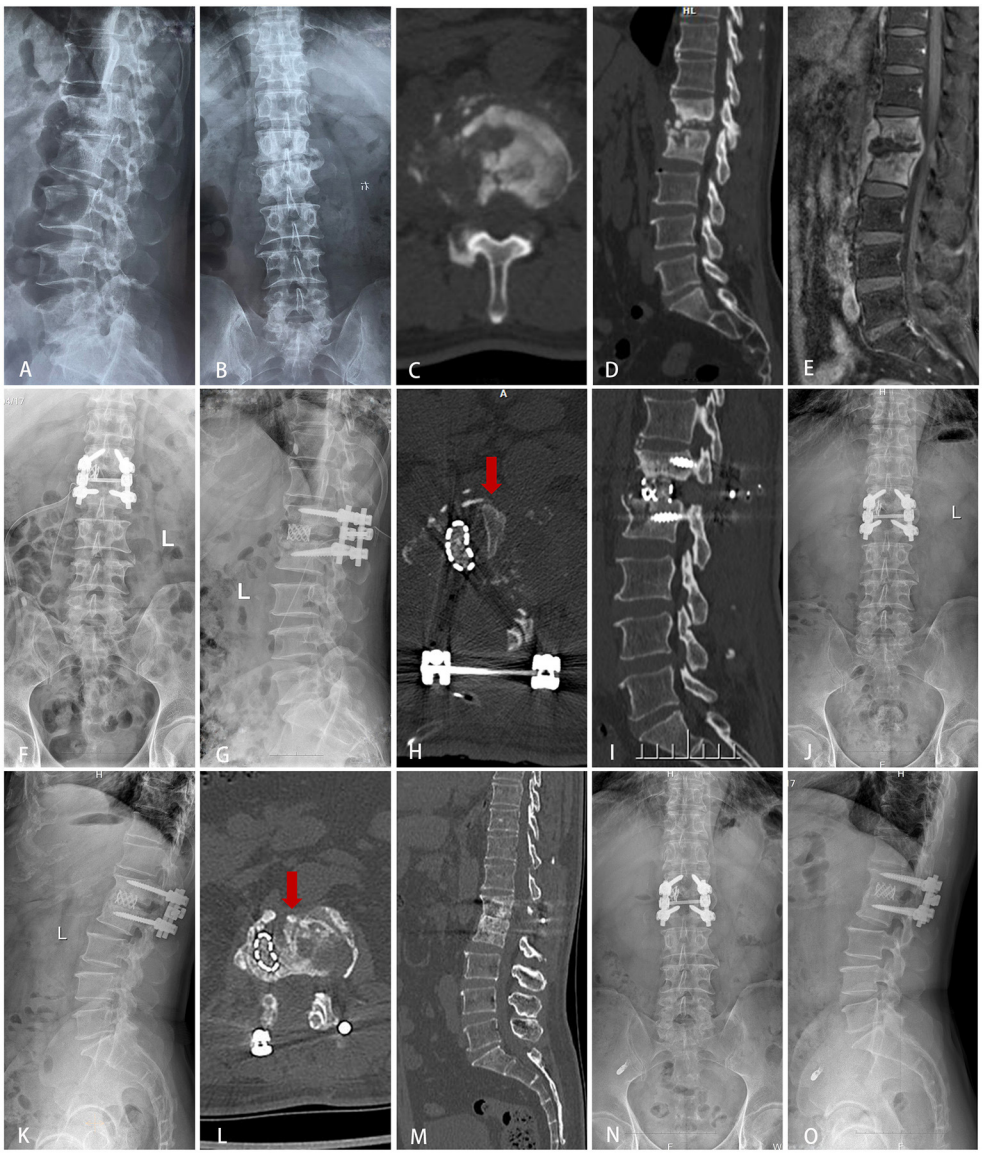

FIGURE 1 | Typical cases of group A (SP+TMC bone graft). A 63-year-old male was diagnosed with tuberculous spondylitis after an eight-month history of severe back pain. The infection had been resistant to chemotherapy for 4 months. **(A–E)** Preoperative X-ray, MRI and CT showed that the lesion around the vertebral body of L1/2 developed an abscess with marked bony destruction. The abscess involved in the spinal canal with cord compromise resulted in neurologic deficits. **(F–J)** Postoperative X-ray and CT showed complete resolution of the epidural abscess and decompression of the neural component. Interbody grafts using titanium mesh cages and spinous processes were placed satisfactorily. **(K–O)** Final follow-up (2 years) radiographs showed good bone fusion.

angles. A suitable flush tube was plunged in to wash the cavity with hydrogen peroxide and saline. For patients treated with TMC+SP, we suitably trimmed the TMC and SP depending on the remaining space before implantation; typically, we first implanted the shared SP followed by the TMC. For patients treated with TMCs, one or more TMCs were appropriately trimmed and then implanted according to the space of the bone graft area. Similarly, for patients treated with allografts, the surgeon will shape the allogeneic iliac bones according to the size of the bone graft area and then implant them. The titanium rod was tightened with proper pressure, and the TMC and SP were confirmed to be in good position. Streptomycin and isoniazid were locally administered. The vertebral lamina and the small joints were reconstructed afterwards. A drainage tube was placed heading to the specially formed TMC. The incision was closed by layer.

Postoperative Care

The drainage tube was removed when the volume of drainage was <20 ml per day. Anti-TB therapy was continued for 12-18 months. ESR, CRP, and liver function were followed up each month, while X-rays and CT were performed to

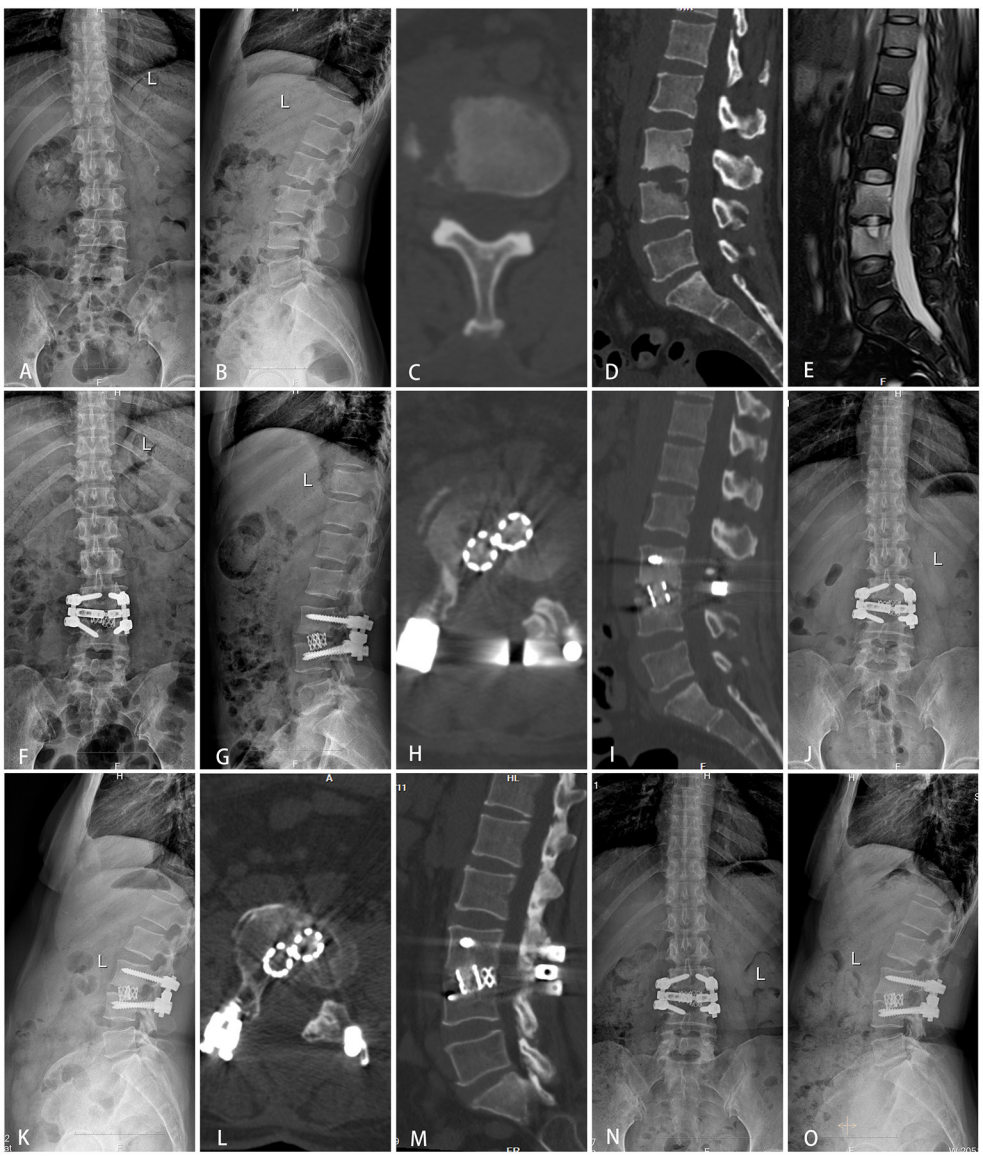

FIGURE 2 | Typical cases of group B (TMC bone graft). A 49-year-old female was diagnosed with tuberculous spondylitis after a six-month history of low back pain. The infection had been resistant to chemotherapy for 1 month. **(A–E)** Preoperative X-ray, MRI and CT showed that the lesion around the vertebral body of L3/4 developed an abscess with marked bony destruction. **(F–I)** Postoperative X-ray and CT showed complete resolution of the epidural abscess and decompression of the neural component. Interbody grafts using two titanium mesh cages were placed satisfactorily. **(J–M)** One year follow-up showed good bone fusion. **(N,O)** Final follow-up (2 years) radiographs showed good bone fusion and no obvious displacement or subsidence of the titanium mesh cage.

evaluate spinal status. Postoperative rehabilitation guidance was performed 1 week after surgery. Patient follow-up (FU) was recommended at 3 months, 6 months, 1 year, and then annually after surgery.

Outcome Assessment

Demographic Data

The following demographic data were collected from each patient: age, sex, residence, occupation, annual individual income in USD, and infected spinal level.

Clinical Assessments

For all patients, the following indexes were recorded at each timepoint (preoperative, before discharge, and at FFU): patient residence and income, average operation time, blood loss, hospital stay and cost, VAS score, ODI, ASIA grade, ESR and CRP.

Radiological Assessments

(1) Fixation segment: fusion of one disc is considered to be one fixation segment; (2) number of pedicle screws; (3) Cobb angle in the sagittal plane: the angle between the upper endplate and the

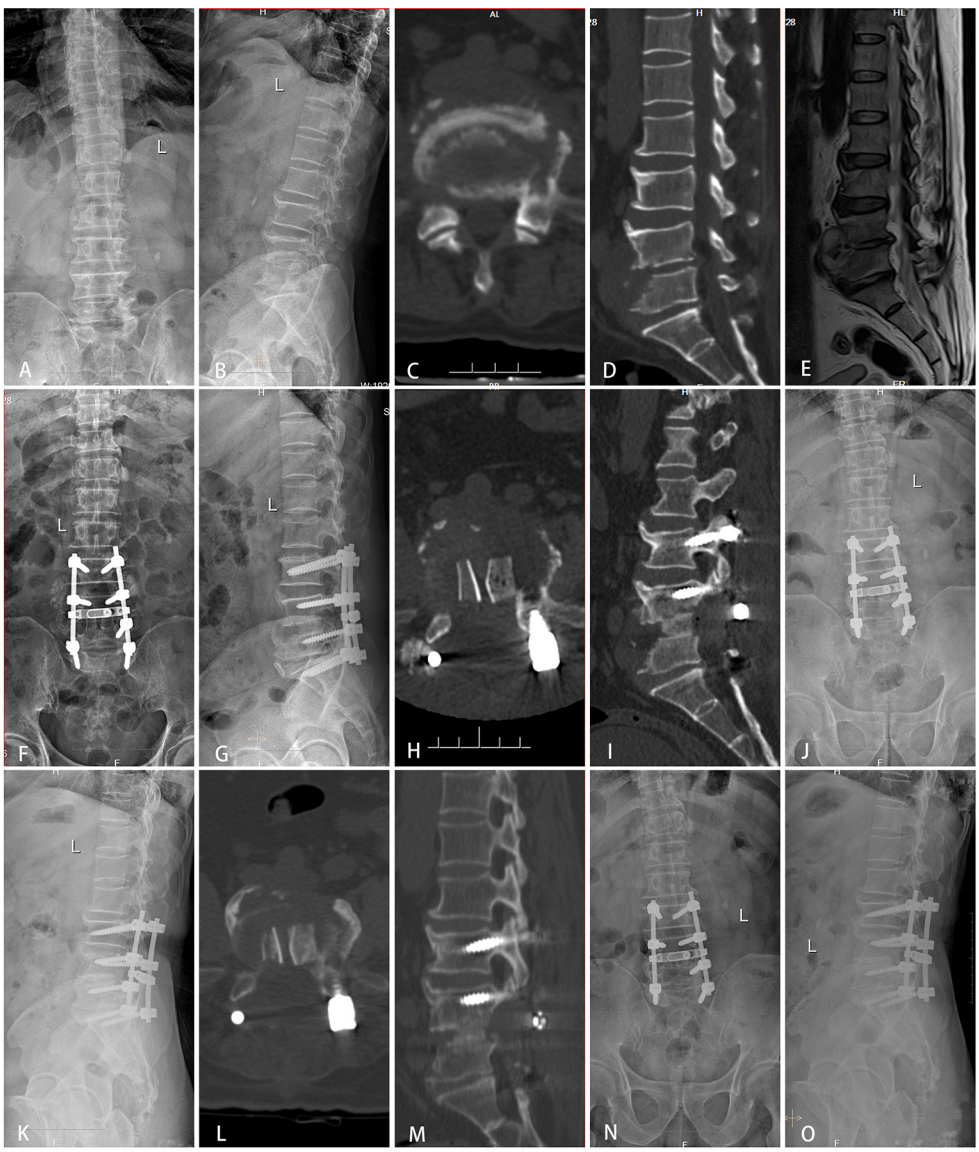

FIGURE 3 | Typical cases of group C (allogeneic bone graft). A 55-year-old male was diagnosed with tuberculous spondylitis after a one-year history of severe low back pain. The infection had been resistant to chemotherapy for 3 months. **(A–E)** Preoperative X-ray, MRI and CT showed that the lesion around the vertebral body of L4/5 developed an abscess with marked bony destruction. **(F–I)** Postoperative X-ray and CT showed complete resolution of the epidural abscess and decompression of the neural component. Interbody grafts using two allogeneic bones were placed satisfactorily. **(J–M)** One-year follow-up showed good bone fusion. **(N,O)** Final follow-up (3 years) radiographs showed good bone fusion and no obvious bone absorption or fractures.

TABLE 1 | Demographics of study populations.

Clinical features	Group A ($n = 12$)	Group B ($n = 30$)	Group C ($n = 27$)	*P* value	
Age (yr.)	48.52 ± 14.32	50.4 ± 13.20	46.67 ± 15.06	0.62	$P_{AB} = 0.52$ $P_{AC} = 0.84$ $P_{BC} = 0.33$
Male sex (no. [%])	6 (50%)	15 (50%)	17 (63%)	0.51	$P_{AB} = 0.87$ $P_{AC} = 0.29$ $P_{BC} = 0.33$
Residence (no. [%])					
Rural	9 (75%)	22 (74%)	21 (78%)		
Urban	3 (25%)	8 (26%)	6 (22%)	0.87	
Occupation					
Farmer	6 (50%)	16 (53%)	15 (56%)		
Worker	2 (17%)	6 (20%)	5 (18%)		
Student	1 (8%)	3 (10%)	3 (11%)		
Others	3 (25%)	5 (17%)	4 (15%)	1	
Annual individual income (US)					
<$2000	1(8%)	5 (17%)	5 (18%)		
$2,000–$4,999	9 (75%)	21 (70%)	18 (67%)		
≥$5,000	2 (17%)	4 (13%)	4 (15%)	0.98	
Hospital cost (US)	$14,710.42 ± 2,354.55	$16,680.23 ± 3,614.73	$19,260.34 ± 33,100.75	0.00	$P_{AB} = 0.03$ $P_{AC} < 0.01$ $P_{BC} < 0.01$
Hospital stays (day)	24.71 ± 8.85	26.20 ± 5.95	26.89 ± 5.31	0.54	$P_{AB} = 0.48$ $P_{AC} = 0.30$ $P_{BC} = 0.65$
Duration of follow-up (months)	35.29 ± 6.69	34.57 ± 6.65	35.15 ± 6.46	0.92	$P_{AB} = 0.71$ $P_{AC} = 0.94$ $P_{BC} = 0.74$

inferior endplate of the lesion vertebral body in the sagittal lane is defined as the Cobb angle in our study; (4) pelvic parameters: pelvic tilt (PT), pelvic incidence (PI), sacral slope (SS), lumbar lordosis (LL), and PI-LL; (5) bone grafting fusion: bone graft fusion was assessed using the radiologic criteria reported by Bridwell et al. (15).

Statistical Analysis

The results were recorded and analyzed using SPSS software version 25.0 (SPSS Inc., Chicago, IL). Quantitative data are expressed as the mean ± standard deviation. ANOVA was used for intergroup comparisons of quantitative data, and paired *t* tests were used for intragroup comparisons. The chi-square test was performed for intergroup comparisons of nonnormally distributed qualitative data. For normally distributed qualitative data, the Wilcoxon rank sum test and Mann–Whitney rank sum test were used (intragroup and intergroup, respectively). $P < 0.05$ was considered a significant difference.

RESULTS

A total of 69 patients were divided into three groups: group A (TMC+SP bone graft: 12 patients, **Figure 1**), group B (TMC bone graft: 30 patients, **Figure 2**) and group C (allogeneic bone graft: 27 patients, **Figure 3**). The mean follow-up times were 35.29 ± 6.69 months, 34.57 ± 6.65 months and 35.1 ± 6.46 months, respectively ($p = 0.92$). No significant differences were observed in sex ($p = 0.57$), age ($p = 0.58$), ODI ($p = 0.87$), ODI-FFU ($p = 0.80$), VAS score ($p = 0.72$), VAS-FFU ($p = 0.78$), or hospital stay ($p = 0.54$) (**Tables 1**, **2**). No significant difference in ESR or CRP was found at any time point (**Supplementary Table 1**). A total of 74–78% of patients were from rural areas, while 67–74% of patients were farmers and workers. Regarding income, 87–92% of patients had an annual individual income <$5,000 (**Table 1**).

Regarding the number of fixation segments and pedicle screws, both groups A and B had significantly fewer fixation segments and pedicle screws than group C ($p < 0.001$), while no significant difference was found between groups A and B ($p > 0.01$, **Table 2**). Consequently, the hospital costs of group A and group B were lower than that of group C ($14,710.42 ± 2,354.55 vs. $16,680.23 ± 3,614.73 vs. $19,260.34 ± 3,310.75, $p < 0.01$; $P_{AC} < 0.01$ $P_{BC} < 0.01$, respectively, **Table 1**). There was a significant difference in hospital cost between groups A and B ($P_{AB} = 0.03$). In terms of operative time, a significant difference was observed among all three groups ($p = 0.02$), with group A (166.43 ± 44.11 min) having a shorter operative time than group C (205.93 ± 51.73 min, $p < 0.01$). There was no significant difference between groups A and B ($p = 0.1$) or between groups B and C ($p = 0.19$) (**Table 1**). There was a significant difference in blood loss among the three groups (543.81 ± 230.81 ml vs. 584.00 ± 229.06 ml vs. 803.70 ± 446.78 ml; $p = 0.01$, $P_{AB} = 066$. $P_{AC} < 0.01$ $P_{BC} = 0.01$) (**Table 1**).

No significant difference was observed in the preoperative, postoperative, or final follow-up Cobb angles among groups A, B, and C ($p = 0.99$, 0.71 and 0.99). Moreover, there was no significant difference in Cobb angle correction or loss among the three groups ($p = 0.88$ and 0.98). The pelvic parameters (PT, PI, SS) of the three groups were not significantly different at any time point (**Supplementary Table 2**). The LL of the three groups was not significantly different at the preoperative, postoperative, or final follow-up ($p = 0.94$, 0.78 and 0.81, respectively). In addition, the LL correction and loss among the three groups were not significantly different ($p = 0.68$ and 0.33, respectively). Similarly, the PI-LL of the three groups showed no significant difference in preoperative, postoperative, final follow-up or loss of correction parameters ($p = 0.38$, 0.19, 0.14 and 0.23, respectively). There

TABLE 2 | Clinical data of study populations.

Clinical features	Group A ($n = 12$)	Group B ($n = 30$)	Group C ($n = 27$)	p value	
Infected spinal level					
L1–2	2	3	4		
L2–3	3	7	3		
L3–4	2	5	6		
L4–5	4	9	10		
L5–S1	1	6	4		
Fixation Segment	1.67 ± 0.64	1.83 ± 0.90	2.81 ± 0.94	0.00	$P_{AB} = 0.47$ $P_{AC} < 0.01$ $P_{BC} < 0.01$
Number of pedicle screw	5.05 ± 1.29	5.53 ± 1.73	6.85 ± 1.37	0.00	$P_{AB} = 0.28$ $P_{AC} < 0.01$ $P_{BC} < 0.01$
ODI	0.75 ± 0.16	0.73 ± 0.12	0.73 ± 0.11	0.87	$P_{AB} = 0.62$ $P_{AC} = 0.69$ $P_{BC} = 0.89$
ODI-FFU	0.18 ± 0.05	0.19 ± 0.04	0.19 ± 0.06	0.80	$P_{AB} = 0.68$ $P_{AC} = 0.54$ $P_{BC} = 0.73$
VAS	7.05 ± 1.53	7.27 ± 1.46	6.96 ± 1.26	0.72	$P_{AB} = 0.61$ $P_{AC} = 0.83$ $P_{BC} = 0.41$
VAS-FFU	1.38 ± 0.84	1.53 ± 0.76	1.52 ± 0.79	0.78	$P_{AB} = 0.51$ $P_{AC} = 0.57$ $P_{BC} = 0.94$
Operation blood loss (ml)	543.81 ± 230.81	584.00 ± 229.06	803.70 ± 446.78	0.01	$P_{AB} = 066.$ $P_{AC} < 0.01$ $P_{BC} = 0.01$
Operation time (min)	166.43 ± 44.11	189.00 ± 41.64	205.93 ± 51.73	0.02	$P_{AB} = 0.1$ $P_{AC} < 0.01$ $P_{BC} = 0.19$
Duration of follow-up (months)	35.29 ± 6.69	34.57 ± 6.65	35.15 ± 6.46	0.92	$P_{AB} = 0.71$ $P_{AC} = 0.94$ $P_{BC} = 0.74$

FFU, Final follow-up.

TABLE 3 | The neurological function evaluated by the ASIA impairment scale.

ASIA scale	Group A ($N = 12$)	Group B ($N = 30$)	Group C ($N = 27$)	P value
	Pre	**Pre**	**Pre**	
A	0	0	0	0.883
B	0	0	0	
C	2	5	3	
D	4	12	10	
E	6	13	14	
	FFU	**FFU**	**FFU**	0.957
A	0	0	0	
B	0	0	0	
C	0	2	0	
D	2	3	2	
E	10	25	25	

Pre, Preoperation; FFU, Final follow-up.

TABLE 4 | Comparison of postoperative complications of study populations.

Complications	Group A ($N = 12$)	Group B ($N = 30$)	Group C ($N = 27$)	P value
Systemic complications				
Pulmonary infection	1	2	2	
Hepatic dysfunction	1	1	2	
Renal dysfunction	1	3	2	
Urinary tract infection	1	0	2	
Deep vein thrombosis	0	2	1	
Local complications				
Cerebrospinal fluid linkage	0	1	1	
Sinus formation	1	2	2	
TMC dislocation	0	2	0	
Bone graft absorbed	0	0	1	
Total	5	13	14	0.805

was no significant difference in bone graft fusion time among the three groups (8.90 ± 2.11 months vs. 8.60 ± 2.39 months vs. 9.59 ± 2.04 months, $p = 0.25$) (**Supplementary Table 2**).

With respect to neurological status, the ASIA grade showed no difference among the three groups before surgery ($p = 0.88$) or at the last follow-up ($p = 0.957$) (**Table 3**). As shown in **Table 4**, there were no significant postoperative complications among the three groups ($p = 0.81$), and all patients were cured after active treatment.

DISCUSSION

STB often causes damage in the anterior and middle column of the spine, leading to vertebral destruction, abscess formation, angular deformation, and neurological dysfunction (2). Surgical intervention plays an important role in lesion debridement, decompression, and spinal stability reconstruction, which is beneficial to treat STB and to prevent recurrence (16). Three main surgical approaches for treating lumbar TB exist: the anterior approach, posterior approach, and the posterior combined anterior approach. The anterior approach allows the surgeon to directly focus on implanting the bone graft; however, it has a disadvantage in correcting kyphosis and preventing correction loss (17). Considering this defect, the posterior combined anterior approach has been applied to enhance kyphosis correction and prevent correction loss and graft failure. However, this combined approach requires a longer operation time, greater surgical trauma, and longer recovery times (18). The posterior-only approach seems to be a better

choice, as numerous studies have reported that the posterior-only approach can safely and effectively achieve the same clinical results as the posterior combined anterior approach but with less trauma, lower cost, and fewer complications (19). However, lesions are mainly in the anterior and middle columns, which requires surgeons to perform lesion debridement and reconstruct spine stability (20).

According to the 3-column theory of Denis et al. (21), integrating the anterior column and the middle column is of key importance for the reconstruction of spinal stability. For interbody fusion in patients with tuberculosis spondylitis, autogenous iliac bone has long been considered the best method since it results in good osteogenesis, bone induction, bone conductibility, and biocompatibility (13). However, the preparation of autogenous iliac bone prolongs the operative time, increasing trauma and the risk of donor site complications. It has been reported that up to 40% of cases suffer from chronic pain and wound infection (22). There is also a risk of bone absorption (23). Allogeneic iliac bone may cause a mild chronic inflammatory reaction, which slows the formation and growth of blood vessels and interferes with osteoclast and osteoblast remodeling on the bone contact surface. The bone fusion time is relatively longer than that of autologous bone (24, 25). Previous studies reported that TMCs provide better structural support for kyphosis and intervertebral height correction than autogenous iliac bone, and they are immune to the degradative enzymes that reside in an infected environment. However, a TMC has a risk of subsiding or displacement, which is related to the contact area, bone strength, and surgery (26, 27). Recently, several authors have reported on the use of SP bone for the treatment of spinal infection (12, 13, 28). Zhong et al. (12) reviewed 35 cases treated with SP bone in one-level thoracic or lumbar tuberculosis and found that the mean bone fusion time was 12.90 ± 3.91 months. Tang (13) compared SP, transverse process (TP) and iliac bone grafts in single-segment thoracic tuberculosis, and the mean bone fusion times were 12.90 ± 3.91 months, 6.75 ± 1.55 months, and 5.52 ± 1.64 months, respectively. According to their reports, the use of the SP could be suitable for strutting the bone defect space, representing an additional choice for surgeons in segmental stability construction. However, because using a single SP as a bone graft conveys a risk of delayed bony fusion or even nonunion, the author suggested prolonged brace treatment.

In our study, we chose SP combined with a TMC for reconstruction of the anterior and middle columns of the spine. Usually, we first implant the shaped SP followed by the TMC (filled with autogenous cancellous bone granules). Finally, we tightened the titanium rod with proper pressure and confirmed that the TMC and SP were in good positions. Since this is the first report on one-level lumbar and lumbosacral STB treated with SP+TMC methods, we compared it to TMCs (group B) and allografts (group C) regarding three aspects: safety, efficacy, and cost-effectiveness.

Safety

There were 12 patients (group A, **Figure 1**) who underwent SP+TMC bone grafts with a significant improvement in the VAS score and ODI at the FFU, at which time CRP and ESR had returned to normal. All patients achieved bone fusion at a mean time of 8.90 ± 2.11 months, and all patients with neurological defects were improved at the FFU, indicating that the STB was cured. Moreover, there was no significant difference in postoperative complications compared to other groups. The above data indicate the safety of SP+TMC graft methods in lumbar and lumbosacral STB surgery.

Efficacy

Our study found that SP+TMC (group A) exhibited fewer fixation segments, fewer pedicle screw implants (5.05 ± 1.29 vs. 6.85 ± 1.37 $P_{AC} < 0.01$), shorter operation times (166.43 ± 44.11 min vs. 205.93 ± 51.73 min $P_{AC} < 0.01$), and reduced intraoperative blood loss (543.81 ± 230.81 ml vs. 803.70 ± 446.78 ml $P_{AC} < 0.01$) compared to the allograft (group C, **Figure 3**). The underlying reason for this phenomenon could be that because allogeneic iliac bone has a weaker osteoinduction ability, surgeons tend to choose a more stable fixation scheme, i.e., lengthening the fixed segment when using allogeneic iliac bone in bone fusion. The postoperative and FFU radiological assessments between the two groups showed no significant difference in Cobb angle or LL correction and maintenance, while the pelvic parameters and PI-LL showed no obvious sagittal imbalance in any group. Although there was no significant difference in bone graft fusion time among the three groups (8.90 ± 2.11 months vs. 8.60 ± 2.39 months vs. 9.59 ± 2.04 months, $p = 0.25$) (**Supplementary Table 2**), compared to previous reports, the SP+TMC group had a significantly shorter time of bone fusion than the SP-only group (12, 13). Moreover, the postoperative and follow-up data showed that the SP+TMC group achieved the same satisfying clinical results in relatively short segment fixation compared to the allograft group with long segment fusion.

Cost-Effectiveness

In the past 5 years, the global total budget for TB has continually increased, reaching $994 million USD in 2020, and the rapid increase in the TB budget has caused a heavy economic burden to society (1). The average annual disposable income per person is approximately $2,000 in rural and urban areas and $5,000 in our areas. In our study, 74%-78% of patients came from rural areas. Regarding careers, 67%-74% of patients were farmers and workers with insufficient health insurance. A total of 87%-92% of patients had an annual individual income of <$5,000. For these people, it is of great significance to reduce the cost of treatment on the premise of ensuring the safety and efficacy of the operation. Since the mean hospital cost was $14,710.42 ± 2,354.55 in group A, $16,680.23 ± 3,614.73 in group B (**Figure 2**), and $19,260.34 ± 33,100.75 in group C, there was a significant decrease in hospital cost in group A compared to groups B ($p = 0.03$) and C ($p < 0.01$). SP+TMC provides a method with high cost-effectiveness for patients in developing countries and areas. The reduction in cost is primarily due to the decrease in the fixation segment, the reduced number of pedicle screws and the use of allogeneic bone and titanium mesh cages.

From the above comparisons, we found that for single-segment lumbar and lumbosacral STBs, TMCs reduce the

fixed segments and achieve the same effect as long segment fixation combined with allogeneic bone grafts. Additionally, the combination of SP bone reduces the cost of hospitalization. The reasons for these observations could be as follows: (1) A TMC provides immediate stability, and its rigid characteristics can tolerate compression forces well. (2) A TMC can be tailored to fit the bone graft area, increasing the contact area and weight-bearing surfaces. (3) SP, as an autogenous bone graft, has advantages with respect to osteogenesis, bone healing, bone conduction, and osteoinduction. (4) SP is present in the surgical exposure area in the posterior approach, which can reduce time, bleeding, and trauma for allogeneic iliac bone. (5) The SP, a cortical bone, has improved structural integrity and can effectively fill the defect space.

The indications for SP combined with TMCs are as follows: (1) One segment needed surgical intervention, or multiple segments were involved, but only one level needed surgical intervention. (2) Spinous process bone was not contaminated by tuberculous abscesses. (3) There is no severe osteoporosis because it may lead to the deterioration of the bone strength of the spinous process and osteogenic ability.

Limitations of the Study

First, this study did not consider intra- or interobserver differences associated with bias. Second, the retrospective nature of the study and small sample size may have introduced bias.

CONCLUSION

Our study revealed that compared to TMC and allograft treatment, SP combined with a TMC as a bone graft may represent an effective and cost-effective approach for the surgical management of one-level lumbar or lumbosacral spinal TB, leading to the effective restoration of spinal stability. This approach is a reliable structural bone grafting method, especially for people living in developing countries or rural areas.

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 Medical Ethics Committee of Xiangya Hospital, Central South University (Ethical Code: 201703358). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HZ designed the study. LX and MT performed the data collection, statistical analysis, and data interpretation. GY contributed to manuscript writing. GY and LX contributed to patient enrolment and follow-up. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.818926/full#supplementary-material

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ORIGINAL RESEARCH
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Factors Associated with Postoperative Lipiduria and Hypoxemia in Patients Undergoing Surgery for Orthopedic Fractures

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We investigated factors associated with postoperative lipiduria and hypoxemia in patients undergoing surgery for orthopedic fractures. We enrolled patients who presented to our emergency department due to traumatic fractures between 2016 and 2017. We collected urine samples within 24 h after the patients had undergone surgery to determine the presence of lipiduria. Hypoxemia was defined as an SpO_2 <95% determined with a pulse oximeter during the hospitalization. Patients' anthropometric data, medical history, and laboratory test results were collected from the electronic medical record. Logistic regression analyses were used to determine the associations of clinical factors with postoperative lipiduria and hypoxemia with multivariate adjustments. A total of 144 patients were analyzed (mean age 51.3 ± 22.9 years, male 50.7%). Diabetes (odd ratio 3.684, 95% CI, 1.256–10.810, $p = 0.018$) and operation time (odd ratio 1.005, 95% CI, 1.000–1.009, $p = 0.029$) were independently associated with postoperative lipiduria, while age (odd ratio 1.034, 95% CI, 1.003–1.066, $p = 0.029$), body mass index (odd ratio 1.100, 95% CI, 1.007–1.203, $p = 0.035$), and operation time (odd ratio 1.005, 95% CI, 1.000–1.010, $p = 0.033$) were independently associated with postoperative hypoxemia. We identified several factors independently associated with postoperative lipiduria and hypoxemia in patients with fracture undergoing surgical intervention. Operation time was associated with both postoperative lipiduria and hypoxemia, and we recommend that patients with prolonged operation for fractures should be carefully monitored for clinical signs related to fat embolism syndrome.

Keywords: fracture, hypoxemia, lipiduria, orthopedics, surgery

INTRODUCTION

Fat embolism syndrome (FES) is a clinical condition that arises as a consequence of fat globules in the systemic circulation (1, 2). It usually developed after orthopedic trauma, such as long bone fractures (3, 4). The clinical presentations of FES may vary widely, while the diagnostic criteria remain ill-defined (5). This may result in a wide range of reported incidences of this serious

complication (4). The incidence of FES was found to be less than 1% in patients with orthopedic fractures (4, 5). Nevertheless, the rate could be as high as 30% in patients with multiple fractures (6, 7). Moreover, FES is associated with a high mortality rate (8), though its treatment is largely supportive.

The proposed pathophysiology of FES (5) includes endothelial injury followed by release of inflammatory cytokines and acute respiratory distress, hypoxemia, neurological deficit, thrombocytopenia and disseminated intravascular coagulation, all of which may contribute to detrimental outcomes. Currently, there is no established treatment for FES to improve its outcomes, and its care mainly involves supportive measures (5, 9). Early awareness of patients who are at risk for FES might be helpful. Unfortunately, the pathophysiologic mechanisms of FES have not been well-established (5).

Among the proposed diagnostic criteria of FES (5, 10), respiratory involvement (hypoxemia) is an important manifestation, which may result from endothelial injury and subsequent acute respiratory distress syndrome (5). Lipiduria (5) is another criterion for the diagnosis of FES that may be related to renal endothelial injury. Both lipiduria and hypoxemia are not well studied in patients with orthopedic fractures. As postoperative hypoxemia is not uncommon (11), we investigated factors associated with postoperative lipiduria and hypoxemia in patients undergoing surgery for orthopedic fractures in this study.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan (approval number: SF17001B). All patients provided written informed consent. We enrolled patients who presented to our emergency department due to traumatic fractures between 2016 and 2017. After initial assessment and preoperative preparation, these patients underwent surgical intervention for their fractures and were admitted. Patients' anthropometric data, medical history, and laboratory test results were collected from electronic medical records.

We collected urine samples within 24 h after the operation to determine the presence of lipiduria. Approximately 5 mL of urine sample was mixed with 5 mL diethyl ether (E Merck, D-6100 Darmstadt, F.R. Germany), and the mixture was centrifuged at 1,500 rpm for 2 min (**Figure 1**). We removed the upper layer of transparent fluid, and extracted the opaque layer for determination of lipiduria. Neutral fat stain solution was added to the samples, which were then examined using a microscope. **Figure 2** shows a sample with positive neutral fat stain.

SpO_2 <90% (~PaO_2 <60 mm Hg) (12) has been used to define FES (13). In this study, we defined hypoxemia as an SpO_2 <95% (14) determined with a pulse oximeter during the hospitalization. The monitoring of SpO_2 was accompanied with vital signs measurements (usually every 6–8 h). More frequent monitoring may be required, depending on the patients' clinical condition. Patients' renal function was determined using estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (15). Information about operation time, blood loss, and blood transfusion was recorded according to the operation notes.

The statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS version 22.0;

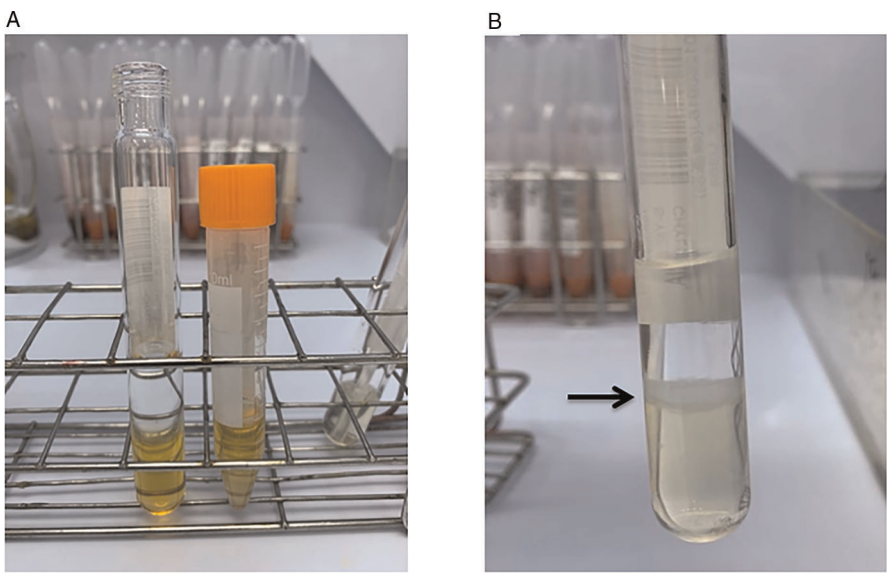

FIGURE 1 | (**A**) A urine sample before the experiment and (**B**) after mixing with 5mL diethyl ether (E Merck, D-6100 Darmstadt, F.R. Germany) and centrifugation at 1,500rpm for 2min. The black arrow indicates the opaque layer we extracted for determination of lipiduria.

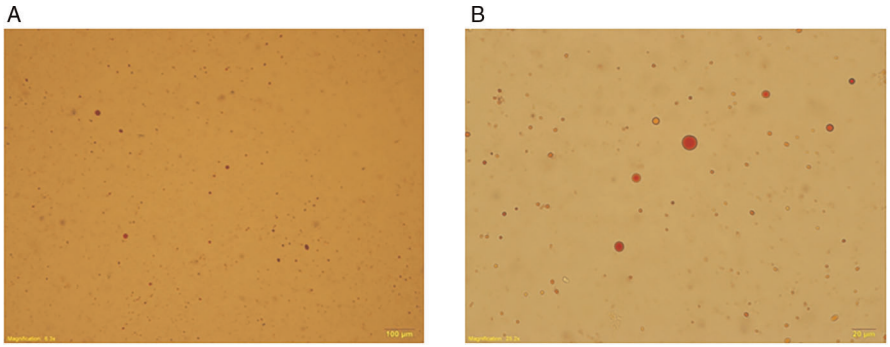

FIGURE 2 | A urine sample stained with neutral fat stain solution observed using a microscope. (**A**) 100×. (**B**) 400×.

International Business Machines Corp, NY, USA). We divided our patients into two groups according to whether or not they had lipiduria within 24 h after the operation. The statistical differences in continuous and categorical variables between the two groups were examined using the Student's t test and the Chi-square test, respectively. Logistic regression analyses were used to determine the associations of clinical factors with postoperative lipiduria and hypoxemia with multivariate adjustments. In all of the analyses, a two-sided P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 144 patients were analyzed (mean age 51.3 ± 22.9 years, male 50.7%). **Table 1** shows the characteristics of the study population according to whether or not they had lipiduria after the surgery. Patients who had lipiduria after operation had a higher proportion of diabetes (25.0% vs. 11.3%, $p = 0.030$), a longer operation time (214 ± 124 vs. 174 ± 84 min, $p = 0.027$), and a higher rate of postoperative hypoxemia (SpO_2 <95%) (40.6% vs. 20.0%, $p = 0.007$) compared with those who had no lipiduria. There were no significant between-group differences in the other variables.

Table 2 shows the associations between clinical factors and postoperative lipiduria. In the univariate analysis, diabetes (odd ratio 2.630, 95% CI, 1.074–6.436, $p = 0.034$) and operation time (odd ratio 1.001, 95% CI, 1.000–1.007, $p = 0.025$) were significantly associated with postoperative lipiduria. The associations of diabetes (odd ratio 3.684, 95% CI, 1.256–10.810, $p = 0.018$) and operation time (odd ratio 1.005, 95% CI, 1.000–1.009, $p = 0.029$) with postoperative lipiduria remained significant after adjustments for age, sex, and other relevant variables (**Table 2**).

We examined the associations between clinical factors and postoperative hypoxemia (SpO_2 <95%), as shown in **Table 3**. Significant associations of age, diabetes, hypertension, eGFR, and operation time with postoperative hypoxemia were noted in the univariate analysis. After adjustments for relevant variables, age (odd ratio 1.034, 95% CI, 1.003–1.066, $p = 0.029$), body mass index (odd ratio 1.100, 95% CI, 1.007–1.203, $p = 0.035$), and operation time (odd ratio 1.005, 95% CI, 1.000–1.010, $p = 0.033$) were independently associated with postoperative hypoxemia.

TABLE 1 | Characteristics of the study population according to postoperative lipiduria.

Variables	Lipiduria (–)	Lipiduria (+)	*P* value
N	80	64	
Age, years	51.3 ± 23.0	51.2 ± 22.8	0.974
Male sex, *n* (%)	36 (45.0)	37 (57.8)	0.126
Body mass index, kg/m^2	24.1 ± 4.4	25.6 ± 5.1	0.055
Smoking, *n* (%)	8 (10.0)	5 (7.8)	0.649
Diabetes, *n* (%)	9 (11.3)	16 (25.0)	0.030
Hypertension, *n* (%)	19 (23.8)	15 (23.4)	0.965
White blood cell, per μL	11,525 ± 4,572	12,246 ± 5,473	0.390
Hemoglobin, g/dL	13.1 ± 1.9	13.2 ± 2.1	0.762
Platelet, 10^3/μL	221 ± 64	241 ± 79	0.096
eGFR, mL/min/1.73 m^2	92.8 ± 28.1	93.5 ± 24.7	0.869
ALT, U/L	28.9 ± 27.9	40.0 ± 47.0	0.087
Blood glucose before operation, mg/dL	130 ± 34	134 ± 44	0.642
Long bone fracture, *n* (%)	67 (83.8)	56 (87.5)	0.526
Blood loss during operation, mL	220 ± 284	279 ± 357	0.279
Blood transfusion, *n* (%)	18 (22.5)	12 (18.8)	0.615
Operation time, min	174 ± 81	214 ± 124	0.027
SpO_2 <95% after operation, *n* (%)	16 (20.0)	26 (40.6)	0.007

Values are mean ± SD or n (%). ALT, alanine aminotransferase. eGFR, estimated glomerular filtration rate.

DISCUSSION

In this study, we demonstrated that diabetes and operation time were associated with postoperative lipiduria in patients with fractures undergoing surgical intervention (**Table 2**).

TABLE 2 | Associations between clinical factors and postoperative lipiduria (dependent variable).

Independent variables	Univariate analysis		Multivariate analysis[a]	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*p*
Age (year)	1.000 (0.985–1.014)	0.974	1.012 (0.986–1.039)	0.361
Sex (male vs. female)	1.675 (0.863–3.252)	0.128	1.971 (0.863–4.503)	0.107
Body mass index (kg/m^2)	1.072 (0.997–1.152)	0.059	1.069 (0.989–1.154)	0.092
Smoking (yes vs. no)	0.763 (0.237–2.455)	0.650	0.319 (0.073–1.385)	0.127
Diabetes (yes vs. no)	2.630 (1.074–6.436)	0.034	3.684 (1.256–10.810)	0.018
Hypertension (yes vs. no)	0.983 (0.453–2.132)	0.965	0.801 (0.293–2.189)	0.666
eGFR (mL/min/1.73 m^2)	1.001 (0.989–1.014)	0.868	1.004 (0.983–1.027)	0.687
Operation time (min)	1.004 (1.000–1.007)	0.025	1.005 (1.000–1.009)	0.029

eGFR, estimated glomerular filtration rate.
[a]Adjusted for age, sex, body mass index, smoking, diabetes, hypertension, eGFR, and operation time.

TABLE 3 | Associations between clinical factors and SpO_2 <95% after operation (dependent variable).

Independent variables	Univariate analysis		Multivariate analysis[a]	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*p*
Age (year)	1.027 (1.010–1.045)	0.002	1.034 (1.003–1.066)	0.029
Sex (male vs. female)	0.641 (0.311–1.323)	0.229	1.009 (0.402–2.535)	0.984
Body mass index (kg/m^2)	1.061 (0.984–1.143)	0.122	1.100 (1.007–1.203)	0.035
Smoking (yes vs. no)	0.183 (0.023–1.454)	0.108	0.117 (0.012–1.160)	0.067
Diabetes (yes vs. no)	2.738 (1.128–6.649)	0.026	1.417 (0.504–3.985)	0.509
Hypertension (yes vs. no)	2.872 (1.285–6.419)	0.010	1.270 (0.459–3.516)	0.645
eGFR (mL/min/1.73 m^2)	0.980 (0.966–0.994)	0.006	0.992 (0.970–1.015)	0.512
Operation time (min)	1.005 (1.000–1.009)	0.030	1.005 (1.000–1.010)	0.033

eGFR, estimated glomerular filtration rate.
[a]Adjusted for age, sex, body mass index, smoking, diabetes, hypertension, eGFR, and operation time.

Moreover, operation time was independently associated with postoperative hypoxemia (**Table 3**). Both postoperative lipiduria and hypoxemia are common presentations of FES (5, 11), which is an uncommon but severe postoperative complication with a poor prognosis (8, 16). Our findings are clinically relevant and might help identify patients with high risk of postoperative FES.

Lipiduria has been associated with nephrotic syndrome (17). The cause of lipiduria in nephrotic syndrome may be secondary to hyperlipidemia (18). Our finding that diabetes was associated with lipiduria (odd ratio 3.684, 95% CI, 1.256–10.810, $p = 0.018$, **Table 2**) is perhaps not surprising, as diabetes has been associated with proteinuria and nephrotic syndrome (19). We speculate that an increase in oxidative stress after acute trauma and surgical intervention (20–22) might be related to postoperative lipiduria. Oxidative stress has been reported to contribute to acute kidney injury after orthopedic trauma in an animal model (23). Oxidative stress may result in an increase in glomerular permeability (24), which has been associated with lipiduria (25, 26). This scenario may help explain the finding in a recent study (16) that showed delayed time to operation was associated with FES in patients with acute trauma, and may also account for our result, which indicated operation time (odd ratio 1.005, 95% CI, 1.000–1.009, $p = 0.029$) was independently associated with postoperative lipiduria.

Moreover, we found that operation time was independently associated with postoperative hypoxemia (odd ratio 1.005, 95% CI, 1.000–1.010, $p = 0.033$). An increase in oxidative stress associated with surgical intervention could lead to an increase in pulmonary permeability (22), which in turn may result in postoperative hypoxemia. Both age and body mass index were also independently associated with postoperative hypoxemia, and these findings were consistent with previous reports (27–29). Twenty-five of our patients had both lipiduria and hypoxemia after surgery for their fractures. The mean operation time of these patients was 227 ± 130 min, compared with 178 ± 82 min ($p = 0.034$) for the 64 patients who did not have postoperative lipiduria and hypoxemia. As bone marrow manipulation during orthopedic surgery might increase the risk of FES (30), it is reasonable to postulate that this could explain the association of operation time with postoperative lipiduria and hypoxemia. Based on our findings, we recommend that patients who had prolonged operation for fractures should be carefully monitored for clinical signs related to the FES.

There were several limitations in this study. First, the number of our study patients was relatively small. As the incidence of FES was less than 1% (4, 5), a larger number of patients are needed to investigate predisposing factors of this serious complication. Second, we did not investigate proteinuria and lipiduria before the operation for all study patients. We cannot exclude the possibility that some of our patients had preoperative lipiduria which was not related to the operation. Third, we used SpO_2 <95% determined using a pulse oximeter, rather than low PaO_2 determined by an arterial blood gas analysis, as the definition of hypoxemia. This must be acknowledged as a potential confounder, although low SpO_2 (<90%) was used to define FES in a recent study (13).

CONCLUSION

In summary, we identified several factors independently associated with postoperative lipiduria and hypoxemia in patients with fracture undergoing surgical intervention. Operation time was associated with both postoperative lipiduria and hypoxemia, and we recommend that patients with prolonged operation for fractures should be carefully monitored for clinical signs related to FES.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

C-HC, Y-CW, and C-HL designed and conducted the research; Y-CW, Y-CL, F-AT, J-YL, and J-SW contributed acquisition of data, analysis and interpretation of data; J-SW and Y-CW wrote the first draft of the manuscript; and C-HC, Y-CL, F-AT, J-YL, and C-HL revised the manuscript critically for important intellectual content. All authors approved the final draft of the manuscript.

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Effect Analysis of Preoperative Intravenous Tranexamic Acid Combined With Intraoperative Immersion in Reducing Perioperative Blood Loss of One Stage Posterior Thoracolumbar Tuberculosis

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Background: To investigate the efficacy and safety of preoperative intravenous tranexamic acid (TXA) combined with intraoperative immersion in reducing perioperative blood loss in one-stage posterior thoracolumbar tuberculosis.

Methods: All patients were divided into four groups: Group A received an intravenous drip of TXA before surgery, group B received multiple local immersions during the operation, group C received an intravenous drip combined with multiple local immersions, and the control group (group CG) were not treated with TXA during the same period. The total blood loss (TBL), intraoperative blood loss (IBL), hidden blood loss (HBL), postoperative drainage volume, maximum hemoglobin drop value (max Hb drop), liver and kidney function, coagulation indexes, blood transfusion rate, hospital stay and incidence of complications were compared among the four groups.

Results: TBL, IBL, HBL, max Hb drop, POD1 drainage, and POD2 drainage in group A, group B, and group C were significantly lower than those in group CG. TBL, IBL, HBL and max Hb drop were group C < group A < group B < group CG. The drainage volume of group C was significantly lower than that of the other groups. There was no significant difference in blood coagulation index (PT, D-D) or liver and kidney function (ALT, Cr) among the four groups. There was no difference in postoperative hospital stay between group A and group B, but it was significantly lower in group C than in the other three groups. All patients achieved satisfactory bone graft fusion at the last follow-up.

Abbreviations: TBL, Total blood loss; HBL, Hidden blood loss; VBL, Visible blood loss; IBL, Intraoperative blood loss; TXA, Tranexamic acid; Hct, Hematocrit; Hb, Hemoglobin.

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Conclusion: Preoperative intravenous drip of TXA combined with intraoperative multiple immersion can effectively reduce perioperative blood loss while not increasing the risk of thrombosis without affecting liver and kidney function, coagulation function or tuberculosis prognosis.

Keywords: thoracolumbar tuberculosis, tranexamic acid, blood loss, local immersion, drainage

INTRODUCTION

Typical thoracolumbar tuberculosis (T11-L2) is characterized by intervertebral disc involvement, destruction of adjacent vertebrae and formation of paraspinal abscesses, which usually require surgical treatment. Compared with other approaches, one-stage posterior focus debridement, bone grafting and pedicle screw internal fixation have the advantages of less trauma, faster recovery, stable internal fixation and better effect of deformity correction, which is accepted by the majority of spinal surgeons (1, 2). In spite of this, tuberculosis surgery itself still has the problems of long operation time and large blood loss, which brings great challenges to the safety of operation, and most tuberculosis patients are accompanied by anemia and hypoproteinemia due to long-term chronic nutritional consumption. For patients with poor physique, perioperative blood loss is not conducive to postoperative rehabilitation. Blood transfusion not only increases medical expenses but also may cause complications such as disease transmission, hemolysis, postoperative epidural hematoma, and allergic reaction (3, 4). Therefore, it is particularly important to control perioperative blood loss in patients with spinal tuberculosis.

In addition to improving surgical skills and shortening the time of operation to reduce bleeding, the rational use of hemostatic drugs is also a good choice. Tranexamic acid (TXA) is a synthetic lysine derivative. It binds to the lysine binding site of plasmin/plasminogen and then inhibits the fibrinolysis mediated by plasmin to achieve hemostasis (5). It was first used in clinical practice in the 1960s, and most studies have proven that it can effectively reduce perioperative blood loss and the blood transfusion rate in cardiology, obstetrics, urology, orthopedics and other specialties (6–9). The route of TXA is mainly divided into intravenous and topical routes. The effectiveness and safety of intravenous, intra-articular or combined medication for reducing perioperative blood loss in knee arthroplasty has been confirmed (10, 11). There are many studies about intravenous TXA in spinal surgery, and it is basically agreed that TXA can reduce blood loss and hospital stay (12). However, there are few reports of topical TXA, and its effect is still controversial (13, 14).

To the best of our knowledge, there are no reports about the application of TXA in one-stage posterior thoracolumbar tuberculosis surgery. We achieved a good hemostatic effect by using a preoperative intravenous drip combined with multiple immersions during the operation. The purpose of this study was to evaluate the efficacy and safety of intravenous, topical and combined TXA administration in reducing perioperative blood loss in thoracolumbar tuberculosis and to provide a reference for clinical treatment.

MATERIALS AND METHODS

Patients

This study was approved by the Ethics Committee of The Second Xiangya Hospital of Central South University, and all the patients signed the informed consent form before the operation. Patients who underwent one-stage posterior focus debridement, interbody fusion and pedicle screw fixation for thoracolumbar tuberculosis from July 2014 to February 2019 were included in the study. The inclusion criteria were as follows: (1) patients with clinical manifestations, laboratory examination and postoperative pathology confirmed as tuberculosis; (2) single segmental thoracolumbar tuberculosis; (3) destruction of the anterior column with or without kyphosis and nerve injury; and (4) poor effect of conservative treatment. The exclusion criteria were as follows: (1) active pulmonary tuberculosis; (2) combined anterior and posterior surgery or conservative treatment; (3) coagulation dysfunction; (4) severe hepatic and renal dysfunction; (5) cardiovascular and cerebrovascular diseases such as myocardial infarction, cerebral infarction, atrial fibrillation, and angina pectoris; and (6) use of anticoagulants and antiplatelet drugs within 7 days before the operation.

Eligible patients were divided into four groups: group A ($n = 32$) received 20 mg/kg TXA intravenously 15 min before the operation; group B ($n = 30$) was treated with 300 mL of 3 g TXA saline solution to soak the wound during the operation; group C ($n = 34$) received a preoperative intravenous drip combined with intraoperative multiple immersion; and the control group (group CG, $n = 32$) were not treated with TXA during the same period (**Figure 1**).

Ninety-six patients using TXA were followed up for more than 18 months, including 55 males and 41 females (mean age 45.43 years, range 27–67 years). There were 22 cases with T10-T11, 24 cases with T11-T12, 21 cases with T12-L1 and 29 cases with L1-L2. The control group included 18 males and 14 females (mean age 47.69 years, range 29–66 years). Of these, 7 were T10-T11, 8 were T11-T12, 7 were T12-L1, and 10 were L1-L2, Similarly, 32 patients in the control group were also followed up for more than 18 months.

Preoperative Treatment

All patients were treated with four regular antituberculosis drugs (isoniazid 5 mg/kg, rifampicin 10 mg/kg, ethambutol 15 mg/kg, pyrazinamide 25 mg/kg) for 2 to 4 weeks. Surgical treatment was performed after the erythrocyte sedimentation rate,

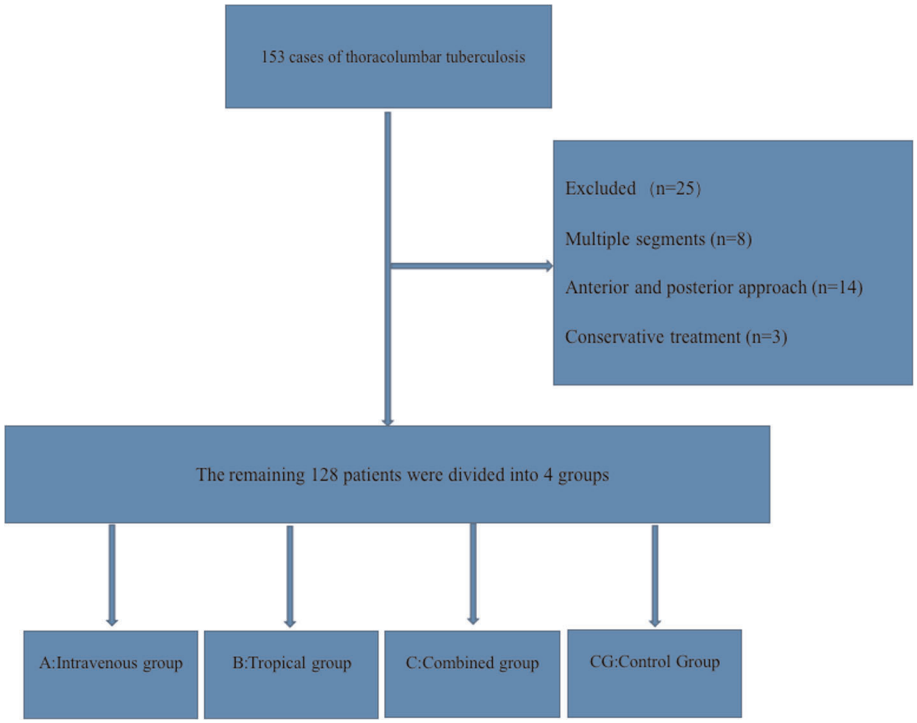

FIGURE 1 | Experimental flow chart.

C-reactive protein, body temperature returned to normal or significantly decreased, anemia and hypoproteinemia were corrected, and the general condition improved.

Operation Method

The operation was performed by the same group of doctors. A posterior midline incision was made, and the paravertebral muscles were dissected under the periosteum to expose the lamina, articular process, transverse process, costal transverse process and medial rib. Pedicle screws were inserted into the two vertebral bodies above and below the affected vertebra, and short screws were placed in the affected vertebra as appropriate. To avoid spinal cord injury caused by spinal instability during the operation, temporary rod fixation was used on the side with mild lesions. A small piece of rib (approximately 2 cm) and part of the facet joint were removed on the severe side, and then the pleura was carefully pushed outward. The intercostal nerves on one side could be sacrificed as needed to fully expose the lesions. The dead bone, tuberculous granulation tissue and pus were removed under direct vision. Then, a prebending rod was used to correct kyphosis, and the trimmed ribs or ilium was implanted into the intervertebral body. After proper compression, the screw tail cap was locked, and a posterolateral bone graft was performed. The gelatin sponge containing 0.4 g isoniazid and 0.8 g amikacin was placed into the focus. The drainage tube was placed, and the incision was sutured layer by layer.

Usage of TXA

Patients in group A were given 100 mL of 20 mg/kg TXA saline solution intravenously before the operation, and 100 mL saline was used for local irrigation after paravertebral muscle dissection, after lesion exposure and before incision closure. In group B, 100 mL saline was intravenously dripped 15 min before the operation. Meanwhile, 300 mL of 3 g TXA saline solution was divided into three equal parts, local immersion was performed after paravertebral muscle dissection, after lesion exposure and before incision closure for 2 min, 2 min, 5 min, and then sucked away; group C received intravenous drip of 100 mL of 20 mg/kg TXA saline 15 min before operation, and 100 mL of 1 g TXA saline solution was used to soak the wound after paravertebral muscle dissection, after lesion exposure and before incision closure, respectively.

Postoperative Management and Evaluation Index

After the operation, patients were given air pressure pump treatment of both lower extremities, and patients were encouraged to perform isometric contractile exercise of lower limb muscles to prevent deep venous thrombosis (DVT)). The drainage tube was removed when the drainage volume was less than 30 mL/d. Antibiotics were used for 5–7 days, and the treatment of four antituberculosis drugs was continued. Pyrazinamide was stopped after 3 months, and the other three antituberculosis drugs lasted for 12–18 months. The patient can wear a brace and leave the bed for appropriate activities

after 2 weeks, but bed rest should still be the mainstay before bone graft fusion. All patients were followed up at 1, 3, 6, 12, and 18 months after surgery and then reviewed once a year.

The operation time, postoperative hospital stay, hemoglobin (Hb), hematocrit (HCT), D-dimer (D-D), prothrombin time (PT), glutamic pyruvic transaminase (ALT) and creatinine (Cr) were recorded before and after the operation.

The total blood loss (TBL) was calculated according to the estimated blood volume (EBV) formula of Nadler et al. (15). TBL = 2*EBV (Hctpre-Hctpost)/(Hctpre + Hctpost), Hctpre was Hct on the day before the operation, and Hctpost was Hct on the third day after the operation. Visible blood loss (VBL) = intraoperative blood loss (IBL) + postoperative drainage, hidden blood loss (HBL) = TBL-VBL. If the patient received a blood transfusion during the period, HBL = TBL+ transfusion volume-VBL. The maximum hemoglobin drop value (Max Hb drop) = Hbpre-Hblowest (Hbpre is the level of Hb one day before operation; Hblowest is the lowest value within 3 days after operation).

Routine ultrasound examination of the lower extremities was performed before discharge or at any time when the patient had lower limb pain and swelling to determine whether there was deep venous thrombosis (DVT). Perioperative complications, such as incision infection, epidural hematoma, epilepsy, DVT, pulmonary embolism, visual impairment, myocardial ischemia and ischemic encephalopathy and final bone graft fusion, were recorded.

Statistical Processing

Spss23.0 was used to analyze the data. Continuous variables were expressed as the mean ± SD. The data of four groups were compared by one-way ANOVA. When there was a significant difference among the four groups, the Bonferroni test was used for pairwise comparisons. The chi-square test was used to compare categorical variables. When $P < 0.05$, the difference was considered statistically significant.

TABLE 1 | Baseline parameters of patients in the 4 groups.

Variable	Group A	Group B	Group C	Control Group	*P*-value
M/F	20/12	16/14	19/15	18/14	0.750
Age (years)	45.24 ± 9.85	45.44 ± 9.58	45.61 ± 9.65	45.43 ± 9.72	0.597
BMI (kg/cm^2)	20.06 ± 1.67	20.12 ± 1.59	20.14 ± 1.44	20.09 ± 1.67	0.645
Lesion location (*n*)					0.965
T10~T11	7	6	9	7	
T11~T12	7	9	8	8	
T12~L1	8	7	6	7	
L1~L2	10	8	11	10	
Preopertive Hb	130.31 ± 10.38	130.49 ± 10.80	129.96 ± 10.32	130.36 ± 10.78	0.069
Operative time (min)	244.15 ± 26.10	244.08 ± 24.52	243.57 ± 25.70	243.95 ± 25.91	0.291
Incision length (cm)	9.62 ± 1.49	9.74 ± 1.73	9.87 ± 1.60	9.77 ± 1.69	0.149

M, male; F, female; BMI, body mass index; Hb, hemoglobin.

RESULTS

All patients were followed up for at least 18 months, and satisfactory implant fusion was achieved at the last follow-up. There were no significant differences between the four groups in terms of age, sex, BMI, lesion segment, time to surgery, or other baseline data (**Table 1**).

TBL, IBL, HBL, max Hb drop, POD1 drainage, and POD2 drainage in group A, group B, and group C were significantly lower than those in group CG. TBL, IBL and HBL in group C were significantly lower than those in groups A and B, while group A was significantly lower than group B. There was no significant difference in preoperative Hb between the four groups, and the max Hb drop after surgery was (group C < group A < group B < group CG). On the first postoperative day, the drainage in group C was significantly lower than that in group A, group B and group CG, while group A was lower than group B and group CG, and group CG had the most drainage; on the second day, there was no significant difference between group A and group B, while group C was still lower than the other three groups. On the third day, there was no significant difference between the four groups. The transfusion rates of the four groups were 18.75%, 16.67%, 5.88% and 15.63%, respectively, but were not statistically significant. There was no difference in the postoperative hospitalization time between groups A and B, but the hospitalization time in group CG was significantly higher than that in the other groups, and the hospitalization time in group C was the shortest (**Table 2**).

There was no significant difference in the coagulation indexes (PT, D-D) before and 3 days after surgery, and there was no significant difference in the liver and kidney function indexes (ALT, Cr) before and 3 days after surgery among the four groups (**Table 3**).

No serious adverse events, such as pulmonary embolism, epidural hematoma, epilepsy, myocardial ischemia, visual impairment or ischemic encephalopathy, occurred in any patient. Only one patient in each of the B and CG groups developed slight swelling of the lower extremities at 5 and 7 days postoperatively. B-ultrasound showed intermuscular venous thrombosis, and the symptoms improved with active treatment. One patient in group A had sinus tract formation, which was cured with local debridement and intensive dressing changes. In addition, two case in group A, one case in group B, three cases in group C, and two cases in group CG had superficial infection of the incision, which was cured after anti-infection, drug change and other symptomatic treatment.

DISCUSSION

The local blood supply of the spine is abundant, and exposure of the operative area and osteotomy will lead to hyperfibrinolysis

TABLE 2 | Postoperative outcome among the 4 groups.

Variable	Group A	Group B	Group C	Control Group	*P* value	*P* AvsB	*P* AvsC	*P* BvsC	*P* CGvsA	*P* CGvsB	*P* CGvsC
Max Hb drop (g/L)	28.06 ± 6.73	31.73 ± 5.57	22.65 ± 5.13	55.31 ± 10.39	<0.001	0.046	0.001	<0.001	<0.001	<0.001	<0.001
TBL (mL)	1047.08 ± 111.97	1146.99 ± 137.29	878.04 ± 103.04	1411.06 ± 153.67	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
IBL (mL)	365.52 ± 73.71	405.52 ± 67.18	318.38 ± 71.43	512.73 ± 79.79	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HBL (mL)	432.16 ± 80.02	461.28 ± 63.49	384.07 ± 56.04	497.63 ± 91.32	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
POD1 drainage (mL)	161.95 ± 31.69	186.46 ± 38.70	123.70 ± 30.64	201.39 ± 51.68	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
POD2 drainage (mL)	95.85 ± 15.31	96.66 ± 14.15	59.33 ± 19.13	102.33 ± 25.61	<0.001	0.159	<0.001	<0.001	<0.001	<0.001	<0.001
POD3 drainage (mL)	35.59 ± 10.84	35.11 ± 9.93	34.81 ± 11.66	35.44 ± 11.22	0.258	/	/	/	/	/	/
Transfusion (case)	6	5	2	5	0.235	/	/	/	/	/	/
Post-op HOS (days)	13.75 ± 2.08	13.55 ± 1.81	12.02 ± 1.75	14.07 ± 1.98	<0.001	0.387	<0.001	<0.001	<0.001	<0.001	<0.001
Wound infection (case)	2	1	3	2	0.869	/	/	/	/	/	/
DVT (case)	0	1	0	1	0.312	/	/	/	/	/	/

Max Hb drop, the maximum hemoglobin drop value; TBL, total blood loss; IBL, intraoperative blood loss; HBL, hidden blood loss; POD1-3, post-operative day 1-3; Post-op HOS, postoperative hospital stay; DVT, deep venous thrombosis.

TABLE 3 | Preoperative and postoperative blood biochemical indexes among the 4 groups.

Varible	Group A	Group B	Group C	Control Group	*P* value
Pre-op D-D (μg/mL)	0.48 ± 0.23	0.64 ± 0.36	0.58 ± 0.34	0.55 ± 0.33	0.490
POD3 D-D (μg/mL)	1.39 ± 0.35	1.48 ± 0.39	1.30 ± 0.37	1.49 ± 0.36	0.158
Pre-op PT (s)	12.11 ± 1.36	12.80 ± 1.04	12.60 ± 1.12	12.51 ± 1.09	0.065
POD3 PT (s)	12.97 ± 1.13	13.59 ± 1.04	13.11 ± 1.11	13.37 ± 1.03	0.060
Pre-op ALT (U/L)	21.38 ± 8.86	22.70 ± 8.08	19.74 ± 7.44	21.19 ± 7.96	0.348
POD3 ALT (U/L)	24.62 ± 9.40	25.11 ± 8.12	24.32 ± 9.31	25.02 ± 8.49	0.274
Pre-op Cr (μmol/L)	75.26 ± 13.70	77.33 ± 11.21	76.98 ± 12.16	76.86 ± 12.03	0.778
POD3 Cr (μmol/L)	78.58 ± 12.78	81.47 ± 11.86	77.84 ± 10.60	79.85 ± 11.66	0.439

D-D, D dimer; PT, prothrombin time; ALT, Alanine transaminase; Cr, Creatinine; Pre-OP, pre-operation; POD 3, post-operative day 3.

and increased blood loss (16). Compared with combined anterior and posterior surgery, one-stage posterior tuberculosis focus debridement and bone graft internal fixation shorten the operation time and reduce the amount of trauma and blood loss to a certain extent, but its exposure range and visual field are limited, which is not conducive to hemostasis during the operation. The exposed bone surface is not suitable for standard hemostasis in soft tissue surgery, and the deeper wound cannot be effectively oppressed, resulting in large postoperative drainage (17). Tuberculosis patients are prone to malnutrition, anemia and hypoproteinemia due to long-term poor appetite and lack of sleep, so ensuring a good systemic condition is an important part of anti-tuberculosis treatment (18). Perioperative blood loss will lead to worse immunity in tuberculosis patients and prolong the time of hospitalization and rehabilitation. The successful application of TXA in other orthopedic surgeries provides us with a good reference. We used different methods of TXA for perioperative hemostasis of spinal tuberculosis and achieved satisfactory results in long-term follow-up.

TXA can effectively reduce bleeding by inhibiting fibrinolysis and stabilizing blood clots. A number of studies have shown that intravenous administration of the antifibrinolytic drug TXA during spinal surgery can significantly reduce blood loss, blood transfusion volume and blood transfusion rate; however, there is no consensus on the optimal timing and dosage of intravenous administration (19, 20). In view of the fact that the half-life of single-dose intravenous administration is 120 min, it is generally reported that dual-dose or preoperative load dose supplemented by maintenance dose. Raksakietisak et al. (21) used 15 mg/kg TXA intravenously at the beginning of 39 cases of complex spinal surgery and 3 h later, which resulted in lower blood loss and transfusion rates than the placebo group. Elwatidy et al. (22) used 2 g TXA intravenously before spinal surgery in 64 cases, and supplemented with a 100 mg/h maintenance dose within 5 h

after the operation, the blood loss was 49% less than that of the placebo group. Raman et al. (16) considered that the hemostatic effect of a high dose (load 30 mg/kg, maintenance dose 1–10 mg/kg/h) was better than that of a low dose (load dose 10 mg/kg, maintenance dose 1–2 mg/kg/h) in adult spinal deformities. However, the incidence of postoperative atrial fibrillation and myocardial infarction was higher in the high-dose group.

A high load dose, additional maintenance dose or repeated use of TXA can significantly inhibit fibrinolytic activity, and the imbalance of the fibrinolytic system is closely related to thrombosis (23). Systemic administration of TXA can penetrate the blood–brain barrier and then spread throughout the central nervous system (5). Although complications of intravenous TXA are rare, they do exist, especially in patients with hypercoagulability, severe renal failure and ischemic heart disease (24). High-dose intravenous administration of TXA in patients undergoing cardiac surgery has been reported to lead to nonischemic seizures (25). On the other hand, single-dose application also achieved good results. Sun et al. (26) intravenously dripped 15 mg/kg TXA 30 min before lumbar fusion surgery, and IBL and drainage volume 24 h after surgery were significantly reduced compared with the placebo group. Wang (27) et al. used 15 mg/kg TXA intravenously 15 min before lumbar degeneration surgery, and the postoperative blood loss was 13% less than that of the control group. To reduce the potential complications caused by systemic medication and considering the time-consuming operation of tuberculosis and the ceiling effect of drugs, we chose to intravenously drip 20 mg/kg TXA 15 min before surgery, combined with multiple immersions during the operation, in an attempt to enhance its hemostatic effect. The results are satisfactory.

The application of topical TXA in joint surgery is relatively mature. A multicenter randomized controlled study showed that topical 1–3 g TXA was effective in knee arthroplasty (28). A meta-analysis of topical application of TXA in spine surgery showed that methods such as local soaking or indwelling gelatin sponge with TXA before incision closure can also reduce blood loss and drainage while not increasing the risk of complications (29). Xu et al. (30) found that local immersion with 1 g TXA before closing the incision in spinal fusion surgery significantly reduced postoperative drainage compared with gelatin sponge and collagen hemostatic sponge. Ren et al. (17) used 100 mL of 1 g TXA saline to soak the wound for 5 min before incision closure in 50 patients undergoing lumbar fusion, and the postoperative blood loss was 44.29% of the control group, while shortening the hospital stay. Compared with intravenous medication, this method is convenient to manage and can provide a higher concentration in the bleeding area, inhibiting the fibrinolytic activity of the local tissue and preventing the fibrin clot from dissolving, increasing the volume and strength on the wound surface, thereby enhancing microvascular coagulation while reducing system exposure (31, 32). In theory, it may be better to prolong the soaking time and increase the absorption of drugs by local tissues, but that will prolong the time of operation and anesthesia, and spine surgery cannot prolong drug absorption time by clamping the drainage tube as it does after joint replacement. Therefore, unlike the previously reported single-dose local administration before incision closure, we used TXA solution to soak wounds after paravertebral muscle dissection, after lesion exposure and before incision closure. The results showed that although the hemostatic effect was slightly worse than that of intravenous administration alone, the combination was better than that of single administration.

In this study, the combined group was superior to the single-medication group in reducing TBL, IBL, and HBL, which indicated that intravenous drip before the operation, soaking and flushing during the operation simultaneously not only reduced the total blood loss but also made the surgical field cleaner and increased the safety of the operation. A single intravenous administration could maintain the effective plasma concentration for approximately 16 h (33), and resoaking the wound at the end of the operation further prolonged the action time of the drug, so the postoperative drainage was significantly less than that of the other groups. The blood transfusion rate in the combined group (5.88%) was lower than that in the other two groups (16.67%, 18.75%), but there was no statistical significance in the blood transfusion rate among the three groups. The result may be due to the small sample size on the one hand and the strict grasp of the indication for blood transfusion on the other hand. Less blood loss in the combined group means that the general condition recovers quickly, and early functional exercise makes the length of hospital stay significantly lower than that in the other two groups. TXA has a low price, which is much lower than the cost of blood transfusion and prolonged hospitalization. Therefore, preoperative intravenous drip combined with intraoperative multiple local immersion for hemostasis not only contributes to the recovery of spinal tuberculosis but also reduces their economic pressure.

Due to the antifibrinolytic effect of TXA, most users are concerned about whether it increases the risk of thrombosis, leading to DVT, ischemic cerebral infarction, myocardial infarction and pulmonary embolism. In this study, there was no significant difference in the indexes of coagulation function among the four groups, and there were no serious complications of thrombosis in the perioperative period, which again proved that TXA could inhibit fibrinolysis within the effective drug action window but had no significant effect on coagulation function and did not increase the incidence of thrombosis (34, 35). The reason may be attributed to the fact that the inhibitory effect of TXA on fibrinolysis is mainly located in the surgical wound rather than in the circulatory system, and it has no effect on the vein wall (36). Among them, 1 case of postoperative intermuscular venous thrombosis was considered to be related to his refusal to use a lower limb air pressure pump after the operation. Therefore, for the sake of safety, we believe that postoperative intervention measures such as active use of a lower limb air

pressure pump and encouraging patients to carry out isometric contraction of lower limb muscles are of great benefit to the prevention of thrombosis. In addition, the number of incision infections in the four groups was similar, and satisfactory bone graft fusion was achieved in the four groups after long-term follow-up, indicating that the drug would not affect the short-term and long-term prognosis of patients with spinal tuberculosis.

Limitations

There are some limitations in this study. First, this is a single-center retrospective cohort study. Due to the low incidence of perioperative complications, the small sample size may not be able to identify all complications, e.g. the conclusion that "while not increasing the risk of thrombosis without affecting liver and kidney function, coagulation function or tuberculosis prognosis" may be inaccurate Secondly, the medication method of this study is empirical medication, and the optimal dosage and administration time need to be further explored. In the future, further large-scale prospective experiments are needed to further explore and verify this conclusion.

CONCLUSION

Preoperative intravenous drip of TXA combined with intraoperative multiple immersion can effectively reduce perioperative blood loss and shorten hospital stay while not increasing the risk of thrombosis without affecting liver and kidney function, coagulation function or tuberculosis prognosis.

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 Second Xiangya Hospital of Central South University, Hunan, P.R. China. 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

All authors participated in data acquisition. BWZ, JL, BYZ and JYW contributed to the conception and design of the study. BWZ, GHL and XBW did the data analysis and interpretation. HQN, XBW, BYZ, JL and JYW contributed to drafting and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Does Abnormal Preoperative Coagulation Status Lead to More Perioperative Blood Loss in Spinal Deformity Correction Surgery?

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This study aims to analyze the potential association between the preoperative coagulation status and perioperative blood loss in spinal deformity correction surgery. The preoperative coagulation status and estimated blood loss (EBL) during operation, postoperative wound drainage, and allogeneic transfusion during and after operation were recorded and analyzed. Among the 164 patients, 26 had a longer prothrombin time (PT), 13 had a lower fibrinogen level, 55 had a longer activated partial thromboplastin time (APTT), and 2 had a longer thrombin time (TT), and the platelet count (PLT) was all normal or higher than the normal level. The mean EBL per surgical level was 77.8 ml (range, 22–267 ml), and the mean drainage per surgical level was 52.7 ml (range, 7–168 ml). Fifty-five patients and 12 patients underwent allogeneic transfusion during and after the operation, respectively. The differences in EBL per surgical level, mean drainage per surgical level, the occurrences of allogeneic transfusion during and after operation between the patients with a longer PT, lower fibrinogen level, longer APTT or longer TT, and the normal controls were not significant (all P's > 0.05). The Spearman correlation analysis showed that there was no correlation between PT, fibrinogen, APTT, TT or PLT with EBL per surgical level, mean drainage per surgical level, or allogeneic transfusion during and after the operation (all P's > 0.05). The abnormal preoperative coagulation status but not hemophilia does not lead to more perioperative blood loss or a higher rate of perioperative allogeneic transfusion in spinal deformity correction surgery.

Keywords: spinal deformity, blood loss, preoperative coagulation status, activated partial thromboplastin time, estimated blood loss

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Abbreviations: APTT, activated partial thromboplastin time; EBL, estimated blood loss; PLT, platelet count; PT, prothrombin time; TT, thrombin time.

INTRODUCTION

Scoliosis correction surgery is major surgery with a large estimated blood loss (EBL) during the operation (1–6). Normal clotting requires normal coagulation status of the coagulation factors, and patients with obvious abnormal coagulopathy may experience more perioperative blood loss and a high incidence of bleeding complications in scoliosis correction surgery (7–10). In 2005, Ho et al. found a high prevalence of coagulation abnormalities among their adolescent idiopathic scoliosis (AIS) patients (9). In Ryan et al.'s study, children with scoliosis also have a higher prevalence of preoperative coagulation abnormalities compared with healthy patients (10), so the coagulation status test should be carried out prior to the surgery. Carling et al. reported that total bleeding volume in AIS correction surgery correlated significantly with preoperative fibrinogen concentration (11). Geck et al. also reported that preoperative fibrinogen levels exhibited a significant negative logarithmic correlation with total blood loss in their AIS correction surgeries (12). However, there are few studies focusing on the association between abnormal coagulation and blood loss in scoliosis correction surgery. In our department, preoperative coagulation screening tests are routinely performed in patients undergoing spinal deformity correction surgery. Our study analyzed whether there were potential associations between preoperative coagulation status and perioperative blood loss.

MATERIALS AND METHODS

After obtaining approval from the institutional review board, we performed the current study. One hundred and sixty-four patients, 61 males and 103 females with an average age of 14.6 years (range, 10–20), who underwent scoliosis correction surgery in our hospital from May 2010 to April 2012 were included. The medical records, radiographic parameters of the deformity, and laboratory blood tests were recorded, and laboratory blood tests were performed 2 days before the operation. The preoperative coagulation status [platelet count (PLT), prothrombin time (PT), fibrinogen, activated partial thromboplastin time (APTT), thrombin time (TT)] and EBL during operation, postoperative wound drainage, and allogeneic transfusion during and after operation were also recorded and analyzed. None of the patients had received a prophylactic regimen or were treated with aspirin.

The normal limits of the PLT, PT, fibrinogen, APTT, and TT were 10–35 G/L,10.4–12.6 s, 1.80–3.50 g/L, 22.7–31.8 s and 14.0–21.0 s, respectively. We defined the abnormal coagulative from these numerical ranges.

Statistics

SPSS 17.0 for Windows was used in this study; a *t*-test or *U*-test was used for comparison; and the correlation between PT, international normalized ratio (INR), fibrinogen, APTT, TT or PLT, EBL per surgical level, mean drainage per surgical level, or allogeneic transfusion during and after the operation was analyzed by Spearman correlation analysis.

RESULTS

The etiology of the deformity included idiopathic scoliosis in 63 patients, congenital scoliosis in 70 patients, neuromuscular scoliosis in 20 patients, neurofibromatosis scoliosis in five patients, and Marfan syndrome scoliosis in six patients. The mean Cobb angle of the major curve, fusion level, operation time, total EBL, EBL per surgical level, total wound drainage, and wound drainage per surgical level are listed in **Table 1**. Fifty-five patients and 12 patients underwent allogeneic transfusion during and after the operation, respectively. The details of allogeneic transfusion are listed in **Table 1**.

The results of the blood screening test for the coagulation factors are listed in **Table 2**.

Among the 164 patients, 26 had a longer PT, 13 had a lower fibrinogen level, 55 had a longer APTT (30 with 3 s or longer than normal, 14 with 5 s or longer than normal), and two had a longer TT, and the PLT values were all higher than the normal level. Among the 26 patients with a longer PT, six also had a longer INR. Each of the 17 patients had both longer PT and APTT and a lower fibrinogen level. Five patients had a longer APTT and a lower fibrinogen level.

TABLE 1 | Details of the Cobb angle of the major curve, fusion level, operation time, EBL, and allogeneic transfusion.

	Min	Max	Mean	SD
Cobb angle of major curve (degree)	30.0	158.0	64.2	25.2
Operation time (h)	1.3	8.5	4.1	1.3
Fusion level (vertebra)	5.0	17.0	10.9	3.0
Total EBL	200.0	2,500.0	809.6	415.4
EBL per level	22.2	266.7	77.8	43.7
Total drainage (ml)	100.0	1,850.0	557.0	268.6
Drainage per level (ml)	7.0	168.2	52.7	24.9
RBC transfusion (during operation) (U)	0	8.0	0.96	1.59
Plasma transfusion (during operation) (ml)	0	800.0	104. 3	190.4
RBC transfusion (after operation) (U)	0	9.0	0.4	1.3
Plasma transfusion (after operation) (ml)	0	800.0	25.5	106.4

EBL, estimated blood loss; RBC, red blood cells.

TABLE 2 | Details of the blood screening test of the coagulation factors.

	Min	Max	Mean	SD
PT (10.4–12.6 s)	10.70	15.30	12.07	0.702
INR (0.86–1.14)	0.89	1.30	1.03	0.06
Fibrinogen (1.80–3.50 g/L)	1.16	3.84	2.34	0.45
APTT (22.7–31.8 s)	22.60	42.40	30.50	4.22
TT (14.0–21.0 s)	15.70	22.80	18.17	1.08
PLT (100–350 G/L)	124.00	475.00	256.20	54.18

PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; PLT, platelet count.

The differences in EBL per surgical level, mean drainage per surgical level, the occurrences of allogeneic transfusion during and after the operation between the patients with a longer PT time, lower fibrinogen level, longer APTT or longer TT, and the normal controls were not significant (all P's > 0.05). The patients with both abnormalities of the PT and APTT did not have more EBL per surgical level, more mean drainage per surgical level, and more occurrences of allogeneic transfusion during and after the operation compared to the other patients.

The Spearman correlation analysis showed that there was no correlation between PT, INR, fibrinogen, APTT, TT or PLT with EBL per surgical level, mean drainage per surgical level, or allogeneic transfusion during and after the operation (all P's > 0.05) (**Table 3**).

DISCUSSION

The most common, routinely collected coagulation markers are APTT, PT, and PLT (10, 13, 14). This has important implications for clinical practice because the identification of hemostatic defects prior to surgery may allow affected patients to be targeted with specific interventions to reduce the risk of bleeding (11, 15, 16).

In the literature, some doctors have reported a higher rate of coagulation abnormalities in scoliosis patients (9, 10, 17). In Ho et al.'s report, eight patients (25%) had a prolonged APTT, while the INR and fibrinogen were all normal (9). Ryan et al. compared 165 pediatric scoliosis patients with 175 controls and found that scoliosis patients had a significantly greater prevalence of abnormal coagulation screening tests (67%) compared with controls (43%; OR, 2.6; 95% CI, 1.5–4.6, $P <$ 0.001). In our series, 74 patients had abnormal results from the screening coagulation tests, and 65 patients had prolonged PT, APTT, or lower fibrinogen, which was similar to Ho's report. In our series, 26 (15.8%) patients had prolonged PT, of which six patients also had prolonged INR, and 55 (33.5%) patients had prolonged APTT. In Ryan et al.'s study, 62.6% (103/165) of scoliosis cases had an abnormal PT, and they thought that their results might be heavily influenced by the PT results. However, in the current study, APTT abnormalities were more often than others.

TABLE 3 | Spearman correlation analysis.

Spearman	EBL per surgical level	Mean drainage per surgical level	Allogeneic transfusion during operation	Allogeneic transfusion after operation
PT	0.564	0.831	0.621	0.120
INR	0.877	0.284	0.587	0.919
Fibrinogen	0.091	0.907	0.127	0.841
APTT	0.780	0.364	0.919	0.809
TT	0.162	0.051	0.304	0.606
PLT	0.453	0.186	0.528	0.269

PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; PLT, platelet count.

Two pathways lead to the formation of a fibrin clot: the intrinsic and extrinsic pathways. The common point in both pathways is the activation of factor X to factor Xa. Factor Xa activates prothrombin (factor II) to thrombin (factor IIa). The PT is an assay designed to measure activities of the extrinsic pathway of coagulation, while the APTT is used to assess for defects in the intrinsic pathway of coagulation. The most common measure of PT is to divide the time of coagulation of a patient's blood by that of a known standard, and this value is referred to as the INR (10, 14, 18).

In Carling et al.'s study, there was no correlation between the mean total bleeding volume and PLT, APTT, or PT ($P = 0.61$, 0.46, and 0.57, respectively). Also, the differences in PLT, APTT, or PT between patients with an extensive transfusion or bleeders with the controls were none significant (all P's > 0.05), too. In Ryan et al.'s report, the mean values of PT, APTT, and TT were all significantly higher in the scoliosis cases compared with those in non-scoliosis controls ($P <$ 0.001, after adjusting for age and gender). However, they did not analyze the association between these abnormalities and blood loss during the operations (10). Ialenti et al. studied the effects of PT/PTT on intraoperative blood loss (IOBL) and found no significant associations between PT/PTT and IOBL (5). In 2015, Li et al. performed a study to analyze the preoperative factors and IOBL in female AIS patients. Of the 161 patients, the PLT, PT, and TT were not found to be significantly related to IOBL, while the APTT was found to be significantly associated with IOBL (19). Horlocker et al. found that the screening tests of PT and APTT gave limited information about how much a patient will bleed during and after the procedure (7). Shaw et al. analyzed 48 consecutive referrals for abnormal PTs, partial thromboplastin times, or closure times obtained as preprocedural screens and found only 9 patients (19%) had a possible or true mild bleeding disorder. Thus, they concluded that the usefulness of using PT and APTT in diagnosing bleeding disorders in pediatric patients preoperatively was limited (20). In the current series, the differences in blood loss and allogeneic transfusion between the patients with a longer PT time, lower fibrinogen level, longer APTT or longer TT, and the normal controls were none significant (all P's > 0.05) neither did the patients with both abnormalities of the PT and APTT. Also, the correlation analysis did not show a significant association between PT, APTT, perioperative blood loss, and allogeneic transfusion. The current results were similar to Carling, Ialenti, Horlocker, and Shaw et al.'s studies, while there was a little difference from Li et al.'s study.

Fibrinogen is a key protein in the coagulation cascade, which is one of the first coagulation factors consumed during bleeding. During coagulation, thrombin lyses the soluble fibrinogen into the insoluble fibrin net as the final step of clotting (7, 16, 21).

Carling et al. studied the preoperative fibrinogen plasma concentration to investigate the potential association between fibrinogen, bleeding, and transfusion requirements after scoliosis surgery. Among their 82 patients, the mean total

bleeding volume was correlated significantly with preoperative fibrinogen concentration ($r = 0.31$, $P = 0.005$). According to their study, a lower preoperative fibrinogen plasma concentration was associated with bleeding >1920 ml and extensive transfusion (both P's = 0.002). They also found that an individual patient with a fibrinogen value above 2.8 g/L is unlikely to bleed extensively, while lower fibrinogen concentration patients have an increased risk of high bleeding volume or transfusion rate. They concluded that the preoperative measurement of the fibrinogen concentration provides more information about bleeding volume and transfusion requirements than standard screening tests (11). Geck et al. also performed a study focused on the association between preoperative fibrinogen, bleeding, and transfusion requirements. In their 110 AIS patients, the preoperative fibrinogen was significantly correlated with the total bleeding volume and transfusion (12). In Li et al.'s report, fibrinogen was found to be significantly associated with IOBL (20). The current study did not find significant differences in blood loss or allogeneic transfusion between patients with lower and normal preoperative fibrinogen, and there was no significant association between preoperative fibrinogen, perioperative blood loss, and allogeneic transfusion. These results were different from the above-mentioned studies.

However, there were also some limitations of the current study: first, although the sample was relatively large, it was still small; second, it was a single-center case series, and intrinsic selective bias was inevitable; third, the results would have been more convincing if there were normal controls to match the scoliosis patients; last, some doctors also used thromboelastography to assess the coagulation status of the scoliosis patients (8, 12), while in the current study, this was not analyzed.

In summary, from the limited number of scoliosis patients, the present study found that patients with abnormal coagulation screening tests did not have more blood loss during and after the operation and a high possibility of perioperative allogeneic transfusion. Associations between these abnormalities and perioperative blood loss and allogeneic transfusion were not found, either. Therefore, abnormal preoperative coagulation status but not hemophilia does not appear to lead to more perioperative blood loss or a higher rate of perioperative allogeneic transfusion in spinal deformity correction surgery. In the future, further studies are needed to assess the clinical significance of our 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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Peking Union Medical College Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ZL, BY, JG Z, JX S, Yp W, Gx Q, and Xq C conceived and designed the experiments. ZL and BY analyzed the data. JG Z, JX S, and Yp W wrote this manuscript. JG Z, JX S, and Yp W performed the experiments. All authors contributed to the article and approved the submitted version.

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Predicting prolonged postoperative length of stay risk in patients undergoing lumbar fusion surgery: Development and assessment of a novel predictive nomogram

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Objective: The purpose of this study was to develop and internally validate a prediction nomogram model in patients undergoing lumbar fusion surgery.

Methods: A total of 310 patients undergoing lumbar fusion surgery were reviewed, and the median and quartile interval were used to describe postoperative length of stay (PLOS). Patients with PLOS > P_{75} were defined as prolonged PLOS. The least absolute shrinkage and selection operator (LASSO) regression was used to filter variables for building the prolonged PLOS risk model. Multivariable logistic regression analysis was applied to build a predictive model using the variables selected in the LASSO regression model. The area under the ROC curve (AUC) of the predicting model was calculated and significant test was performed. The Kappa consistency test between the predictive model and the actual diagnosis was performed. Discrimination, calibration, and the clinical usefulness of the predicting model were assessed using the C-index, calibration plot, and decision curve analysis. Internal validation was assessed using the bootstrapping validation.

Results: According to the interquartile range of PLOS in a total of 310 patients, the PLOS of 235 patients was ≤P_{75} (7 days) (normal PLOS), and the PLOS of 75 patients was > P_{75} (prolonged PLOS). The LASSO selected predictors that were used to build the prediction nomogram included BMI, diabetes, hypertension, duration of surgery, duration of anesthesia, anesthesia type, intraoperative blood loss, sufentanil for postoperative analgesia, and postoperative complication. The model displayed good discrimination with an AUC value of 0.807 (95% CI: 0.758–0.849, $P < 0.001$), a Kappa value of 0.5186 (cutoff value, 0.2445, $P < 0.001$), and good calibration. A high C-index value of 0.776 could still be reached in the interval validation. Decision curve analysis showed that the prolonged PLOS nomogram was clinically useful when intervention was decided at the prolonged PLOS possibility threshold of 3%.

Conclusions: This study developed a novel nomogram with a relatively good accuracy to help clinicians access the risk of prolonged PLOS in lumbar

fusion surgery patients. By an estimate of individual risk, surgeons and anesthesiologists may shorten PLOS and accelerate postoperative recovery of lumbar fusion surgery through more accurate individualized treatment.

KEYWORDS

PLOS, lumbar fusion surgery, nomogram, predictive model, LASSO regression

Introduction

In recent years, with the prevalence of the concept of enhanced recovery after surgery (ERAS), clinicians related to the perioperative period are gradually beginning to pay attention to the implementation of this concept. The essence of ERAS is to improve the preoperative state of patients, ensure the safety of patients, minimize perioperative stress response, shorten the postoperative length of stay (PLOS), and accelerate the recovery of patients (1, 2).

In spine surgery, lumbar fusion surgery is one of the common surgical procedures. Studies have shown that the PLOS of lumbar fusion ranges between 3 and 6.7 days (3). The prolongation of PLOS not only does not meet the requirements of ERAS but also is disadvantageous to the patients, causing physical, mental, and financial burden for them. Prolonged PLOS is associated with many perioperative adverse outcomes, such as increasing the risk of hospital-acquired infection and deep venous thrombosis, and even endangering the lives of patients (4, 5). During the perioperative period, the PLOS of patients is affected by many factors (6–11). As a visual presentation of the relationship between risk factors and outcome, predictive nomogram is favored by clinicians. However, there is no nomogram for predicting the risk of prolonged PLOS in lumbar fusion surgery.

The aim of this study was to develop a valid but simple prediction nomogram model in lumbar fusion surgery to assess the risk of prolonged PLOS using only those clinical variables easily available.

Patients and methods

Patients

Research approval was obtained from the Ethics Committee of Fuzhou Second Hospital. The subjects were 310 patients who underwent lumbar fusion surgery in the Fuzhou second Hospital from 1 January 2019 to 1 December 2019. The median and quartile interval were used to describe PLOS. Patients with PLOS > P_{75} were defined as prolonged PLOS (12, 13). According to whether PLOS was prolonged, the patients were divided into a case group and a control group. A total of 75 patients with prolonged PLOS were included in the case group, and 235 patients were included in the control group. Data such as demographic, preoperative data (ASA class, diabetes, hypertension, number of comorbidities), intraoperative data (duration of surgery, anesthesia type, fluid infusion volume, blood transfusion, and blood loss volume), and postoperative data (PLOS, analgesia dosage of sufentanil, and postoperative complications) were collected from medical records.

Inclusion and exclusion criteria

We included patients aged 18 years and older undergoing the elective lumbar fusion surgery. Exclusion criteria: (1) patients treated with minimally invasive technique or requiring more than three segmental internal fixation; (2) trauma patients; and (3) patients with spinal tumors, abscesses, spinal deformities (i.e. scoliosis and kyphosis), spinal fractures, vertebroplasty, osteomyelitis, and cauda equina syndrome.

Statistical analysis

All data were expressed as count (%). Statistical analysis was performed using the R software (Version 4.1.3; https://www.R-project.org), IBM SPSS version 23.0, and MedCalc (Version 19.2; https://www.medcalc.org).

The least absolute shrinkage and selection operator (LASSO) method was used to select the optimal predictive variables in risk factors from the patients undergoing lumbar fusion surgery (14, 15). Variables with nonzero coefficients in the LASSO regression model were selected (16). Then, multivariable logistic regression analysis was used to build a predicting model by incorporating the variables selected in the LASSO regression model (17). The variables were considered as odds ratio (OR) having 95% confidence interval (CI) and as *P*-value. The statistical significance levels were all two-sided. The area under the ROC curve (AUC) of the predicting model was calculated and significant test was performed by using MedCalc software. The Kappa consistency test between the predictive model and the actual diagnosis was performed by using IBM SPSS version 23.0. All potential predictors selected in the LASSO regression model were applied to develop a predicting model nomogram for prolonged PLOS risk.

Calibration curves were plotted to assess the calibration of the prolonged PLOS risk nomogram. The prolonged PLOS risk nomogram was subjected to bootstrapping validation

(1,000 bootstrap resamples) to calculate a relatively corrected C-index (18). Decision curve analysis was conducted to determine the clinical usefulness of the prolonged PLOS risk nomogram by quantifying the net benefits at different threshold probabilities in the lumbar fusion surgery cohort. The net benefit was calculated by subtracting the proportion of all patients who were false positive from the proportion of those patients who were true positive and by weighing the relative harm of forgoing interventions compared with the negative consequences of an unnecessary intervention (19, 20).

Results

Definition of prolonged PLOS

According to the inclusion and exclusion criteria, 310 patients undergoing lumbar fusion surgery were analyzed in this study. PLOS was treated as an outcome variable and tested for normality. We found that the PLOS data did not conform to the normal distribution ($P < 0.001$). Therefore, the median and quartile intervals were used to describe the PLOS. The median PLOS was 6 days and P_{75} was 7 days. The patients with PLOS > P_{75} were defined as prolonged PLOS (12, 13).

Patients' characteristics

According to the interquartile range of PLOS in a total of 310 patients, the PLOS of 235 patients was ≤P75 (7 days) (normal PLOS), and the PLOS of 75 patients was >P75 (prolonged PLOS) (**Figure 1**). All data of patients, including demographic and perioperative clinical features in the two groups, are given in **Table 1**.

Variables selection

Of demographic and perioperative clinical features, 15 variables were reduced to 9 potential predictors on the basis of 310 patients in the cohort with nonzero coefficients in the LASSO regression model (**Figures 2A,B**). These variables included BMI, diabetes, hypertension, duration of surgery, duration of anesthesia, anesthesia type, intraoperative blood loss, sufentanil for postoperative analgesia, and postoperative complication (**Table 2**).

Development of an individualized prediction model

The results of the logistic regression analysis among BMI, diabetes, hypertension, duration of surgery, duration of anesthesia,

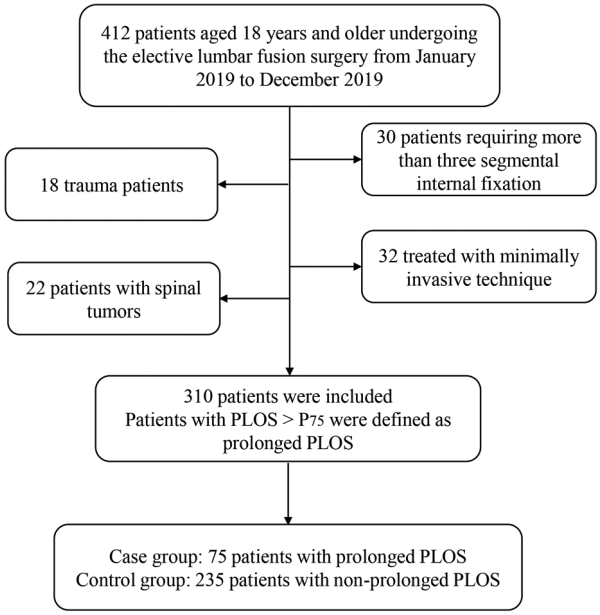

FIGURE 1
Study flowchart. PLOS, postoperative length of stay.

TABLE 1 Differences between demographic and clinical characteristics of prolonged PLOS and non-prolonged PLOS groups.

Variables	Prolonged PLOS		Standardize diff.	*P*-value
	No (*n* = 235)	Yes (*n* = 75)		
Age (years)			0.1 (−0.2, 0.3)	0.508
<65	154 (65.5%)	46 (61.3%)		
≥65	81 (34.5%)	29 (38.7%)		
BMI (kg/m^2)			0.2 (−0.0, 0.5)	0.070
<28	217 (92.3%)	64 (85.3%)		
≥28	18 (7.7%)	11 (14.7%)		
ASA class			0.0 (−0.2, 0.3)	0.819
1–2	224 (95.3%)	71 (94.7%)		
3–4	11 (4.7%)	4 (5.3%)		
Comorbidities			0.2 (−0.1, 0.4)	0.169
<3	170 (72.3%)	48 (64.0%)		
≥3	65 (27.7%)	27 (36.0%)		
Diabetes			0.2 (−0.1, 0.5)	0.108
No	203 (86.4%)	59 (78.7%)		
Yes	32 (13.6%)	16 (21.3%)		
Hypertension			0.0 (−0.2, 0.3)	0.865
No	151 (64.3%)	49 (65.3%)		
Yes	84 (35.7%)	26 (34.7%)		
			0.6 (0.3, 0.8)	<0.001

(*continued*)

TABLE 1 Continued

Variables	Prolonged PLOS		Standardize diff.	*P*-value
	No (*n* = 235)	Yes (*n* = 75)		
Duration of surgery (hours)				
<2	86 (36.6%)	10 (13.3%)		
≥2	149 (63.4%)	65 (86.7%)		
Duration of anesthesia (h)			0.4 (0.2, 0.7)	0.004
<2	46 (19.6%)	4 (5.3%)		
≥2	189 (80.4%)	71 (94.7%)		
Anesthesia type			0.4 (0.1, 0.6)	0.004
CIIA	170 (72.3%)	41 (54.7%)		
TIA	65 (27.7%)	34 (45.3%)		
Intraoperative blood loss (ml)			0.3 (0.1, 0.6)	0.010
<500	218 (92.8%)	62 (82.7%)		
≥500	17 (7.2%)	13 (17.3%)		
Blood transfusion			0.1 (−0.1, 0.4)	0.276
No	219 (93.2%)	67 (89.3%)		
Yes	16 (6.8%)	8 (10.7%)		
Intraoperative fluid infusion volume (ml/kg)			0.3 (0.1, 0.6)	0.148
<17.2	61 (26.0%)	11 (14.7%)		
≥17.2, <22.2	62 (26.4%)	18 (24.0%)		
≥22.2, <28.6	57 (24.3%)	24 (32.0%)		
≥28.6	55 (23.4%)	22 (29.3%)		
Intraoperative urine volume (ml/kg/h)			0.2 (−0.1, 0.5)	0.532
<0.71	59 (25.1%)	20 (26.7%)		
≥0.71, <1.27	56 (23.8%)	19 (25.3%)		
≥1.27, <2.32	57 (24.3%)	22 (29.3%)		
≥2.32	63 (26.8%)	14 (18.7%)		
Sufentanil for postoperative analgesia (μg/kg)			0.2 (−0.0, 0.5)	0.054
<2	206 (87.7%)	59 (78.7%)		
≥2	29 (12.3%)	16 (21.3%)		
Postoperative complication			1.0 (0.7, 1.2)	<0.001
No	232 (98.7%)	49 (65.3%)		
Yes	3 (1.3%)	26 (34.7%)		

PLOS, postoperative length of stay; BMI, body mass index; ASA, American Society of Anesthesiologists; CIIA, combined intravenous and inhaled anesthesia; TIA, total intravenous anesthesia.

anesthesia type, intraoperative blood loss, sufentanil for postoperative analgesia, and postoperative complication are given in Table 2. The model that incorporated the above predictors was developed and presented as the nomogram (Figure 3).

Apparent performance of the prolonged PLOS risk nomogram in the cohort

The area under the ROC curve for the prediction model nomogram was 0.807 (95% CI: 0.758–0.849, $P < 0.001$) for the cohort (Figure 4) and was confirmed to be 0.776 through bootstrapping validation, which suggested the model's good discrimination. The calibration curve of the prolonged PLOS risk nomogram for the prediction of prolonged PLOS risk in lumbar fusion surgery patients demonstrated good agreement in this cohort (Figure 5).

In addition, the prediction model was used to distinguish and classify the prolonged PLOS, and the prediction probability was used as the cutoff value 0.2445. There was no statistical difference between the model predictive ability and the diagnostic criteria in our study ($\chi^2 = 0.9245$, $P = 0.3363$). The discriminant consistency was tested (Kappa value = 0.0.5186, $P < 0.001$), which ranged from 0.41 to 0.60, indicating that the discriminant ability of the model had good consistency. The Youden index was 53.7%, and the total correct rate was 82.9%, indicating that the model has good predictive efficiency (Table 3).

Clinical use of the prediction model nomogram

The decision curve analysis for the prolonged PLOS nomogram is presented in Figure 6. The decision curve shows that if the threshold probability of a patient and a doctor is >3% and <92%, respectively, using this prolonged PLOS nomogram to predict prolonged PLOS risk adds more benefit than the scheme. Within this range, net benefit was comparable with several overlaps, on the basis of the prolonged PLOS risk nomogram.

Discussion

In recent years, the concept of enhanced recovery after surgery (ERAS) has been gradually introduced into clinical practice. The length of stay of surgical patients is undoubtedly extremely important to patients and hospitals, but the total length of stay is affected perioperatively by many factors. However, PLOS can more accurately reflect the speed of recovery of patients after surgery, and shortening the PLOS of patients is the core goal of ERAS. Therefore, we developed and validated a novel prediction tool for prolonged PLOS risk among the patients of lumbar fusion surgery by using nine easily available variables. The prediction model nomogram greatly simplifies the complicated operation process and is easy to understand and convenient for clinicians to aid better

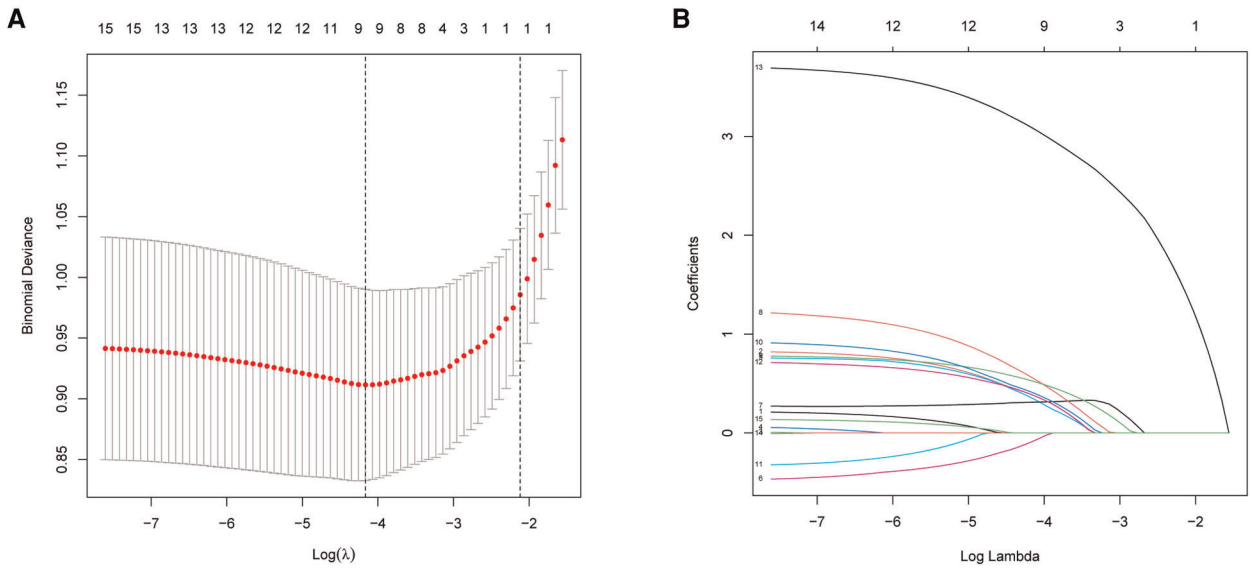

FIGURE 2
Demographic and clinical feature selection using the LASSO binary logistic regression model. (A) Optimal parameter (lambda) selection in the LASSO model used 5-fold cross-validation *via* minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus log (lambda). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 SE of the minimum criteria (the 1-SE criteria). (B) LASSO coefficient profiles of the 15 features. A coefficient profile plot was produced against the log (lambda) sequence. A vertical line was drawn at the value selected using 5-fold cross-validation, where optimal lambda resulted in five features with nonzero coefficients. LASSO, least absolute shrinkage and selection operator; SE, standard error.

TABLE 2 Prediction factors for prolonged PLOS in lumbar fusion surgery.

Intercept and variable	Prediction model		
	B	**Odds ratio (95% CI)**	***P*-value**
BMI	−0.684	0.504 (0.191–1.331)	0.167
Diabetes	−0.778	0.459 (0.198–1.068)	0.071
Hypertension	−0.458	1.581 (0.762–3.282)	0.219
Duration of operation	−0.282	0.754 (0.287–1.986)	0.568
Duration of anesthesia	−1.165	0.312 (0.068–1.437)	0.135
Anesthesia type	−0.772	0.462 (0.243–0.879)	0.019
Estimated blood loss	−0.730	0.482 (0.186–1.249)	0.133
Dose of sufentanil for postoperative analgesia	−0.714	0.490 (0.215–1.118)	0.090
Postoperative complication	−3.659	0.026 (0.007–0.092)	0.000
Intercept	4.973		

CI, confidence interval; PLOS, postoperative length of stay; BMI, body mass index. β is the regression coefficient.

clinical decision making (21). This was the first study in which a nomogram was applied in lumbar fusion surgery and PLOS. Internal validation in the cohort demonstrated good discrimination and calibration power, suggesting that this nomogram can be widely and accurately used due to its large sample size.

The PLOS of patients is affected by many factors, among which the diagnosis and treatment level of surgeons also plays an important role in addition to the condition of the patients themselves. The PLOS of a certain type of surgery may be different in different medical institutions with different levels of diagnosis and treatment. Therefore, there is no fixed standard for the diagnosis of prolonged PLOS of a certain type of surgery in previous studies. A previous study has shown that if the PLOS data of patients were in accordance with normal distribution, patients with PLOS greater than mean plus 1 standard deviation were defined as prolonged PLOS. For PLOS data that did not conform to normal distribution, patients with PLOS more than P_{75} were defined as PLOS prolongation by calculating median and quartile intervals (P_{25}, P_{50}, and P_{75}) (12, 22). In our study, the PLOS data of 310 patients undergoing lumbar fusion surgery were analyzed, and the results of the normality test showed that they did not conform to the normal distribution. Therefore, we defined patients with PLOS > P_{75} as prolonged PLOS.

We included the variable of postoperative complications in the present study. The results of multivariate regression analysis showed that postoperative complication was an independent risk factor for prolonged PLOS of lumbar fusion surgery. Many postoperative complications are related to the prolonged PLOS of patients, such as postoperative delirium, postoperative cognitive dysfunction, and so on. For anesthesiologists and surgeons, it is necessary to fully predict

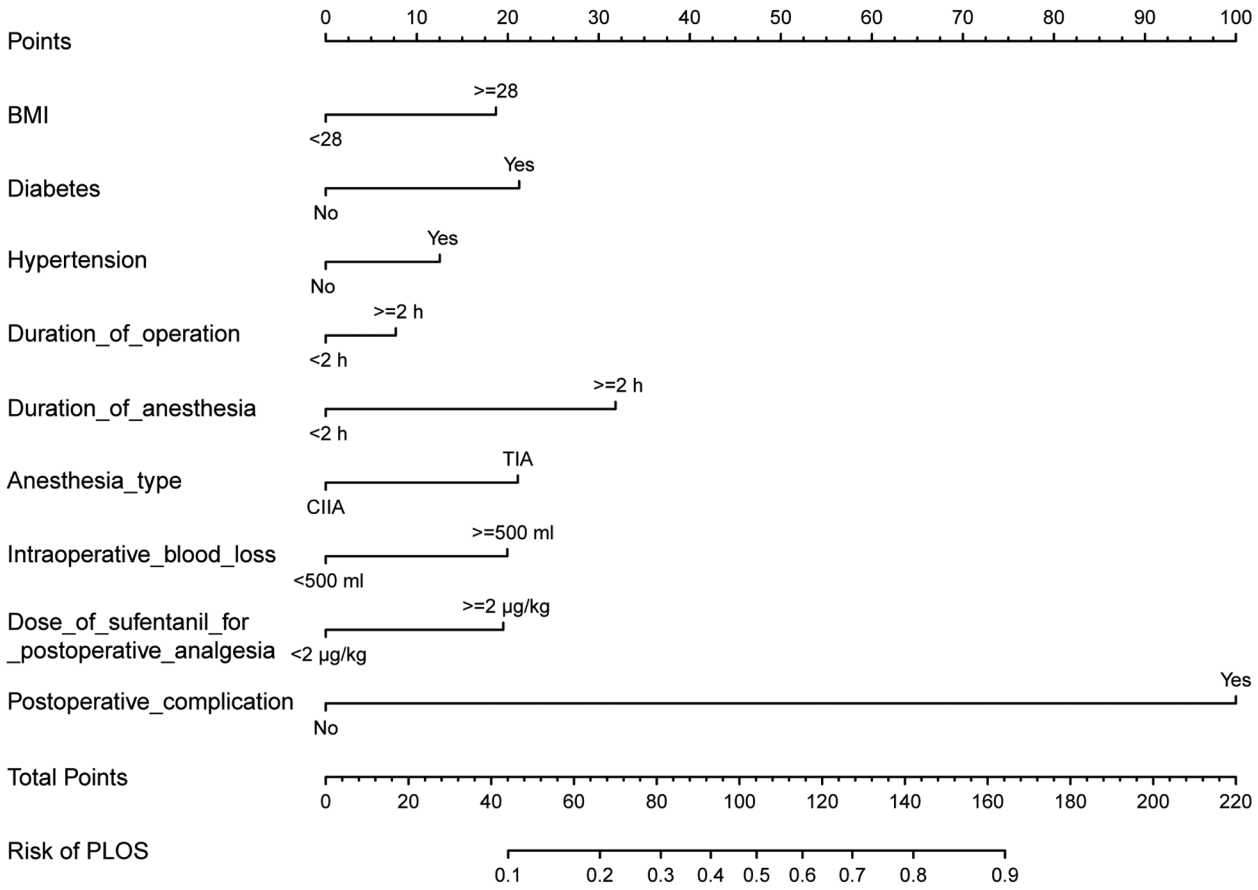

FIGURE 3
Developing a nomogram for prolonged PLOS risk. The prolonged PLOS risk nomogram was developed in the cohort, with BMI, diabetes, hypertension, duration of operation, duration of anesthesia, anesthesia type, estimated blood loss, dose of sufentanil for postoperative analgesia, and postoperative complication by R software (Version 4.1.3; https://www.R-project.org) with packages ("rms"). PLOS, postoperative length of stay; BMI, body mass index; ASA, American Society of Anesthesiologists; CIIA, combined intravenous and inhaled anesthesia; TIA, total intravenous anesthesia.

the possible postoperative complications before surgery and give intervention perioperatively to minimize the occurrence of postoperative complications, so as to facilitate the postoperative recovery of patients and save medical resources. In ERAS, anesthesiologists play an extremely key role, and the management of the peri-anesthetic period is closely related to the postoperative recovery of patients. In the past, anesthesia-related factors were rarely included in PLOS-related studies. Interestingly, in this study, variables such as anesthesia type, duration of anesthesia, and use of sufentanil for postoperative analgesia were included in the analysis of PLOS. Univariate regression analysis found that anesthesia type and duration of anesthesia were associated with the risk of prolonged PLOS, while multivariate regression analysis showed that total intravenous anesthesia (TIA) significantly increased the risk of prolonged PLOS compared with combined intravenous and inhaled anesthesia (CIIA). Therefore, TIA was an independent risk factor for prolonged PLOS in our study and may be used as a predictor of prolonged PLOS. The possible reasons are as follows: there is no monitoring of the depth of anesthesia in this research institution, and there may be excessive depth of anesthesia in the process of TIA, which may affect the postoperative PLOS of patients. In clinical anesthesia, the choice of TIA and CIIA is still controversial. As to whether TIA is related to prolonged PLOS, an analysis of a larger sample size needs to be done, or this aspect should be confirmed by conducting randomized controlled trials.

Previous studies have shown that the duration of surgery is related to the postoperative outcome of patients. Andersen K et al analyzed 335 patients with oral and maxillofacial LeFortI osteotomy. PLOS was defined as the duration from the operation date to the discharge date. The multiple regression model showed that the predictors of PLOS prolongation were duration of surgery and relative blood loss (23). Similarly, another multivariate analysis by Reid Fletcher of 11,430 patients undergoing laparoscopic gastrectomy suggested that

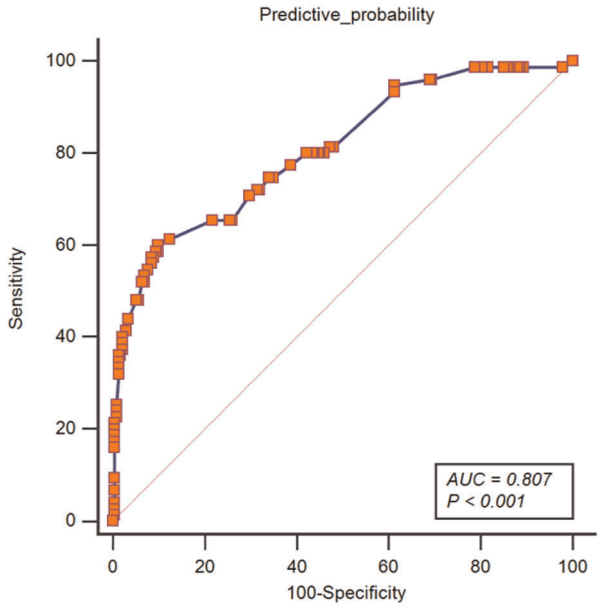

FIGURE 4
ROC of a predictive nomogram model. The ROC of this model was drawn with the variables of BMI, diabetes, hypertension, duration of operation, duration of anesthesia, anesthesia type, estimated blood loss, dose of sufentanil for postoperative analgesia, and postoperative complication by MedCalc (Version 19.2; https://www.medcalc.org). PLOS, postoperative length of stay; BMI, body mass index.

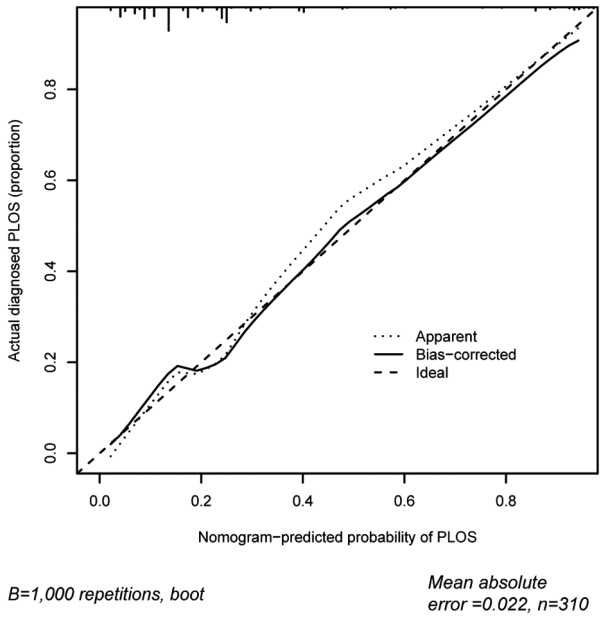

FIGURE 5
Calibration curves of the prolonged PLOS prediction in the cohort. The *x*-axis represents the predicted prolonged PLOS risk. The *y*-axis represents the actual diagnosed prolonged PLOS. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction.

prolonged duration of surgery was a predictor of prolonged PLOS (24). However, in our study, the duration of surgery and intraoperative blood loss were not independent predictors for prolonged PLOS. The possible reasons are as follows: (1) the variable definition of intraoperative blood loss is different. In the previous study, the relative blood loss was defined as a variable, while in our study, the amount of blood loss was defined as a binary variable (<500 ml or >500 ml); (2) different types of surgery and different types of blood loss may have different effects on a certain type of surgical PLOS; and (3) the sample size of this study is small and therefore statistically significant results cannot be obtained. In the follow-up study, we will expand the sample size and comprehensively consider the definition standard of variables, which will make our conclusion more reliable.

Many studies have shown that age >65 years old was closely related to prolonged PLOS of spine surgery (10, 22). In our study, age variable was divided into an elderly group (>65 years old) and a non-elderly group (≤65 years old) based on the criteria of WHO diagnosis. However, univariate regression analysis showed that age was not a risk factor for prolonged PLOS. Therefore, our conclusion is inconsistent with the above two studies, and the possible reasons are as follows: (1) The standard for defining prolonged PLOS is different. Jordan et al defined PLOS greater than mean plus a standard deviation as prolonged PLOS, while we defined PLOS greater than 75 percentile (non-normal distribution) as prolonged PLOS. (2) There were different data types when the age variable was included in the regression analysis. Previous studies included age as a continuous variable in the regression analysis, while in our study, the age included in the regression analysis was a binary variable (10, 22). (3) The sample size of our study is still not enough to draw the conclusion that age is a risk factor for predicting prolonged PLOS of lumbar fusion surgery. A further study of expanded sample size and multifaceted analysis will be needed to draw a more reliable conclusion.

Previous studies showed that ASA class ≥3 was significantly associated with prolonged PLOS in patients undergoing hip fracture and colorectal resection surgery (25, 26). However, in our study, ASA class was not associated with prolonged PLOS either in univariate analysis or in multivariate logistic regression analysis. The possible reasons are as follows: (1) the number of patients with ASA 3–4 of this study is relatively small, with only 11 cases (4.7%) and 4 cases (5.3%) of patients in the control group and case group, respectively, which may not have enough impact on the results; and (2) patients with ASA 3–4 may undergo better perioperative treatment. In addition, we found that none of the preoperative comorbidities were associated with prolonged PLOS of lumbar

TABLE 3 Discrimination and classification ability of the prolonged PLOS prediction model in lumbar fusion surgery.

Diagnostic criteria	Prediction		Total	χ^2	*P*	Kappa value (*P*)	Youden index
	+ (PLOS > 7)	− (PLOS ≤ 7)					
+ (PLOS > 7)	45	30	75				
− (PLOS ≤ 7)	23	212	235				
Total	68	242	310	0.9245	0.3363	0.5186 ($P < 0.001$)	0.5378

PLOS, postoperative length of stay.

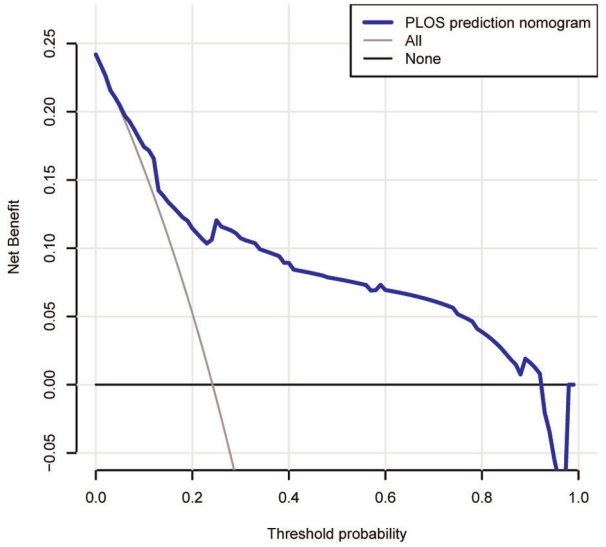

FIGURE 6
Decision curve analysis for the prolonged PLOS prediction nomogram. The *y*-axis measures the net benefit. The dotted line represents the prolonged PLOS prediction nomogram. The thin solid line represents the assumption that all patients have prolonged PLOS. The thin thick solid line represents the assumption that no patients have prolonged PLOS. The decision curve shows that if the threshold probability of a patient and a doctor is 3% and 92%, respectively, using this prolonged PLOS prediction nomogram in the current study to predict prolonged PLOS risk adds more benefit than the intervention-all-patients scheme or the intervention-none scheme.

fusion surgery. Then, we identified high-risk patients by combining preoperative comorbidities (three or more), suggesting that the number of preoperative comorbidities was not related to the prolonged PLOS of lumbar fusion surgery. However, in previous studies, the increase in preoperative comorbidities score was related to the prolongation of PLOS (27, 28). Our study failed to conclude that the number of comorbidities was a risk factor for the prolonged PLOS. The possible explanations are as follows: (1) There are many kinds of comorbidities before surgery, and some patients do not undergo a perfect examination, which may omit the diagnosis of some comorbidities and cause bias; (2) In previous studies, the number of three or more comorbidities was usually taken as the critical point, and our study also followed this classification method, which may not reach a statistically significant level because the sample size is small; (3) Comorbidity is a perioperative factor that clinicians, especially anesthesiologists, pay special attention to, which is closely related to the perioperative safety of patients. For patients with preoperative comorbidities, anesthesiologists and surgeons may do a more detailed preoperative follow-up, so as to make a more perfect anesthetic plan.

In the present study, although univariate and multivariate logistic regression analyses showed that many variables were not associated with the increased risk of prolonged PLOS in lumbar fusion surgery, in order to avoid omitting some important clinical variables, we used LASSO regression to screen variables and constructed a prolonged PLOS risk prediction nomogram of lumbar fusion surgery. Additionally, the predictive model had certain predictive discriminant ability and clinical benefits. Prolonged PLOS increased the financial burden of patients and was associated with many perioperative adverse outcomes such as increased hospital-acquired infection and the risk of deep venous thrombosis, even endangering the lives of patients (4, 5). This demonstrates that developing prolonged PLOS risk prediction tools might improve patient outcomes with individualized risk prediction and interventions. We developed a valid prolonged PLOS risk prediction tool, which assisted clinicians with an early identification of patients at a high risk of prolonged PLOS in lumbar fusion surgery.

Limitations

There are also several limitations in our study. First, our collected data might be only a part representation of lumbar fusion surgery patients. The cohort was not representative of all patients undergoing lumbar fusion surgery. Second, although the robustness of our nomogram was examined extensively with internal validation using bootstrap testing, external validation could not be conducted, and the generalizability was uncertain for other lumbar fusion surgery populations in other regions and countries. It needs to be externally evaluated in wider populations of lumbar fusion surgery. Third, we did not compare it with other machine learning approaches as well, such as support vector, bier

score, etc., to understand whether this predictive model had similar AUC in those approaches.

Conclusion

This study developed a novel nomogram with a relatively good accuracy to help clinicians access the risk of prolonged PLOS in lumbar fusion surgery patients. By an estimate of individual risk, surgeons and anesthesiologists may shorten PLOS and accelerate postoperative recovery of lumbar fusion surgery through more accurate individualized treatment.

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 Fuzhou Second Hospital. 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

Z-BH and X-DW conceived and designed the project. Z-BH analyzed all data. C-XL collected the data. Z-BH wrote the paper with the assistance of X-MC and X-DW. 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

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Poor bone mineral density aggravates adjacent segment's motility compensation in patients with oblique lumbar interbody fusion with and without pedicle screw fixation: An *in silico* study

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Objective: Motility compensation increases the risk of adjacent segment diseases (ASDs). Previous studies have demonstrated that patients with ASD have a poor bone mineral density (BMD), and changes in BMD affect the biomechanical environment of bones and tissues, possibly leading to an increase in ASD incidence. However, whether poor BMD increases the risk of ASD by aggravating the motility compensation of the adjacent segment remains unclear. The present study aimed to clarify this relationship in oblique lumbar interbody fusion (OLIF) models with different BMDs and additional fixation methods.

Methods: Stand-alone (S-A) OLIF and OLIF fixed with bilateral pedicle screws (BPS) were simulated in the L4–L5 segment of our well-validated lumbosacral model. Range of motions (ROMs) and stiffness in the surgical segment and at the cranial and caudal sides' adjacent segments were computed under flexion, extension, and unilateral bending and axial rotation loading conditions.

Results: Under most loading conditions, the motility compensation of both cranial and caudal segments adjacent to the OLIF segment steeply aggravated with BMD reduction in S-A and BPS OLIF models. More severe motility compensation of the adjacent segment was observed in BPS models than in S-A models. Correspondingly, the surgical segment's stiffness of S-A models was apparently lower than that of BPS models (S-A models showed higher ROMs and lower stiffness in the surgical segment).

Abbreviations

AFD, additional fixation device; ASD, adjacent segment diseases; BEP, bony endplate; BMD, bone mineral density; BMI, body mass index; BPS, bilateral pedicle screw; CEP, cartilage endplate; DD, disc degeneration; FE, finite element; GB, grafted bone; HU, hounsfield unit; IVD, intervertebral disc; LDD, lumbar degenerative diseases; LIF, lumbar interbody fusion; OLIF, oblique lumbar interbody fusion; S-A, stand-alone; ROM, range of motion; ZJ, zygapophyseal joint.

Conclusion: Poor BMD aggravates the motility compensation of adjacent segments after both S-A OLIF and OLIF with BPS fixation. This variation may cause a higher risk of ASD in OLIF patients with poor BMD. S-A OLIF cannot provide instant postoperative stability; therefore, the daily motions of patients with S-A OLIF should be restricted before ideal interbody fusion to avoid surgical segment complications.

KEYWORDS

adjacent segment diseases, oblique lumbar interbody fusion, motility compensation, bone mineral density, finite elemant analysis

Introduction

Lumbar interbody fusion (LIF) surgeries are widely used to treat lumbar degenerative diseases (LDDs) (1, 2). Adjacent segment diseases (ASDs) are a common complication of spinal fusion surgery (3, 4). Motility compensation is an essential mechanism of biomechanical deterioration of the adjacent segment (5, 6). The stiffness of the interbody cage and grafted bone (GB) is higher than that of intervertebral disc (IVD) components. During LIF surgeries, the nucleus, cartilage endplates (CEPs), and parts of the annulus are replaced by the cage and GB (1, 7). Thus, the fusion segment shows higher stiffness than the original IVD. Consequently, the stiffness of the fusion segment is increased, and its range of motions (ROMs) is decreased under the same moments. ROMs of adjacent segments must be increased to achieve similar ROMs of the lumbar spine in different body positions (5, 6). This pathological process increases the risk of accelerated disc degeneration (DD) and instability in adjacent segments, leading to a poor prognosis for LIF patients (3, 4).

As mentioned above, biomechanical deterioration leads to an increased risk of developing ASDs (8, 9). According to surgeons, the demographic characteristics of patients with ASDs are closely related to certain types of biomechanical deterioration. Specifically, clinical follow-up studies have shown that patients with high body mass index (BMI) have a higher incidence of ASDs; correspondingly, biomechanical studies have confirmed that overweight patients have higher intradiscal pressure and annulus shear stress, which leads to annulus tear risk (3, 4). Elderly patients are at a greater risk of developing ASD; correspondingly, preexisting DD is confirmed as a risk factor for annulus stress concentration and further acceleration of DD (5, 10). Clinical studies have also shown that patients with osteoporosis have a higher risk of DD and ASD, but the biomechanical significance of poor bone mineral density (BMD) remains unclear (3, 4, 11).

Our previous study showed that poor BMD leads to stress concentration in adjacent segments; however, Zhang et al. reported a contrasting finding by using an approximate research method (8, 12). The indicator selected in both these studies was, however, limited to the stress distribution of IVDs, and there was a lack of explanation of how changes in BMD affect the motility compensation of the adjacent segment. Additional fixation devices (AFDs) are also commonly used to provide instant stability to the LIF segment (13, 14). The bilateral pedicle screw (BPS) is an extensively used AFD. Although BPS removal after interbody bone integration will alleviate biomechanical deterioration of the adjacent segment (5, 6, 15), no study has assessed whether the use of BPS aggravates motility compensation of the adjacent segments in the early postoperative period as compared to the stand-alone (S-A) surgical method (i.e., LIF without any AFD fixation).

On the basis of the abovementioned theoretical and practical knowledge, we hypothesize that poor BMD may cause a high risk of ASD by aggravating pathological motility compensation of the adjacent segment. To confirm this hypothesis, we simulated S-A oblique lumbar interbody fusion (OLIF) and OLIF with BPS fixation in well-validated finite element (FE) models with different BMDs. ROMs and stiffness in both surgical and adjacent segments were computed and recorded to identify surgical segment stability and motility compensation of the adjacent segments.

Methods

Model construction and validation

We simulated S-A OLIF and OLIF with BPS fixation in a well-validated FE lumbosacral model. In this process, we performed a multi-indicator model validation to verify the computational credibility of the FE model (16, 17). To construct bony structures, reconstructed bony outlines were inputted into 3D CAD software, and outlines of bony structures were drawn by fitted curves to construct bony structures with fitted surfaces. In this process, bony structures, including cortical, cancellous, and bony endplates, were constructed separately. The cortical thickness was set to 0.5 mm, and the thickness, concave angles, and depth in both coronal and sagittal planes were defined according to the measurements of imaging data and anatomical samples (18–20). Nonbony components were constructed in the same 3D CAD software. IVD components comprise the annulus,

nucleus, and CEPs, and the outline of the CEP covers the nucleus and inner parts of the annulus (21, 22). Facet cartilages were defined as contact-to-contact surfaces, and ligament structures were defined as cable elements (23, 24). To validate whether the current model represents actual biomechanical situations, computed intradiscal pressure, facet contact force, disc compression value, and different directional ROMs were calculated and compared with the average values of the indicators recorded in in-vitro tests. Given that the differences between the computed and tested values were less than one standard deviation, we believe that the current model adequately represents actual biomechanical situations and can be used in current surgical simulations.

Surgical simulations

We performed OLIF simulations in the L4–L5 IVD because of the highest incidence of LDDs in this motion segment. The length of the OLIF cage was defined according to the measurement of

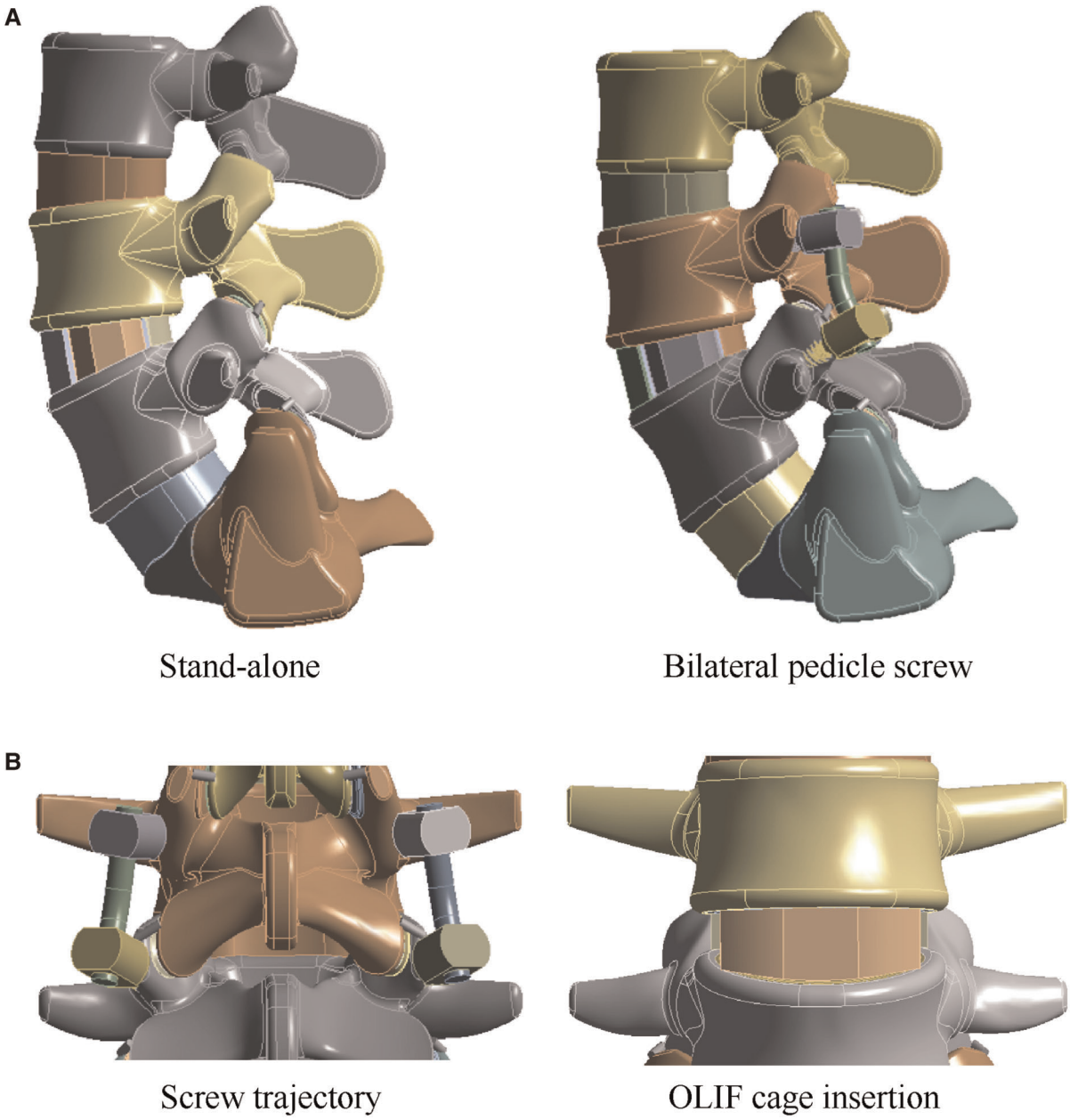

FIGURE 1
Schematic for surgical simulations in the lumbo-sacral model. (**A**) The intact lumbo-sacral model; (**B**) Simulations for S-A OLIF and OLIF fifixed by BPS.

TABLE 1 Material properties of FE models' components.

Components	Elastic modulus (MPa)	Poisson's ratio	Cross-section (mm^2)
Cortical (normal BMD)	E_{xx} = 11,300 E_{yy} = 11,300 E_{zz} = 22,000 G_{xy} = 3,800 G_{yz} = 5,400 G_{xz} = 5,400	V_{xy} = 0.484 V_{yz} = 0.203 V_{xz} = 0.203	
Cancellous (normal BMD)	E_{xx} = 140 E_{yy} = 140 E_{zz} = 200 G_{xy} = 48.3 G_{yz} = 48.3 G_{xz} = 48.3	V_{xy} = 0.45 V_{yz} = 0.315 V_{xz} = 0.315	
Bony endplates (normal BMD)	12,000	0.3	
Cortical (slight reduction of BMD)	Exx = 9,436 Eyy = 9,436 Ezz = 18,370 Gxy = 3,173 Gyz = 4,509 Gxz = 4,509	Vxy = 0.484 Vyz = 0.203 Vxz = 0.203	
Cancellous (slight reduction of BMD)	Exx = 93.8 Eyy = 93.8 Ezz = 150 Gxy = 32.36 Gyz = 36.23 Gxz = 36.23	Vxy = 0.45 Vyz = 0.315 Vxz = 0.315	
Bony endplates (slight reduction of BMD)	10,035	0.3	
Cortical (significant reduction of BMD)	Exx = 7,571 Eyy = 7,571 Ezz = 14,740 Gxy = 2,546 Gyz = 3,618 Gxz = 3,618	Vxy = 0.484 Vyz = 0.203 Vxz = 0.203	
Cancellous (significant reduction of BMD)	Exx = 47.6 Eyy = 47.6 Ezz = 100 Gxy = 16.42 Gyz = 24.15 Gxz = 24.15	Vxy = 0.45 Vyz = 0.315 Vxz = 0.315	
Bony endplates (significant reduction of BMD)	8,070	0.3	
Annulus	Hypoelastic material		
Nucleus	1	0.49	
Cartilage endplates	10	0.4	
Anterior longitudinal ligaments	Calibrated load-deformation curved under different loading conditions	0.3	60
Posterior longitudinal ligaments	Calibrated load-deformation curved under different loading conditions	0.3	21
Ligamentum flavum	Calibrated load-deformation curved under different loading conditions	0.3	60
Interspinous ligaments	Calibrated load-deformation curved under different loading conditions	0.3	40
Supraspinous ligaments	Calibrated load-deformation curved under different loading conditions	0.3	30
Intertransverse ligaments	Calibrated load-deformation curved under different loading conditions	0.3	10
Capsular	7.5 (25%) 32.9 (25%)	0.3	67.5
PEEK OLIF cage	3,500	0.3	
Titanium alloy screw	110,000	0.3	

vertebral body sizes. An OLIF cage model of 50 mm length was constructed in the same 3D CAD software. The nucleus, CEPs, and two lateral sides of the annulus were removed to simulate the discectomy and endplate preparation, and the OLIF cage fully covered with GB was inserted into the interbody space (**Figure 1**) (25, 26). The long axis of the OLIF cage was parallel to the coronal plane of the lumbosacral models. The height of the interbody space and lordotic angles of the surgical segment were kept identical to the corresponding postoperative models to eliminate their biomechanical effects (26, 27). S-A OLIF simulations were accomplished by performing these procedures. For simulating percutaneous BPS fixation, cannulated pedicle screw models of 6.5 mm diameter were constructed. Four identical pedicle screws were inserted into the L4 and L5 vertebral bodies (**Figure 1**) (28, 29).

Boundary and loading conditions

The boundary and loading conditions of the current models were defined according to *in vitro* biomechanical tests. The inferior surfaces of S1 were completely fixed, while different directional moments were applied to the superior surfaces of L3 (8, 21). Models were computed under identical loading conditions, including 8 Nm flexion, 6 Nm extension and bending, and 4 Nm axial rotation (30, 31). Because current models are symmetrical in the central sagittal plane alone, bending and axial rotation loading

conditions can be computed unilaterally. The contact between facet cartilages was set as frictionless. The frictional coefficient between the OLIF cage and BEPs was set as 0.2, and that between the GB and BEPs was set as 0.46 to simulate the instant postoperative biomechanical environment (32, 33).

Mesh generation strategies used in the present study were consistent with those reported in our previous studies, and the mesh convergence test was also performed to eliminate the effect of mesh size on the biomechanical performance of the models (16, 17). The annulus was defined as a hypoelastic material, and the nucleus was set as a semifluid incompressible bag (15, 34). Pedicle screw material was defined as titanium alloy (Ti6Al4 V), and the OLIF cage was defined as polyether ether ketone (PEEK); the elastic modulus of the GB was calculated based on the measurement of Hounsfield unit (HU) values immediately after the CT scan (34, 35). The material properties of cortical and cancellous bones were defined according to anisotropic laws, and BEP was set as an isotropic material (36, 37). For constructing postoperative models with normal BMD, osteopenia, and osteoporosis, the stiffness of cortical, cancellous, and BEPs was adjusted according to the same numerical simulations and tests used for bony material properties (**Table 1**). The morphological parameters of bony structures remained unchanged (37–39).

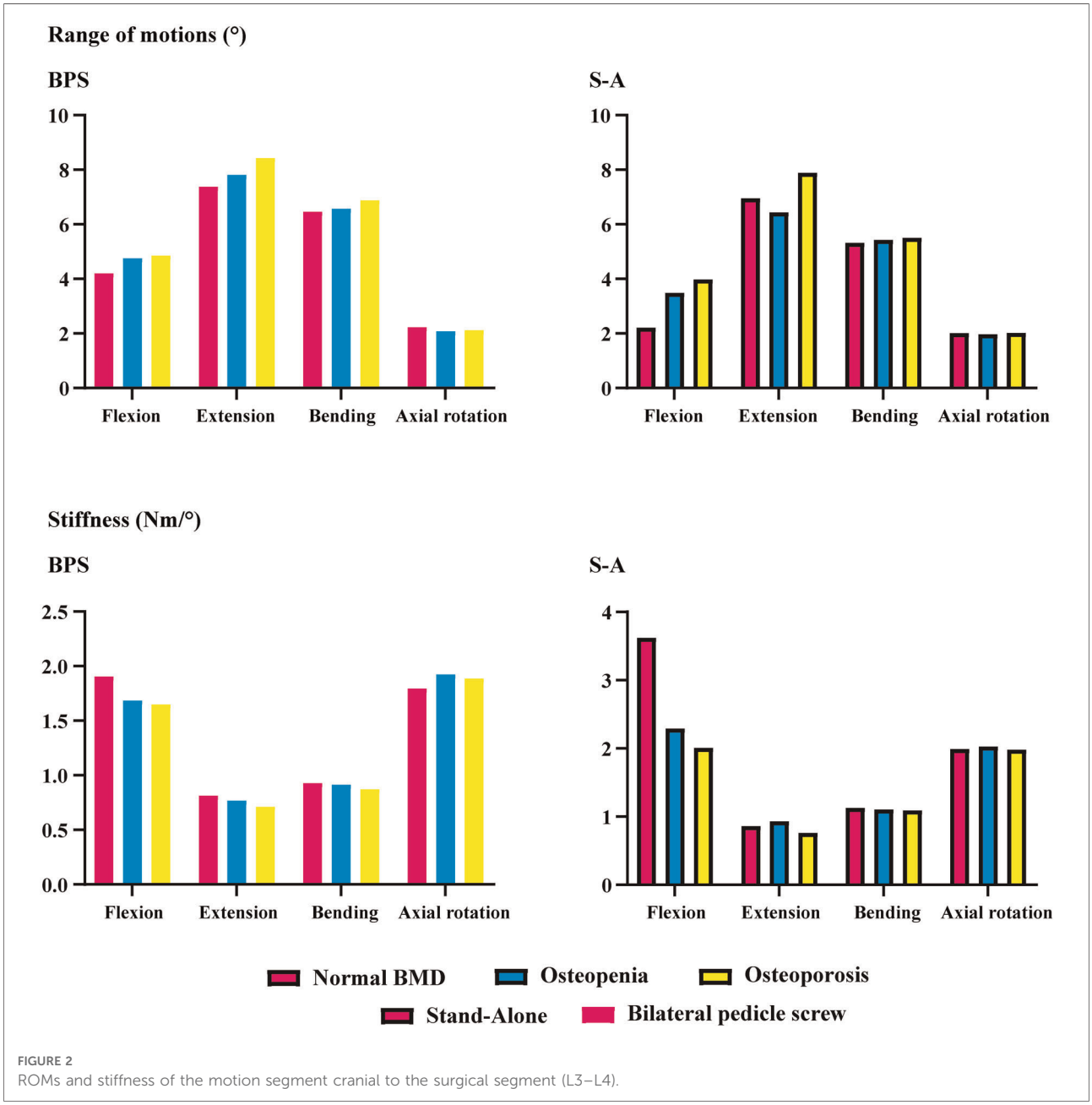

FIGURE 2
ROMs and stiffness of the motion segment cranial to the surgical segment (L3–L4).

Results

Motility compensation of adjacent segments in models with different BMDs

ROMs and stiffness in adjacent segments were computed and recorded in the present study. Both cranial and caudal motion segments exhibited identical overall variation. Specifically, one step decrease in BMD aggravated motility compensation (i.e., ROMs increased and stiffness decreased with the decrease in the bony elastic modulus). Contrary to the common belief, motility compensation was greater on the caudal side than on the cranial side in both BPS and S-A models. Under the flexion loading condition, the most significant motility compensation was observed in S-A models. Compared to the model with normal BMD, ROMs increased by nearly 80% in both cranial and caudal side motion segments (Figures 2, 3).

Only a few exceptions were observed in osteopenia models under axial rotation loading conditions, in which ROMs decreased by 6.73% and 1.99% in BPS and S-A OLIF models, respectively, and decreased by 4.93% in the osteoporosis model with BPS fixation. In addition, under the extension loading condition of BPS models, ROMs increased by 47.35% and 15.99% in osteopenia and osteoporosis models, respectively; compared to osteoporosis models, this was the

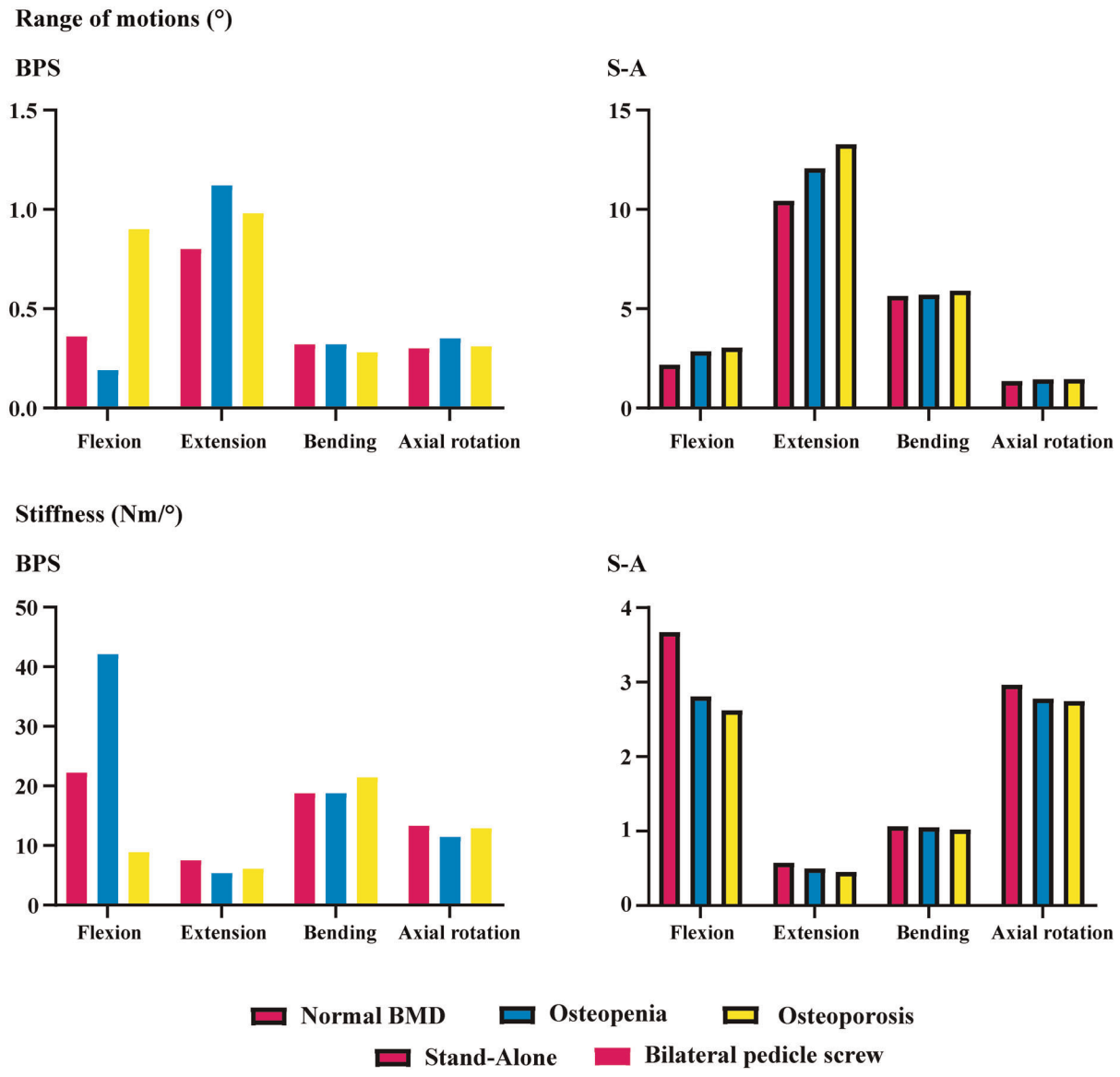

FIGURE 3
ROMs and stiffness of the motion segment caudal to the surgical segment (L5–S1).

only loading condition in which the motility compensation was more severe in osteopenia models (Figures 2, 3).

Instantly postoperative stability in the surgical segment

BPS models showed smaller ROMs and higher stiffness in the surgical segment than S-A models. Under the flexion and axial rotation loading conditions, the ROMs of the S-A models were smaller than 3°, except for the osteoporosis model, whose ROM was slightly larger than 3° under the flexion loading condition. In contrast, poor instant postoperative stability of S-A models was observed under extension and lateral bending loading conditions, in which ROMs were larger than 5° under bending and even larger than 10° under extension loading conditions. As shown in the nephograms, apparent separations were observed between the BEPs and OLIF cage in the S-A models under extension and bending loading conditions (Figures 4, 5).

Discussion

To investigate the biomechanical effects of BMD reduction on motility compensation of segments adjacent to the LIF

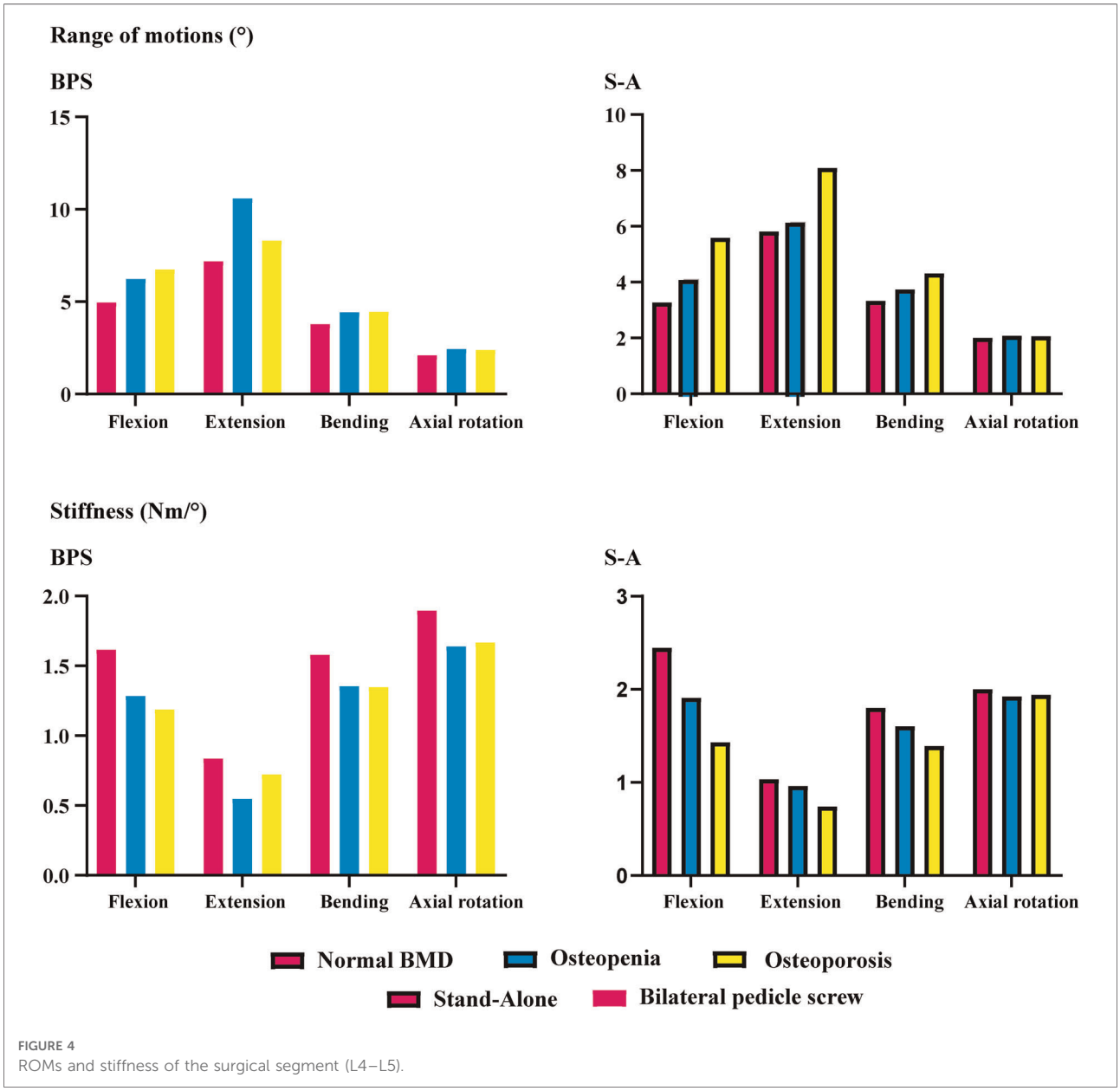

FIGURE 4
ROMs and stiffness of the surgical segment (L4–L5).

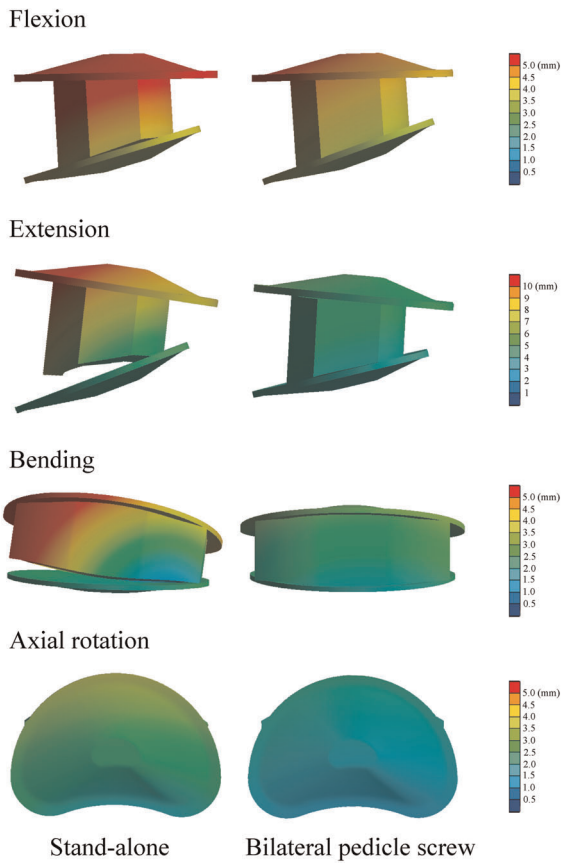

FIGURE 5
Nephograms for BEPs and the OLIF cage under different loading conditions.

operative segment, S-A OLIF and OLIF with BPS fixation were simulated in well-validated lumbosacral FE models with different BMDs. Computational results showed that the decrease in BMD leads to severe motility compensation of both cranial and caudal adjacent segments. This may be a reasonable explanation for the higher incidence of ASD in patients with poor BMD after LIF surgeries.

ASD is a widely reported complication after LIF surgeries. The recurrence of symptoms and the resulting reoperations adversely affect the clinical outcomes of patients. Biomechanical deterioration is an important cause of ASD (40, 41). Stress concentration and motility compensation are two types of biomechanical deterioration. Specifically, LIF surgery induces stress concentration in adjacent segments' IVDs and facet cartilages of zygapophyseal joints (ZJs). These changes increase the incidence of annular tears and cause acceleration of DD and degenerative osteoarthritis of ZJs (6, 23). These pathological changes are common types of ASDs. Additionally, LIF surgeries increase the stiffness of the surgical segment (decrease ROMs under the same sizes of moments). Thus, during daily activities, the reduced ROMs of the surgical segment should be compensated by adjacent segments, which is also a common cause of ASD (3, 4, 9).

In the present study, the extent of motility compensation of adjacent segments steeply increased with the decrease in bony elastic modulus. This computational result partially explains the reason why patients with osteoporosis have a high risk of ASD biomechanically. Moreover, regular antiosteoporosis therapy is recommended in osteoporotic patients after LIF surgery. Generally, surgeons believe that this patient management strategy could reduce the incidence of surgical segment complications (e.g., screw loosening and cage subsidence). On the basis of current computational results, the significance of postoperative anti-osteoporosis has been further emphasized, and we believe that it could optimize clinical outcomes of patients by reducing the risk of both surgical segment and adjacent segment complications.

The pathological process of stress concentration in adjacent segments after LIF surgery has been widely reported. Previous studies have shown that the incidence rate of ASD in the segment cranial to the surgical segment was higher than that in the caudal segment, and the biomechanical mechanism of this phenomenon was the shorter force arm, resulting in higher grades of stress concentration of the cranial side IVD (5, 6, 15). However, the variation in motility compensation was inconsistent with stress concentrations. In the present study, the variation in motility compensation in the caudal segment was overall comparable to that in the cranial segment and even more pronounced in the caudal segment under some loading conditions. Considering the exact effect of motility compensation on the risk of ASD, the incidence of ASD on the caudal side adjacent segment should not be ignored in future clinical studies (**Figures 2**, **3**).

The difference in instant postoperative stability between S-A OLIF and OLIF with BPS fixation was also compared. Consistent with the consensus, as the gold standard of AFD, BPS fixation provides excellent fixation stability (13, 42). However, the apparent separation between the OLIF cage and BEPs in the S-A models was considered for daily size moments (especially under extension and lateral bending loading conditions) (**Figure 5**). Therefore, although the BPS models show more severe motility compensation, we recommend using AFDs in OLIF patients to reduce the incidence of complications related to the separation between BEPs and the OLIF cage (e.g., cage migrations and nonunions). We also recommend restricting daily motions or AFDs (e.g., semirigid waistline) in S-A patients in the early postoperative period to reduce complication risk.

In conclusion, although no consensus was noted on the relationship between poor BMD and ASD incidence by computing stress concentration grades in adjacent segment IVDs and ZJs, a clear variation in motility compensation was observed in current models, and a reasonable explanation can be derived from the biomechanical perspective.

Specifically, following the reduction in bony BMD, differences in stiffness between the LIF motion segment with insertional devices (e.g., OLIF cage, GB, and AFDs) and adjacent segment IVDs and more severe motility compensation can be deduced.

The conclusion of this study should be accepted only after acknowledging the following limitations. As an inherent defect of FE studies, the present study could not simulate *in vivo* biological and morphological changes during the interbody fusion process. Therefore, it is difficult to simulate the influence of BEP damage, cage subsidence, and screw loosening on adjacent segments of biomechanical environments. More significantly, spinal instability could induce *in vivo* self-adaptation mechanics, leading to the generation of osteophytes that affect local biomechanical environments, which was also ignored in this study (43, 44). We hope to address these limitations in future studies by further calibration and optimization of FE models.

Conclusion

Poor BMD aggravates the motility compensation of the adjacent segment after S-A OLIF and OLIF with BPS fixation; this variation may increase the incidence of ASD. The S-A surgical method cannot provide instant postoperative stability; hence, daily motions of S-A patients should be restricted, or AFDs (e.g., semirigid waistline) should be used in the early postoperative period to avoid surgical segment complications.

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 Approval for the current study protocol (including the lumbar CT scan) was obtained from the ethics committees of Jiangsu Province Hospital on Integration of Chinese and Western Medicine (2019LWKY015). We confirm that the subject signed the informed consent and submitted it to the ethics committee for review before the examination, and all methods were carried out in accordance with relevant guidelines and regulations. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conception and design: J-CL, Z-PX, and C-YH; Model construction and finite element analysis: J-CL, Z-XF, and C-YH; Analysis and interpretation of data: C-YH, Z-FZ, FL, and J-CL; Figures preparation: Z-FZ, C-YH, X-YZ, and Z-PX; Manuscript Preparation and modification: C-YH, Z-FZ, Z-PX, and J-CL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The remaining 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. The reviewer WY declared a shared affiliation with the author ZFZ to the handling editor at the time of review.

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Early expansive single sided laminoplasty decompression treatment severe traumatic cervical spinal cord injury

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Background: Severe traumatic cervical spinal cord injury (tcSCI) is a disastrous event for patients and families. Maximizing spinal cord function recovery has become the primary therapeutic goal. This study investigated the effect of early extensive posterior decompression on spinal cord function improvement after severe tcSCI.

Methods: A retrospective review of 83 consecutive patients who underwent extensive open-door laminoplasty decompression within 24 h after severe tcSCI (American Spinal Injury Association (ASIA) impairment scale (AIS) grade A to C) between 2009 and 2017 at our institution was performed. The patient clinical and demographic data were collected. Neurological functional recovery was evaluated according to the Japanese Orthopaedic Association (JOA) score system, ASIA motor score (AMS) and AIS grade.

Results: Among the 83 patients initially included, the baseline AIS grade was A in 12, B in 28, and C in 43. Twenty-three patients (27.7%) had a high cervical injury. Cervical spinal stenosis (CSS) was identified in 37 patients (44.6%). The mean intramedullary lesion length was 59.6 ± 20.4 mm preoperatively and 34.2 ± 13.3 mm postoperatively ($p < 0.0001$). At the final follow-up visit, an improvement of at least one and two AIS grades was found in 75 (90.4%) and 41 (49.4%) patients, respectively. 24 (64.9%) patients with an improvement of least two AIS grades had CSS. The mean AMS and JOA score were significantly improved at discharge and the final follow-up visit compared with on admission ($p < 0.0001$).

Conclusions: Our results suggest that early expansive laminoplasty decompression may improve neurological outcomes after severe tcSCI, especially in patients with CSS. Larger and prospective controlled studies are needed to validate these findings.

KEYWORDS

laminoplasty, expansive decompression, cervical spinal cord injury, intramedullary lesion length, early surgery

Abbreviations

tcSCI, traumatic cervical spinal cord injury; ASIA, American Spinal Injury Association; CSS, cervical spinal stenosis; JOA, Japanese Orthopaedic Association score; AMS, ASIA motor score; SCHS, spinal canal and cord hypertension syndrome; SCPP, spinal cord perfusion pressure; SAS, subarachnoid space.

Background

The cervical spinal cord is the most frequently affected segment in traumatic spinal cord injury (SCI), potentially leading to quadriplegia, lifelong disabling neurological sequelae and even death (1). Studies have shown that SCI can be divided into primary and secondary injury according to different injury stages and pathophysiological mechanisms (2). The primary goal in treatment is to maximize the improvement of spinal cord function and the extent of spinal cord decompression, attenuate secondary injury, and stabilize the spine (3).

To date, the surgical approaches for the treatment of severe tcSCI, including posterior, anterior, and combined posterior and anterior surgical approaches, remain controversial. In previous clinical studies, most researchers preferred an anterior approach because of the cited advantages, including the direct anterior decompression of fragmented intervertebral discs, the reduction of dislocated fractures, minimal surgical trauma, and fewer complications (4–6). However, the extent of spinal cord decompression that can be achieved *via* an anterior approach is inadequate. Research shows that greater degrees of cord decompression are associated with greater degrees of neurological recovery (7). Therefore, extensive posterior decompression (by laminoplasty or laminectomy) and reduction have gained increased attention from clinical researchers over recent years, with results including successful decompression, reduction for zygapophysis interlocking, and better alignment and motor unit preservation (8–12). In addition, in cases of huge disc herniation, burst fracture involving the vertebral posterior wall, and cervical kyphosis, the combined posterior and anterior approach is suitable, with the posterior approach allowing for stabilization and decompression, and the anterior approach for decompression disc and fracture fragments, and correction of kyphosis (13, 14). In this article, we examine the effect of extensive posterior open-door laminoplasty decompression within 24 h after severe tcSCI on spinal cord function improvement and investigate whether extensive decompression can promote the resolution of spinal cord edema.

Patients and methods

General information

This single-center, longitudinal, retrospective study was conducted to investigated the effect of early extensive laminoplasty decompression on spinal cord function improvement after severe tcSCI. The present study was approved by the Institutional Ethics Committee (ethics approval number: ky2018106) and informed consent was obtained from all patients. A cohort of 83 patients with severe tcSCI (AIS grade A to C), who underwent extensive open-door laminoplasty decompression (with or without pedicle screw fixation) within 24 h after trauma between January 2009 and January 2017 were included in the study. The exclusion criteria were as follows: central cord syndrome; complicating traumatic brain injury; history of cervical spine surgery; klippel-Feil syndrome; ankylosing spondylitis; tumors of other tissues or organs; intolerance to posterior approaches due to a poor general condition.

An electronic medical database was used to collect patient clinical and demographic information, including age, gender, mechanism of injury, fractures or dislocations, CSS, patient date of injury to operation, SCI level, operative procedures, operative time, blood loss, hyponatremia (serum sodium concentration <135 mmol/L), hypotension (arterial systolic blood pressure <90 mmHg) and tracheotomy.

Surgical technique

Decompression surgery was performed within 24 h following trauma. The operation program was implemented as follows: all patients underwent posterior open-door laminoplasty; in the patients with fractures and dislocations, pedicle screw fixation was performed simultaneously; a second stage anterior surgery was added when neurological deterioration occurred due to a large nonreduced disc fragment identified on preoperative magnetic resonance imaging (MRI). Following general anesthesia, the patient was placed in the prone position and their position was fixed using a Mayfield head holder, and continuous skull traction was performed with 5–8 kg weights to allow a maximally horizontal head position. The laminae were exposed through detached the bilateral paravertebral muscles, then the processes were removed. The range of laminoplasty decompression was from at least one lamina above and below the edematous segment according to MRI and/or absence of the subarachnoid space (SAS) (15). Then, single open-door laminoplasty was performed using a high-speed air-burr drill (15). Usually, the side with severely paralyzed as the door opening side, and the other side as the hinge side. Reduction and pedicle screw fixation was performed in patients with fractures and dislocations using a previously described method (8, 12, 15). To relieve spinal cord compression as soon as possible, we usually implemented open-door first, then inserted the pedicle screw to recovery cervical alignment, kept the door open with titanium plate or threads last.

Postsurgical treatments

Conventional drainage under negative pressure was applied for 1–3 days after the operation. The drainage tube remained in

place for 7–9 days when the patient complicated with cerebrospinal fluid (CSF) leakage. Antibiotics, dexamethasone, mannitol, and neurotrophic agents (ganglioside) were routinely used for 3–5 days after surgery. Patients were protected by a cervical collar for approximately 1 month postoperatively. The patients who were discharged to a rehabilitation center, the mean hospital length of stay were 17.2 ± 4.3 days.

Imaging analysis

Pre- and postoperative and follow-up imaging studies were conducted for patients, and the measurement results were evaluated by two independent, blinded spine surgeons and one imaging diagnostician. X-ray and computed tomography (CT) images were used to measure the Torg–Pavlov ratio [TPR; TPR less than 0.82 indicates cervical spinal stenosis (CSS)] (16) and to classify the injury morphology according to the AOSpine subaxial cervical spine injury classification system preoperatively (17). Additionally, radiological examination of the cervical spine was performed postoperatively for patients to determine the exact surgical procedure, cervical anatomical alignment, and degree of bony decompression. MRI of the cervical spine was performed using a 1.5-Tesla Siemens MRI system (Siemens Magnetom; Aera, Erlangen, Germany). Preoperative MRI data were available for review in 95.2% of cases, obtained within 9.3 ± 6.8 h after trauma; postoperative MRI data were available for review in 90.4% of cases, obtained at 10.8 ± 0.95 days after trauma. Quantitative and qualitative measurements obtained for this study included the intramedullary lesion length (IMLL), hematoma length, decompression, injury and intervertebral disc sequestration, as previously described (**Figures 1**, **2**, **3**) (18). Successful decompression was defined as the patency of CSF pathways and the presence of an open SAS around a contused and swollen spinal cord (**Figures 1G**, **2J**, **3G**).

Clinical assessment

Neurological functional recovery and grade conversion were evaluated according to the ASIA motor score (AMS) and impairment scale (AIS) grade on admission, at hospital discharge, and at the final follow-up visit (19). In addition, Japanese Orthopaedic Association (JOA) score (20) was recorded at the same time points. The recovery rate was calculated using the method described by Hirabayashi to compare the pre- and postoperative JOA scores (21). Patients were followed for at least 1 year (3.7 ± 2.4 years) after trauma.

Statistical analysis

Statistical data analysis was performed using SPSS software version 19.0 (IBM, New York, NY, United States). All data were expressed as mean ± standard deviation (SD). Independent samples t test was used for the statistical analysis of parametrically distributed variables. Fisher's exact test and chi-squared test were used for categorical variables. The Manne-Whitney *U* test was used to evaluate the association of postoperative scores (AMS, JOA score). $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics

A total of 83 patients (male: 76; female: 7) met the eligibility criteria. The key demographic, clinical, and outcome parameters of these patients are summarized in **Table 1**. Among the 83 patients initially included in the trial, the baseline AIS grade was A in 12, B in 28, and C in 43. The level of SCI is shown in **Figure 4**; of the patients, 23 had a high cervical injury (C1 to C4, 27.7%). Of the 83 patients, 8 (9.6%) underwent four-level laminoplasty, 73 underwent five-level laminoplasty, and 2 underwent six-level laminoplasty. In addition to the laminoplasty, an additional dorsal spinal stabilization was performed in 29 cases. No patients required an anterior surgical intervention for additional decompression of a large, nonreduced disc fragment.

Postoperative complications

Dural leakage was observed in 7 (8.4%) cases after surgery and treated by pressure suture drainage orifice after 7–9 days of drainage. Two patients had incision infection and one had central nervous system infection. They were cured by changing dressings, using sensitive antibiotics and lumbar cistern drainage. Six patients developed pneumonia. The incidence of hyponatremia, hypotension and tracheotomy was 59%, 14.5% and 3.6%, respectively. A follow-up period of least 1 year was achieved for 77 patients, with a retention rate of 92.8%. Six patients were lost to follow-up in the acute stage of SCI due to the following reasons: brain death in 1 case; respiratory failure in 3 cases; hypotension and cardiac arrest in 2 cases.

Imaging results

Several studies have provided ample evidence that MRI scanning is useful for providing objective measures of tSCI to

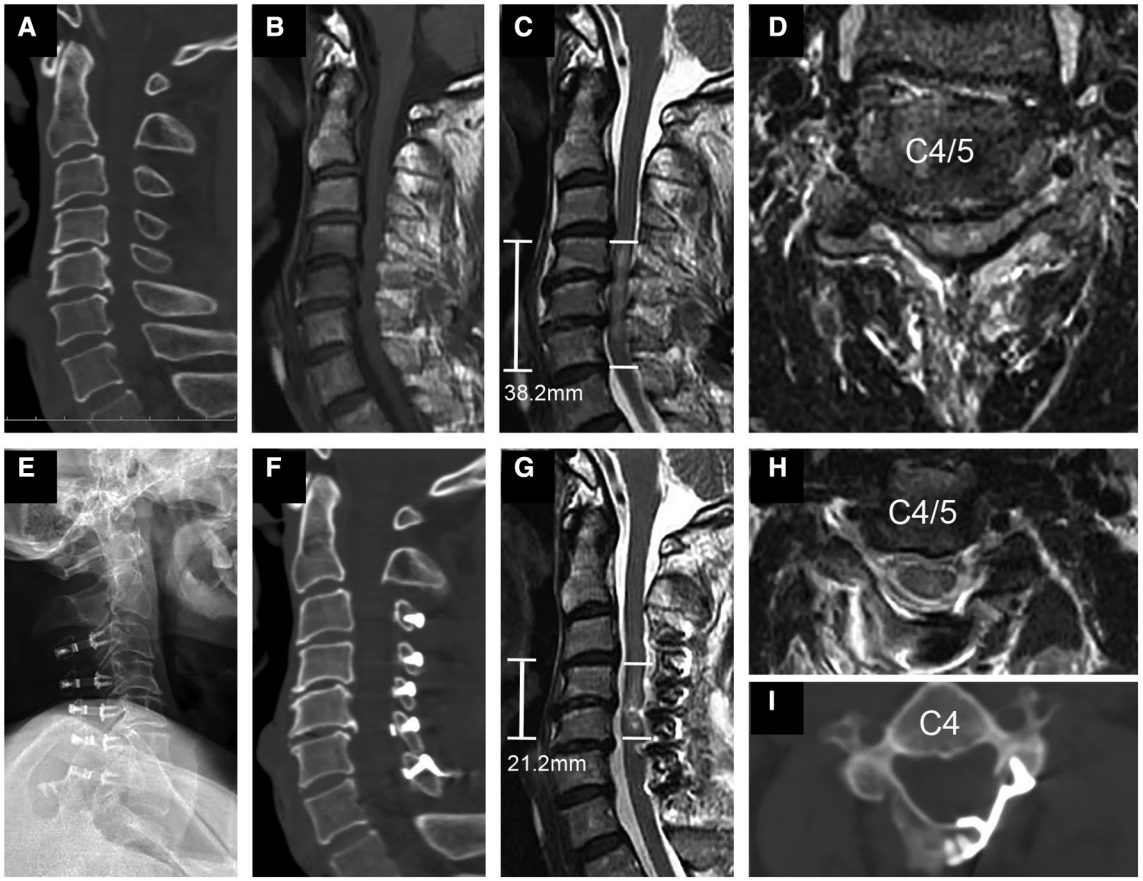

FIGURE 1
Representational preoperative (A–D) and postoperative (E–I) images of a 58-year-old male patient who sustained a spinal cord injury without fracture or dislocation. His AMS was 18 and AIS grade C. Midsagittal subaxial CT (A) indicated cervical spinal stenosis (CSS) from C3 to C6, and MRI (B) SCI with an intramedullary lesion length (IMLL) of 38.2 mm. The subarachnoid space (SAS) was absent at C4 and C5 (C,D). Laminoplasty of C3–7 was performed in this patient 17 h after trauma. Postoperative x-rays (E) and CT (F,I) showed significant enlargement of the osseous spinal canal. Postoperative MRI showed an IMLL of 21.2 mm (G) and successful decompression (G,H) indicated by the presence of an open anterior and posterior SAS 11 days after trauma. One year after injury, the patient recovered from paralysis with an AMS of 100 and AIS grade of E.

both distinguish the injury severity and predict the AIS grade conversion (18). All 79 subjects with MRI records were found to have spinal cord edema on MRI at admission (Table 2). The mean pre- and postoperative IMLL was 59.6 ± 20.4 mm and 34.2 ± 13.3 mm, respectively ($p < 0.0001$). Significant decreases in edema, as indicated by the signal intensity on T2 MRI, were observed far from the damage center postoperatively compared with preoperatively. No patients showed an increased IMLL or complete fading of the edema on MRI after surgery. Intramedullary spinal cord hemorrhage was demonstrated in 20.5% of patients, mostly in AIS grade A and B patients (Figure 3). The mean rostrocaudal hemorrhage length pre- and postoperatively was 5.11 ± 1.64 mm and 4.62 ± 1.41 mm, respectively ($p = 0.55$, Table 2). In 81 of 83 patients (97.6%), complete spinal cord decompression was achieved. The remaining two patients, who underwent C3–C7 laminoplasty, showed insufficient decompression due to large disc herniation and cervical spine sequence problems (anterior decompression was not performed due to significant improvement in spinal cord function).

During the follow-up period, the injury sites were observed to be occupied by cysts and myelomalacia, as depicted by bright signals on T2 MRI. However, no syringomyelia or spinal atrophy was found on follow-up MRI. In all patients treated with a posterior approach, "close the door" was not observed after single open-door decompression. Loosening, dislocation, and breakage of the internal fixation instrumentation were not observed by radiological examination at the follow-up visit. Two patients showed cervical kyphosis during the follow-up period.

Neurological outcomes

In the study group, neurological improvement according to the change in the AIS grade from the preoperative assessment to the final follow-up visit is represented in Table 3. No patients

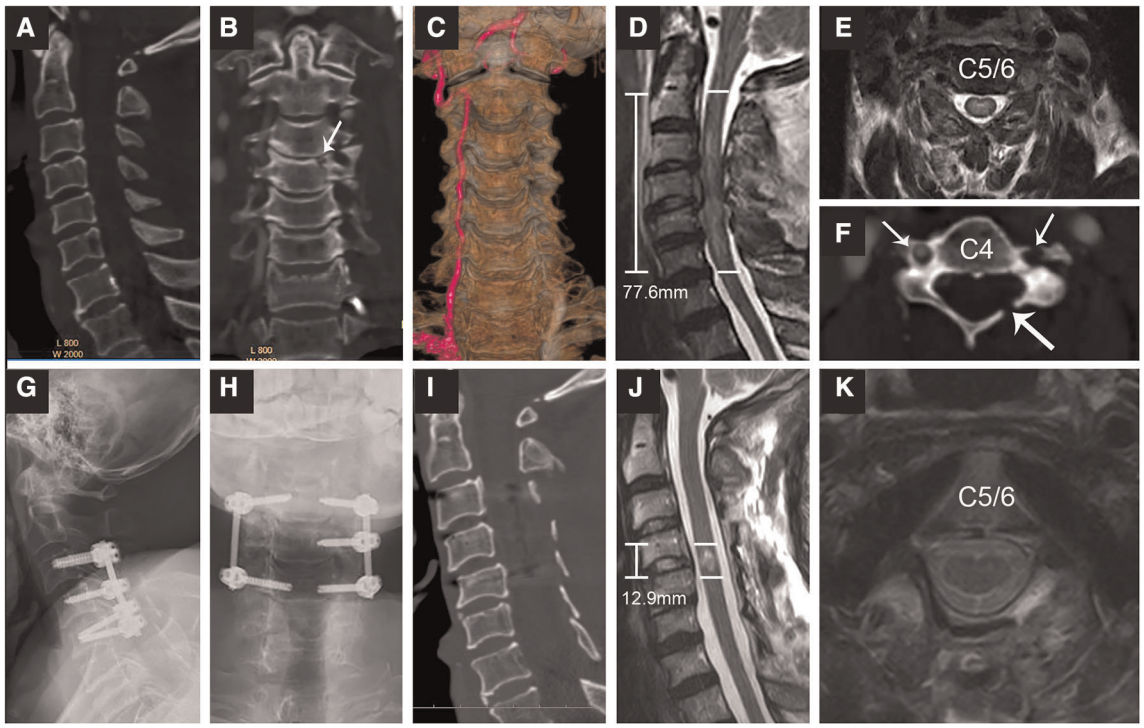

FIGURE 2
Representational preoperative (A–F) and postoperative (G–K) images of a 68-year-old male patient who sustained an A1 type fracture and spinal cord injury. His AMS was 11 and AIS grade B. Midsagittal (A), coronal (B,C) and axial (F) enhanced CT indicated an A1 type fracture at C4 (B) accompanied by fractures of the left lamina (F, long arrow) and transverse foramen (short arrow) and injury to the left vertebral artery (C). MRI (D,E) showed SCI with an intramedullary lesion length (IMLL) of 77.6 mm. The subarachnoid space (SAS) was absent from C3 to C5 (D). Laminoplasty of C3–7 and pedicle screw fixation from C3–C5 were performed in this patient 9 h after trauma. Postoperative x-rays (G,H) and CT (I) showed good screw positioning and significant enlargement of the osseous spinal canal. Postoperative MRI indicated an IMLL of 12.9 mm (J), successful decompression (J), and reduced edema 12 days after trauma. One year after injury, the patient paralysis recovery with an AMS of 72 and AIS grade D.

showed a worsening AIS grade at postoperatively. An improvement of at least two AIS grades and of at least one AIS grade was found in 41 (49.4%) and 75 (90.4%) patients at the final follow-up visit, respectively; 24 (64.9%) patients with an improvement of least two AIS grades had CSS. In some patients with CSS and diffuse hyperintense or faint signals on MRI, neurological function was significantly improved several hours after decompression.

The mean AMS on admission, at discharge and at the final follow-up visit was 24.5 ± 16.7, 49.4 ± 26.8 and 70.8 ± 23.0, respectively (Table 4). The AMS showed a significant improvement at discharge and at the final follow-up visit compared with that on admission ($p < 0.001$). The average JOA score was 1.49 ± 1.61 points on admission, 4.95 ± 3.44 points at discharge, and 10.98 ± 4.72 points at the final follow-up visit (Table 4). A significant improvement in the JOA score was achieved at discharge and at the final follow-up visit compared with that on admission ($p < 0.001$). The average recovery rate of the JOA score was $56.1 \pm 23.1\%$ at the final follow-up visit.

Discussion

We performed a retrospective study at a single trauma center to evaluate the effect of extensive posterior decompression within 24 h after severe tcSCI on neurological outcomes. In accordance with our hypothesis, we found a significant and rapid improvement in neurological function in patients undergoing early extensive decompression by laminoplasty through the rapid resolution of spinal cord edema visualized *via* T2 MRI. An improvement of at least one and two AIS grades was found in 90.4% and 49.4% patients, respectively.

Numerous previous clinical studies on tcSCI have suggested that early surgical decompression might promote neurological recovery (22–26). In a multicenter study, Fehlings et al. demonstrated that early surgery (<24 h) resulted in superior neurological recovery at 6 months compared to late surgery (≥24 h) in patients with cervical SCI (27). In addition, Wilson et al. comparing the effect of early surgical decompression within 24 h to later time frames, they found that

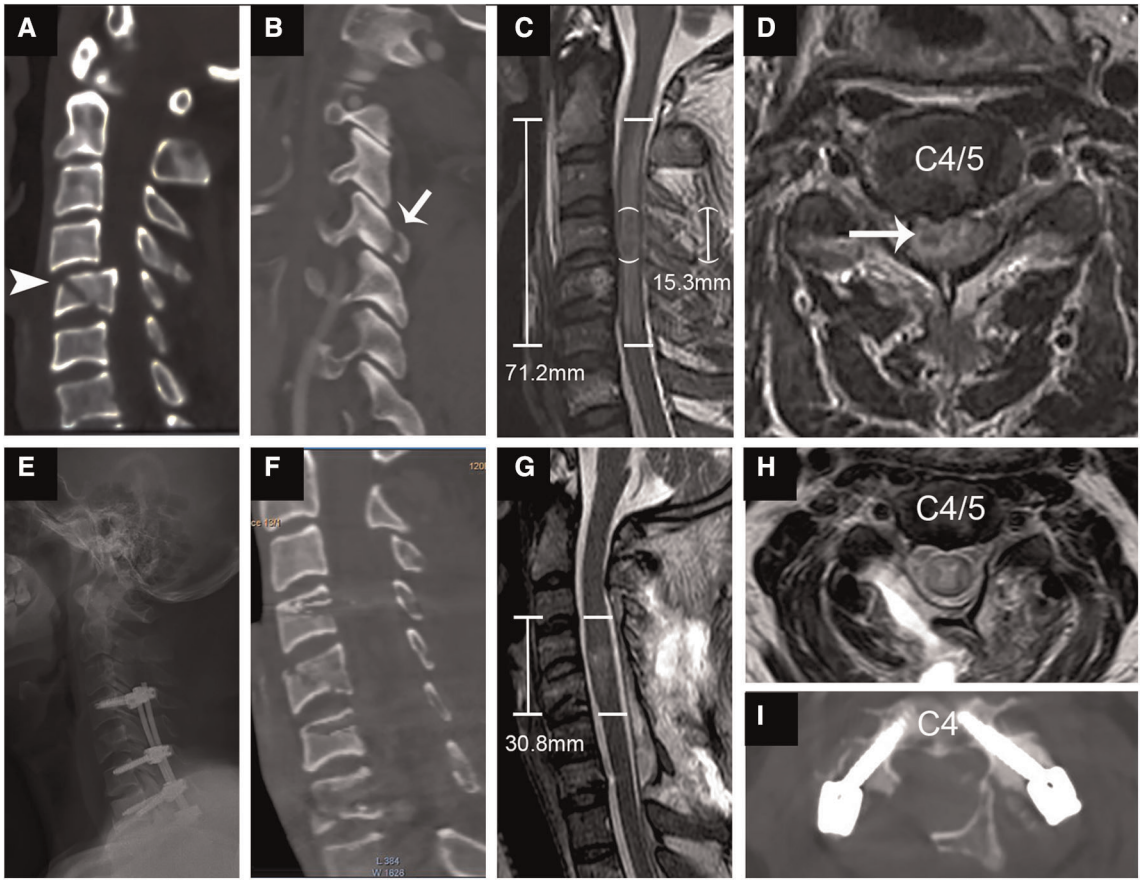

FIGURE 3
Representational preoperative (**A–D**) and postoperative (**E–I**) images of a 44-year-old male patient who sustained a C type fracture and spinal cord injury. His AMS was 3 and AIS grade A. Sagittal subaxial CT indicated C4 translation rotation injury (**A**) accompanied by fracture of the right inferior articular process (**B**, short arrow) and C5 teardrop fracture (arrowhead). MRI (**C**,**D**) showed SCI with an IMLL of 71.2 mm and intramedullary hemorrhage (long arrow) 15.3 mm in length. The subarachnoid space (SAS) was absent from C3 to C5 (**C**). Laminoplasty of C3–7 and pedicle screw fixation from C4–C7 were performed in this patient 14 h after trauma. Postoperative x-rays (**E**) and CT (**F**,**I**) showed good screw positioning and significant enlargement of the osseous spinal canal. Postoperative MRI indicated an IMLL of 30.8 mm (**G**) and successful decompression (**G**,**H**) 12 days after trauma. One year after injury, the patient paralysis recovery with an AMS of 58 and AIS grade **C**.

decompression before 24 h after tSCI was associated with significantly improved neurological outcomes (27, 28). In our study, we included 83 patients with tcSCI who underwent decompression within 24 h. The average AMS and JOA score was 70.8 ± 23.0 and 10.98 ± 4.72 points at the final follow-up visit compared with 24.5 ± 16.7 and 1.49 ± 1.61 points on admission, respectively (**Table 4**). This notable neurological recovery is consistent with previous studies. This result might be explained by early surgical decompression expeditiously relieving mechanical spinal cord compression, thereby improving the spinal cord blood supply to avoid or mitigate secondary damage cascades and SCHS and to facilitate the restoration of spinal cord function (2, 22, 29). Badhiwala and colleagues stated that "time is spine" (30) and highlighted that there is a critical time window after primary injury to the spinal cord during which secondary injury mechanisms, which cause further neural tissue destruction, may be curtailed (31).

Furthermore, Jug et al. demonstrated that patients with tcSCI who undergo surgical decompression within 8 h after injury have superior neurological outcomes than patients who undergo decompression 8–24 h after injury, without any increase in the rate of adverse effects (32). Among 22 patients (19 AIS grade A or B) who underwent decompression within the first 8 h after tcSCI, they found an improvement of at least one and two AIS grades in 72.7% and 45.5% patients, respectively, at 6 months (32). In the current study, an improvement of at least one and two AIS grades was observed in 90.4% and 49.4% patients at the final follow-up visit. The higher odds of achieving an improvement in the AIS grade of at least a one grade in our study than in Jug's study might be due to the difference in the surgical method used for decompression; extensive posterior laminoplasty (assisted with posterior pedicle screw fixation if necessary) was performed in our study, whereas

TABLE 1 Demographic and clinical characteristics of patients.

Characteristic	Value
Number of patients	83
Male-to-female ratio	76:7
Age, years, mean ± SD	54.3 ± 10.9
Duration trauma to MRI, hours, mean ± SD	9.3 ± 6.8
Duration trauma to surgery, hours, mean ± SD	16.5 ± 7.1
AOSpine fractures classification	
Type A0	54
Type B2	10
Type B3	7
Type C	12
Cervical spinal stenosis (%)	37 (44.6)
Injury mechanism	
Traffic accidents (%)	17 (20.5)
Fall injuries (%)	55 (66.3)
Heavy load injuries (%)	11 (13.3)
AIS Grade	
Grade A (%)	12 (14.5)
Grade B (%)	28 (33.7)
Grade C (%)	43 (51.8)
Level of Laminoplasty	
Laminoplasty of four-level (%)	8 (9.6)
Laminoplasty of five-level (%)	73 (88.0)
Laminoplasty of six-level (%)	2 (2.4)
Dorsal spinal stabilization (%)	29 (34.9)
Surgical duration, minutes, mean ± SD	92 ± 43
Blood loss, mL, mean ± SD	173 ± 76
Time of hospital stay, days, mean ± SD	17.2 ± 4.3
Time of follow-up, years, mean ± SD	3.7 ± 2.4

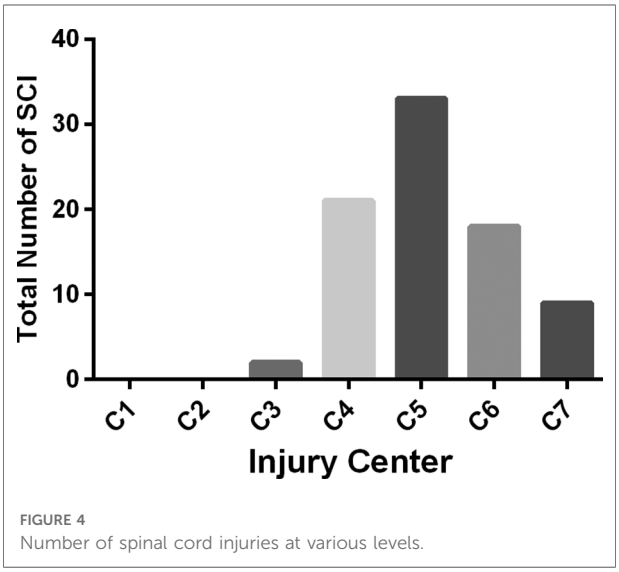

FIGURE 4
Number of spinal cord injuries at various levels.

TABLE 2 Mean intramedullary lesion length and hematoma length.

Variable	Preoperative	Postoperative	*t* value	*p* value
IMLL	59.6 ± 20.4	34.2 ± 13.3	9.46	$p < 0.0001$
Hemorrhage length	5.11 ± 1.64	4.62 ± 1.41	0.94	$p = 0.55$

Values are mean ± SD, mm. IMLL, intramedullary lesion length.

TABLE 3 Changes in American spinal injury association impairment scale (AIS) grade from pre-operative to final follow-up.

Preoperative AIS grade	A	B	C	D	E	Total
A	3	1	6	2		12
B		5	4	17	2	28
C				29	14	43

TABLE 4 AMS and JOA scores at admission, discharge and follow-up.

Scores	Admission	Discharge	Final follow-up
AMS	24.5 ± 16.7	49.4 ± 26.8*	70.8 ± 23.0*
JOA scores	1.49 ± 1.61	4.95 ± 3.44*	10.98 ± 4.72*

Values are mean ± SD.
AMS, American spinal injury association motor score; JOA, Japanese orthopaedic association.
Significant differences for the discharge and final follow-up versus admission ($p < 0.001$).

anterior discectomy (ADF) or corpectomy (ACF) and fusion was preferred in Jug's study.

Obviously, more adequate decompression increases the possibility of upward AIS grade conversion (2, 7, 18). In a recent study, Piazza reported that posterior cervical laminectomy results in better radiological decompression of the posterior CSF space than does ADF (11). Unfortunately, the authors did not evaluate the clinical effect. Another study, by Aarabi, demonstrated that the rate of decompression in patients who underwent ADF and ACF without laminectomy was 46.8% and 58.6%, but that in patients who underwent laminectomy at one, two, three, four, and five levels was 58.3%, 68%, 78%, 80%, and 100%, respectively (9). They indicated that performing laminectomy for motor complete tcSCI patients significantly increased the rate of successful spinal cord decompression, leading to better neurological outcomes, independent of whether anterior surgery was performed (9). Additionally, recent therapeutic trials have confirmed the continued importance on the combined effects of the timing of surgical intervention and extent of surgical decompression on the tcSCI (33–35). Therefore, in this study, we implemented extensive laminoplasty within 24 h for severe tcSCI patients and found a significant increase in the rate of AIS grade conversion (90.4%) and improved neurological

function, as determined by the AMS and JOA score (Table 4). Furthermore, MRI showed that the IMLL was significantly decreased 8–14 days (34.2 ± 13.3 mm) after surgery compared with preoperatively (59.6 ± 20.4 mm), and 97.6% of patients achieved complete decompression. This study indicates that combined early and extensive surgical decompression significantly promotes the recovery of spinal cord function through the rapid resolution of spinal edema.

On the other hand, it is possible that the superior rate of AIS grade conversion in our study compared with that in Jug's (32) study is because of the larger proportion of AIS grade C patients, who may be able to achieve better neurological recovery than AIS grade A and B patients (36, 37). In addition, we found that tcSCI patients without fractures or dislocations but with CSS could achieve significant neurological function recovery within several hours after extensive decompression, with a significantly higher rate of an improvement of two AIS grades than the others patients. This difference may be due to early extensive decompression reducing the ISP, resulting in recovery of the spinal cord blood supply and electrophysiological abnormalities (22).

Compared with laminectomy in previous studies (9, 11), similar clinical improvements can be achieved with extensive laminoplasty, as in the present study (38). However, because the laminae are still available for load bearing and attachment of the paraspinous muscles, laminoplasty can reduce the risk of spinal segment deterioration, daily microtrauma, instability, late kyphosis, and neurological deficits (induced by postlaminectomy membrane) (38–40). In this study, open-door laminoplasty was implemented because of its low surgical difficulty, short time, limited trauma and enough spinal canal area compared with double-door laminoplasty (41). At least one year of follow-up, only two cases cervical kyphosis were found; this low incidence may be related to the routinely protection of the posterior cervical muscles and reconstruction the C2 extensor attachment points (42, 43). In addition, due to the retention of lamina medial cortex on the hinge side and the use of titanium plates, no reclosed open-door was observed during follow-up.

Finally, we acknowledge that this study has inherent limitations as a retrospective, single-center investigation. The sample size and the lack of a comparison between surgery with anterior and combined posterior and anterior approaches are also limitations of this study. Furthermore, in patients with intramedullary hematoma and edema signals in long segments, we did not perform hematoma elimination or duraplasty. Previously several investigations have indicated that even laminectomy may not sufficiently improve the ISP and attenuate SCHS and that duraplasty may have to be required in severe tcSCI patients (9, 12, 44), as is practiced in decompressive craniectomy for diffuse traumatic brain injury (45–47). Therefore, further research is required to explore whether supplemental duraplasty and intramedullary hematoma elimination can further promote spinal cord function recovery compared with stand-alone extensive laminoplasty.

Conclusion

Our retrospective analysis results suggest that early extensive open-door laminoplasty promotes neurological recovery by promoting the rapid resolution of spinal cord edema. The recovery of spinal function was more significant in patients with CSS. Larger, prospective controlled studies are needed to validate these findings, and duraplasty and intramedullary hematoma elimination will be further explored.

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 This work was approved by ethics committee of the Affiliated Hospital of Southwest Medical University (ky2018106). 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

GW and QW were responsible for the study design. CY was responsible for collecting the data, analyzing the data, and drafting the manuscript. GW and CY were responsible for analyzing the data, and revised the manuscript. SX, CG and GL were responsible for statistics and drafting. 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

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Cerebrospinal fluid leaks following intradural spinal surgery—Risk factors and clinical management

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Background: Cerebrospinal fluid leakage (CSFL) following spinal durotomy can lead to severe sequelae. However, while several studies have investigated accidental spinal durotomies, the risk factors and influence of clinical management in planned durotomies remain unclear.
Methods: We performed a retrospective analysis of all patients who underwent planned intradural spinal surgery at our institution between 2010 and 2020. Depending on the occurrence of a CSFL, patients were dichotomized and compared with respect to patient and case-related variables as well as dural closure technique, epidural drainage placement, and timing of mobilization.
Results: A total of 351 patients were included. CSFL occurred in 4.8% of all cases. Surgical indication, tumor histology, location within the spine, previous intradural surgery, and medical comorbidities were not associated with an increased risk of CSFL development (all $p > 0.1$). Age [odds ratio (OR), 0.335; 95% confidence interval (CI), 0.105–1.066] and gender (OR, 0.350; 95% CI, 0.110–1.115) were not independently associated with CSFL development. There was no significant association between CSFL development and the dural closure technique ($p = 0.251$), timing of mobilization ($p = 0.332$), or placement of an epidural drainage ($p = 0.321$).
Conclusion: CSFL following planned durotomy pose a relevant and quantifiable complication risk of surgery that should be factored in during preoperative patient counseling. Our data could not demonstrate superiority of any particular dural closure technique but support the safety of both early mobilization within 24 h postoperatively and epidural drainage with reduced or no force of suction.

KEYWORDS
cerebrospinal fluid leak, drainage, postoperative complications, mobilization, spine

Introduction

Cerebrospinal fluid leakage (CSFL) is a severe complication following incidental or planned durotomy in spinal procedures. Possible sequelae include infectious complications ranging from wound infections to meningitis, intracranial hypotension and hemorrhage, nerve root compression syndromes, and back pain, as well as the

necessity for revision surgery, increased morbidity, a prolonged hospital stay, and higher healthcare costs (1, 2). However, the majority of studies on secondary CSFL investigate the setting of incidental durotomy; hence, there are limited data regarding patient and case-related risk factors for CSFL following planned durotomy, i.e., for the resection of spinal intradural tumors (3, 4). Furthermore, the perioperative management following planned durotomies is highly variable. Different surgical techniques for dural closure are available, the benefit of epidural drainage placement remains unclear, and the utility of postoperative immobilization has been discussed controversially. Thus, we aimed to identify possible risk factors for the occurrence of CSFL following intradural spine surgery in order to improve preoperative patient counseling and to analyze perioperative management strategies.

Materials and methods

This study is a single-center retrospective analysis of 351 consecutive cases of intradural spine surgery conducted at our institution between June 2010 and December 2020, in accordance with the local ethics committee guidelines.

Inclusion and exclusion criteria

All patients who underwent surgery for an intradural spinal pathology at our institution between June 2010 and December 2020 were included in this study. All cases with incomplete data records and patients under the age of 18 years at the time of surgery were excluded, as well as craniocervical pathologies involving the posterior fossa, i.e., Chiari malformations were excluded.

Data collection

A postoperative CSFL was defined as either cerebrospinal fluid (CSF) leakage through the operative wound (CSF fistula) or development of a pseudomeningocele refractory to conservative therapy and requiring revision surgery. The incidence of CSFL within the study cohort was recorded over an observational period of at least 3 months following intradural surgery.

Medical charts were reviewed for the following variables: age, gender, medical comorbidities (hypertension, coronary heart disease, diabetes mellitus type II, chronic obstructive pulmonary disease, history of smoking), obesity (defined as a body mass index > 30), and duration of hospital stay.

In two cases, two different spinal segments distant from each other were operated on during the same procedure and recorded as two separate cases.

Type of surgical indication, tumor histology, surgical approach, and previous intradural operations on the same level were analyzed. Tethered cord syndrome and different forms of spinal dysraphism were summarized as developmental malformations. Tumor histology was determined according to the current WHO classification in effect.

Spinal surgery location was classified as cervical, thoracic, or lumbosacral. In case of a junctional segment, classification was based on the upper vertebra (e.g., a C7/T1 procedure was classified as a cervical case).

Surgical technique

The dural exposure was classified according to the surgical report (laminectomy, hemilaminectomy, or laminoplasty). All durotomies were performed either median or paramedian along the longitudinal axis of the dural sac. All meningiomas were resected without removal of the associated dura, and the dural insertion site was coagulated corresponding to Simpson Grade II.

Perioperative management in our study cohort was based on a case-by-case decision according to the intraoperative findings and the preference of the treating surgeon; there were no institutional protocols regarding dural closure technique, epidural drain placement, or timing of mobilization.

Surgical dural closure technique was categorized into the following: (1) standalone suture repair, (2) suture plus a liquid fibrin sealant (TISSUCOL Duo S Immuno®, Baxter International Inc.), (3) suture plus a patch sealant (TachoSil®, Takeda Pharma and Hemopatch®, Baxter International Inc.), (4) suture plus a liquid fibrin sealant and a patch sealant, or (5) suture plus another combination and/or material [e.g., muscle, fascia or a dura replacement material (DuraGen® Plus, Integra LifeSciences; Neuro-Patch®, B. Braun; GORE PRECLUDE® Pericardial Membrane, W. L. Gore & Associates, Inc.].

The additional placement of an epidural drainage as well as the applied force of suction (full, reduced, none) were recorded. The full force of suction applied by the used drainage system was 150 mbar (150 hPa).

The ordered duration of postoperative strict bed rest was summed into an early mobilization (within 24 h) and a late mobilization group (after 24 h).

Procedure-related complications were classified as wound healing disorders without CSFL, epidural hemorrhage, neurological complications (postoperative new or deteriorated deficit, meningitis), urinary tract infections, pneumonia, or miscellaneous.

Statistical analysis

Patients were dichotomized according to the occurrence of CSFL. Differences between the two groups were analyzed

using descriptive statistics. To compare categorical variables, the Chi-square and Fisher's exact tests were used, when appropriate. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Group means with normally distributed data were compared using the two-sided unpaired Student's *t* test and the Mann–Whitney *U* test in case of non-normally distributed data. Continuous variables are reported as mean and standard deviation (mean ± SD) or as median and range (minimum, maximum). Risk is reported as absolute risk, unless otherwise stated. All calculations were performed using SPSS software (Version 27, IBM SPSS Statistics for Windows, Armonk, NY, USA). A *p*-value <0.05 was considered as statistically significant.

Results

Patient characteristics

A total of 351 patients who underwent surgery for an intradural spinal pathology were included. Median patient age was 55 years (range: 19–94), and 50.1% were female. The most common surgical indication was resection of an intradural tumor (75.5%). Of these, meningiomas (30.9%), intramedullary tumors (30.2%), and nerve sheath tumors (28.3%) were the most frequent histological diagnoses. The most common surgical site was the thoracic spine (49.9%), followed by lumbosacral (33.3%) and cervical spine (16.8%). In 13.1%, intradural surgery had previously been performed at the same level. Detailed patient characteristics including medical comorbidities are displayed in Table 1.

Perioperative factors

Surgical exposure mainly involved a single level (82.9%) and the majority of cases were operated *via* a hemilaminectomy (46.2%) or laminoplasty (21.9%). Dural closure was performed using a combination of suture plus a sealant patch in 72.9%, suture plus a liquid sealant as well as a sealant patch in 10.8%, suture plus other materials (e.g. fascia or muscle) in 12.3%, suture plus a liquid sealant in 1.4%, and dural suture was not augmented in 2.6% of all cases (Table 2). An epidural drainage was placed in 191 (54.4%) cases. Of those, reduced suction was applied in 117 (61.3%) and no suction in 74 (38.7%) cases; full suction was never applied. Mean duration of bed rest was 1.6 (±1.3) days. Of all patients, 53.0% were mobilized within 24 h and 47.0% after 24 h (Table 3).

Risk factors for cerebrospinal fluid leak

CSFL occurred in 17 cases (4.8%). In univariate analysis, age (median 55 vs. 50 years, $p = 0.025$) and gender (2.3% female vs.

TABLE 1 Patient and case-related factors.

	No CSFL $n = 334$ N (row %)	CSFL $n = 17$ N (row %)	*p*-value
Age (median, range)	55 (19-94) years	50 (21-72) years	0.049
≥55 years	159 (92.4%)	13 (7.6%)	0.025
<55 years	175 (97.8%)	4 (2.2%)	
Sex			
Female	172 (97.7%)	4 (2.3%)	0.027
Male	162 (92.6%)	13 (7.4%)	
Surgical indication			
Intradural tumor	255 (95.1%)	13 (4.9%)	0.991
Arachnoid cyst	25 (92.6%)	2 (7.4%)	0.630
Arachnoiditis	12 (100.0%)	0 (0.0%)	1.000
Developmental malformations	21 (91.3%)	2 (8.7%)	1.000
Miscellaneous	21 (100%)	0 (0.0%)	0.655
Tumor histology			
Meningioma	78 (95.1%)	4 (4.9%)	0.987
Nerve sheath tumors	72 (97.3%)	2 (2.7%)	0.389
Intramedullary tumor	65 (94.2%)	4 (5.8%)	0.754
Intradural metastatic tumors	12 (92.3%)	1 (7.7%)	0.482
Miscellaneous	28 (93.3%)	2 (6.7%)	0.616
Location			
Cervical	59 (100%)	0 (0.0%)	0.088
Thoracic	166 (94.9%)	9 (5.1%)	0.810
Lumbosacral	109 (93.2%)	8 (6.8%)	0.291
Previous intradural surgery at the same level			
Yes	52 (91.2%)	5 (8.8%)	0.131
No	282 (95.9%)	12 (4.1%)	
Hypertension			
Yes	105 (95.5%)	5 (4.5%)	0.861
No	229 (95.0%)	12 (5.0%)	
Coronary heart disease			
Yes	19 (100%)	0 (0.0%)	0.612
No	315 (94.9%)	17 (5.1%)	
Diabetes mellitus			
Yes	31 (96.9%)	1 (3.1%)	1.000
No	303 (95.0%)	16 (5.0%)	
Chronic obstructive pulmonary disease			
Yes	11 (91.7%)	1 (8.3%)	0.454
No	323 (95.3%)	16 (4.7%)	
Smoking			
Yes	35 (89.7%)	4 (10.3%)	0.107
No	299 (95.8%)	13 (4.2%)	
Obesity			
Yes	55 (96.5%)	2 (3.5%)	0.839
No	234 (94.7%)	13 (5.3%)	
Not available	45	2	

CSFL, cerebrospinal fluid leakage.

TABLE 2 Intraoperative factors.

	No CSFL $n = 334$ N (row %)	CSFL $n = 17$ N (row %)	p-value
Number of exposed levels			
One level	275 (94.5%)	16 (5.5%)	0.506
Two levels	33 (100%)	0 (0.0%)	0.667
Three or more levels	26 (96.3%)	1 (3.7%)	0.630
Choice of approach			
Laminoplasty	74 (96.1%)	3 (3.9%)	0.774
Hemilaminectomy	154 (95.1%)	8 (4.9%)	0.939
Laminectomy	41 (95.3%)	2 (4.7%)	1.000
Interlaminar access	46 (95.8%)	2 (4.2%)	1.000
Other	17 (89.5%)	2 (10.5%)	0.233
Corpectomy	2 (100%)	0 (0.0%)	1.000
Dural closure technique			
Suture only	9 (100%)	0 (0.0%)	1.000
Suture + liquid sealant	4 (80.0%)	1 (20.0%)	0.221
Suture + patch sealant	245 (95.7%)	11 (4.3%)	0.413
Suture + liquid and patch sealant	37 (97.3%)	1 (2.6%)	1.000
Other	39 (90.7%)	4 (9.3%)	0.141

CSFL, cerebrospinal fluid leakage.

TABLE 3 Perioperative factors.

	No CSFL $n = 334$ N (row %)	CSFL $n = 17$ N (row %)	p-value
Drainage insertion			
Yes	184 (96.4%)	7 (3.7%)	0.321
No	150 (93.8%)	10 (6.3%	
Force of suction			
Full	0 (0.0%)	0 (0.0%)	0.956
Reduced	113 (96.6%)	4 (3.4%)	
None	71 (95.9%)	3 (4.1%)	
Bed rest (mean, standard deviation)	1.5 ± 1.3 days	2.0 ± 1.2 days	0.121
Timing of mobilization			
Early mobilization (<24 h)	179 (96.2%)	7 (3.8%)	0.332
Late mobilization (>24 h)	155 (93.9%)	10 (6.1%)	

CSFL, cerebrospinal fluid leakage.

7.4% male, $p = 0.027$) were significantly associated with CSFL development, but neither age [odds ratio (OR), 0.335; 95% confidence interval (CI), 0.105–1.066] nor gender (OR, 0.350; 95% CI, 0.110–1.115) remained as independent risk factors in multivariate analysis (Table 4). The following disease, surgery, and patient-related variables were tested as potential cofactors and found not to influence the risk of CSFL development: surgical indication (all $p > 0.1$), tumor histology (all $p > 0.1$), location (all $p > 0.05$), previous intradural surgery ($p = 0.131$), medical comorbidities (all $p > 0.1$), number of exposed levels (all $p > 0.1$), choice of approach (all $p > 0.1$), dural closure technique (all $p > 0.1$, Figure 1), drainage insertion ($p = 0.321$), force of suction ($p = 0.537$), and timing of mobilization ($p = 0.332$).

TABLE 4 Binary logistic regression analysis.

Factor	Effect	Odds ratio (95% CI)	p-value
Age	< 55vs. >55 years	0.335 (0.105–1.066)	0.064
Gender	Male vs. female	0.350 (0.110–1.115)	0.076

CI, confidence interval.

Complications following early and late mobilization

Wound healing disorders occurred in 6 cases (1.6%), epidural hematoma in 8 cases (2.3%), urinary tract infection in 12 cases (3.4%), pneumonia in 1 case (0.3%), and new neurological deficits in 26 cases (7.4%, Table 5). The incidence of urinary tract infections was significantly higher in the early mobilization group (5.4% vs. 1.2%; $p = 0.039$), and the two groups did not differ with respect to other complications (all $p > 0.1$).

Discussion

In this series, we report on 351 planned durotomies in adult patients with regard to factors influencing CSFL, making this the second largest series in this regard and the largest to investigate the impact of postoperative mobilization and epidural drainage placement as well as the first to investigate medical comorbidities.

The overall risk of CSFL development was 4.8%, which is in line with previous studies reporting an average risk ranging from 0 to 10% (3–7).

In general, reports regarding risk factors for CSFL following planned durotomies are sparse. Two studies investigating the impact of age and gender on CSFL development found no association, which is in line with the findings of our study. Regarding the impact of location, our study is consistent with previous reports that did not show a significant correlation (6, 8). Of note, no CSFL occurred in the cervical spine in our cohort, possibly attributed to the fact that merely 17% of all intradural surgeries were performed in the cervical spine in our cohort in the first place. Contrary to reports on incidental durotomies, prior epidural surgery does not appear to be a risk factor for CSFL in case of planned durotomies (3, 5, 9, 10).

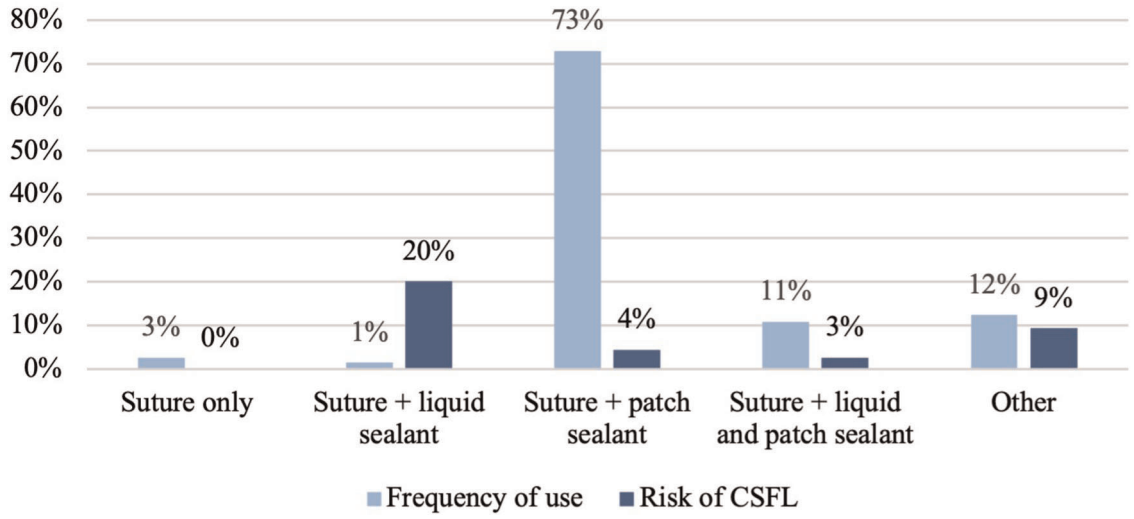

FIGURE 1
Dural closure technique and risk of cerebrospinal fluid leak development.

TABLE 5 Complications following early and late mobilization.

	Early mobilization $n = 186$ N (column %)	Late mobilization $n = 165$ N (column %)	*p*-value
Neurological deficit	18 (9.7%)	8 (4.8%)	0.103
Wound healing deficits	5 (2.7%)	1 (0.6%)	0.220
Epidural bleeding	3 (1.6%)	5 (3.0%)	0.482
Urinary tract infections	10 (5.4%)	2 (1.2%)	0.039
Pneumonia	1 (0.5%)	0 (0.0%)	1.000
Miscellaneous	9 (4.8%)	3 (1.8%)	0.148

As this is the first to examine the impact of medical comorbidities on CSFL in planned durotomies, our study first provides evidence of no significant correlations in this regard.

While the choice of surgical approach and degree of dural exposure and bone removal was not found to influence the risk for CSFL, which is in line with previous findings (6), there was no dedicated analysis comparing open and minimally invasive approaches in our study due to the small number of patients being treated with minimally invasive approaches. However, minimally invasive techniques may offer advantages over open procedures in terms of reduced perioperative complications, including CSFL, for both accidental and planned durotomies (11–13).

Although additional (liquid or patch) sealants are frequently used to reinforce dural suture (97.4% in our study), their benefit remains uncertain (11).

Use of fibrin sealants has been discouraged by several authors following both planned and unplanned durotomies due to a lack of effectiveness in preventing CSFL (10, 14–16), even though two studies reported favorable results (4, 17). The effectiveness and the necessity of patch sealants to prevent CSFL are not sufficiently studied in planned durotomies. Favorable results were reported by Montano et al. who reported no CSFL requiring revision surgery after dural closure with TachoSil® in 35 intradural procedures (18). In contrast, other studies investigating patch sealants found no clinical benefit in terms of CSFL risk reduction, thus questioning their application (3, 6, 11). Overall, further research is warranted to investigate the utility of sealants in planned durotomies. Based on the currently available data as well as our findings, the use of additional sealants in case of adequate dural closure by suture may not provide further benefit.

The placement of an epidural drainage following durotomy is controversially discussed (16, 19). Our data showed no effect on CSFL development, suggesting a generally safe applicability with reduced or no force of suction. It does not allow further conclusions such as previous reports advocating for epidural drainage placement in order to reduce the risk of CSFL by influencing epidural pressure gradients and thus supporting wound healing (16, 20). Furthermore, our results are inconsistent with reports of increased complication rates, including CSFL, following epidural drainage in both planned and accidental durotomy (3, 21–24).

Bed rest following spinal durotomy remains a common measure, although in case of accidental durotomy, studies failed to show any benefit in terms of CSFL reduction. Accordingly, our series of planned durotomies showed no impact of early or late mobilization on the development of CSFL, consistent with the only other study currently available

on this topic (4). Consequently, early mobilization after planned durotomy appears to be beneficial, as it is associated with a reduction in medical complications such as ileus, pneumonia, and deep vein thrombosis, as well as a reduced socioeconomic financial burden due to overall shorter hospital stays (25, 26). Of note, the overall complication rate did not differ significantly between the early and late mobilization groups in our study, possibly due to the small number of patients immobilized for more than three days in our cohort. Accordingly, we attribute the higher rate of urinary tract infections in the early mobilization group to the retrospective study design.

This study carries several limitations. First, our study is limited by its retrospective design and single-center patient population. Second, the risk of CSFL development might be underestimated due to the rather strict definition of a CSFL used in this study. CSFL was defined as cerebrospinal fluid leakage through the operative wound refractory to conservative therapy and necessitating operative revision surgery, which is in contrast with other publications that included conservatively managed cases as well. Third, the technique of dural closure, epidural drain placement, and timing of mobilization were not based on standardized protocols but at the discretion of the treating surgeon, potentially causing a selection bias. Finally, case numbers for certain techniques of dural closure were small, limiting statistical power.

Conclusion

CSFL following planned durotomy pose a relevant complication risk of surgery that can be quantified for preoperative patient-specific counseling and consent. To minimize the risk of CSFL, our data highlight the importance of adequate dural closure by suture, and the use of additional sealants remains optional. In contrast to previous treatment recommendations, our results indicate the safety of both epidural drainage with reduced or no force of suction and early mobilization within 24 h following intradural surgery to prevent further complications.

Data availability statement

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

Author contributions

VN, ML, and MP contributed to the initial conception and study design. ML, MP, ST, and NvS acquired and curated the database. ML and MP conducted the formal analysis and wrote the manuscript. ST, NvS, JP, RG, and VN reviewed and edited the manuscript. RG and VN supervised the project. 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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The efficacy of platelet-rich plasma applicated in spinal fusion surgery: A meta-analysis

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Objective: The purpose of this meta-analysis is to evaluate the effect of the application of platelet-rich plasma (PRP) in spinal fusion surgery on the fusion rate of the spine.

Methods: A comprehensive search of the PubMed, Embase, Cochrane Library, and Science Direct databases was conducted to identify randomized control trials (RCTs) or observational cohort studies that evaluated the efficacy and safety of PRP in spinal fusion. Data on final fusion rate, changes in the visual analog scale (VAS), estimated blood loss (EBL), and operative time was collected from the eligible studies for meta-analysis. Patients were divided into PRP and non-PRP groups according to whether PRP was used during the spinal fusion procedure.

Results: According to the selection criteria, 4 randomized controlled trials and 8 cohort studies with 833 patients and 918 levels were included. The outcomes indicated that PRP application is associated with a lower fusion rat (OR = 0.62, 95% CI: (0.43, 0.89), $P = 0.009$) at final follow-up (>24 months). Subgroup analysis showed a lower rate of spinal fusion in the PRP group compared to the non-PRP group (OR = 0.35, 95% CI: (0.21, 0.58), $P < 0.001$) when spinal fusion was assessed using only anterior-posterior radiographs. When the bone graft material was a combination of autologous bone + artificial bone, the spinal fusion rate was lower in the PRP group than in the non-PRP group (OR = 0.34, 95% CI: (0.16, 0.71), $P = 0.004$). The PRP and non-PRP groups showed no significant differences in VAS changes at the 24th postoperative month (WMD = 0.36, 95% CI: (−0.37, 1.09), $P = 0.33$); Application of PRP does not reduce the estimated blood loss (WMD = −86.03, 95% CI: (−188.23, 16.17), $P = 0.10$). In terms of operation time, using PRP does not prolong operation time (WMD = −3.74, 95% CI: (−20.53, 13.04), $P = 0.66$).

Conclusion: Compared with bone graft fusion alone, PRP cannot increase the rate of spinal fusion. Inappropriate methods of spinal fusion assessment or mixing PRP with artificial/allograft bone may have been responsible for the lower rate of spinal fusion in the PRP group.

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KEYWORDS

fusion rate, platelet-rich plasma (PRP), autologous growth factors, spinal surgery, spinal fusion

Abbreviations

PRP, platelet-rich plasma; RCTs, randomized control trials; VAS, visual analog scale; EBL, estimated blood loss; BMPs, bone morphogenetic proteins; AFGs, autologous growth factors; PDGF, platelet-derived growth factor; TGF-b, transforming growth factor-beta; WMDs, weighted mean differences; ORs, odds ratios; CIs, confidence intervals.

Introduction

Spinal fusion is an important method used to treat degenerative and traumatic diseases of the spine. Spinal non-fusion refers to the failure of bridging of adjacent vertebrae more than 1 year after surgery (1). Failure of spinal fusion will result in pseudoarthrosis, a common complication after spinal surgery. The formation of a pseudarthrosis often leads to loss of correction, recurrence of deformity, instability of the lumbar spine, low back pain with activity or weight bearing, or neurological symptoms (2). The prevalence of pseudarthrosis reported in the literature ranges from 0% to 56% (3). However, since many patients with pseudarthrosis remain asymptomatic, the true incidence may be underestimated by the literature. The use of bone graft extenders, such as bone morphogenetic proteins (BMPs) or platelet-rich plasma (PRP), has been considered to address this problem (4). Several studies (5–7) have shown that BMPs can improve spinal fusion rates. However, the possible side effects of BMPs, including inflammation, heterotopic bone formation, neck swelling, and radiculitis, have been reported (8, 9). In 2008, the FDA Public Health Notification published an alert regarding safety concerns for BMPs, which led to a gradual decline in their use (10). Therefore, an effective and safe method is needed to increase the rate of bone fusion after spinal fusion surgery.

Platelet activation can produce a variety of autologous growth factors (AFGs), such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-b) (11). These growth factors promote mitogenesis in fibroblasts, osteoblasts, and mesenchymal cells by stimulating DNA synthesis, allowing them to proliferate and secrete more growth factors, and these cells then differentiate into osteoblasts. In addition, these growth factors also have a chemotactic effect on undifferentiated stem cells (12, 13). Therefore, high concentration of PRP in the fusion levels shows potential as an excellent osteoinductive agent or mitotic factor, which helps to promote bone fusion (14). At present, the technology of producing ultraconcentrated platelets has been produced and promoted as a result of its generated osteogenic action. However whether PRP promotes spinal fusion is inconclusive, even though many meta-analyses currently exist to resolve this controversy. For example, the pooled results of Saran et al. showed no difference in the final spinal fusion rate with the combination of PRP and autologous bone compared to autologous bone graft alone (15). The pooled results of Yolcu et al. (16) showed that the addition of PRP to the spinal fusion process decreased the final spinal fusion rate. Therefore, the objective of this meta-analysis is to re-evaluate the efficacy of PRP, which can aid in the decision-making process regarding the use of PRP in spinal fusion surgery.

Methods

The guidelines used for this systematic review and meta-analysis were the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17). The protocol for this review was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database with the registration number INPLASY202250055 and DOI number 10.37766/inplasy2022.5.0055.

Search strategy and study selection

A comprehensive literature search was performed through the following databases: PubMed, EMBASE, Cochrane Library, and ScienceDirect. We identified relevant articles published up to 1 May 2022 without language limitations. Studies were found using the following keywords: platelet-rich plasma, PRP, platelet gel, spinal fusion, bone inducer, and bone extenders. Two independent investigators screened eligible studies and reviewed references of the included studies to identify additional articles. When consensus could not be reached, a third reviewer was consulted.

Select strategy

The inclusion and exclusion criteria of studies followed PICOS principles. (1) Participants: Patients with spinal degenerative or traumatic diseases requiring spinal fusion treatment. (2) Interventions: Patients in whom the bone graft material used for spinal fusion is a mixture of grafted bone and PRP. (3) Comparisons: Patients whose bone graft material used for spinal fusion is bone graft alone. (4) Outcomes: Studies should include at least one of the following data: final spinal fusion rate, final changes of VAS, EBL, and operative time. (5) Study design: Observational studies and randomized control trials were eligible. Case reports, case series, commentaries, practice guidelines, systematic review,s an metaanalysiss were excluded.

Data extraction

The following data were extracted from the included studies: (1) study design: first author, country, publication time, and study type; (2) sample demographics: number of patients and fused levels, follow-up time, age, and sex; (3) fusion details: surgical procedure, bone graft material, imaging modalities for fusion assessment; (4) PRP preparation, formulation, and application methods; and (5) analysis variables: final spinal fusion rate (at least 24 months), final changes of VAS, EBL

(excluding the amount of blood consumed for PRP preparation), and operative time. Successful spinal fusion is defined as the presence of bridging bone remodeling between the vertebral bodies or between the bilateral posterolateral intertransverse on static radiographs (anterior-posterior radiographs or CT) (18), or adjacent vertebrae translation <3 mm, angle <5° onflexion-extensionn radiographs (18).

Assessment of risk of bias

Two researchers independently assessed the risk of bias in randomized trials using the revised Cochrane Risk of Bias tool (RoB-2) (19) and the risk of bias in non-randomized trials using Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) (20). Sensitivity analysis was performed by excluding a single study from each study and reanalyzing the data. Publication bias was detected by the Funnel diagram. Sensitivity analysis and publication bias analysis were implemented using RevMan 5.3.

Statistical analysis

The continuous data were calculated by weighted mean differences (WMDs) with 95% confidence intervals (CIs), and dichotomous variables were calculated by using odds ratios (ORs) with 95% confidence intervals (CIs). Statistical heterogeneity was calculated by using a chi-square test and I^2 test. When $I^2 \leq 50\%$, we performed a fixed-effect model for the meta-analysis. Otherwise, the random-effect model was performed. To investigate the impact of fusion assessment tools and the use of different bone grafting materials on spinal fusion rate, we also performed subgroup analysis. The meta-analysis was performed using RevMan 5.3 for Windows (Cochrane Collaboration, Oxford, UK). If the result of the meta-analysis was a probability of $P < 0.05$, it was statistically significant.

Results

Search results

A total of 251 articles from PubMed, EMBASE, the Cochrane Library, and ScienceDirect were initially identified. PubMed ($n = 132$), EMBASE ($n = 62$), ScienceDirect ($n = 53$), and the Cochrane Library ($n = 4$). 231 studies were directly excluded by screening the titles and abstracts. 20 studies underwent a comprehensive full-text analysis. Finally, 12 studies met the inclusion criteria and were included in this meta-analysis. The flow diagram of the search strategy is summarized in **Figure 1**.

Study characteristics and risk of bias

The eligible studies included 4 randomized control trials and 8 cohort studies. A total of 833 patients and 918 levels were involved in the 12 eligible studies. The PRP group included 364 patients and 401 levels, and the non-PRP group included 469 patients and 517 levels. The characteristics of the included studies are presented in **Table 1**. The imaging modalities and successful fusion or pseudarthrosis criteria for each study are shown in **Table 2**. The preparation methods, formulations, and usage of PRP are summarized in **Table 3**. The results of the quality evaluation of randomized controlled studies and non-randomized controlled studies are summarized in **Tables 4**, **5**.

Final fusion rate (at least 24 months)

A total of 11 studies (21–31) reported final fusion rate in 851 levels (369 levels in the PRP group and 482 levels in the non-PRP group). The outcomes indicated that PRP application is associated with a lower fusion rate, and the difference was statistically significant (OR = 0.62, 95% CI: (0.43, 0.89), $P = 0.009$), as shown in **Figure 2**. Subgroup analysis showed a lower rate of spinal fusion in the PRP group compared to the non-PRP group (OR = 0.35, 95% CI: (0.21, 0.58), $P < 0.001$) when spinal fusion was assessed using only anterior-posterior radiographs (**Figure 3**). And when the bone graft material was a combination of autologous bone + artificial bone (**Figure 4**), the spinal fusion rate was lower in the PRP group than in the non-PRP group (OR = 0.34, 95% CI: (0.16, 0.71), $P = 0.004$).

VAS changes

Four studies (25, 30–32) compared the VAS changes between the PRP group and the non-PRP group at the 24th postoperative month. 70 patients were included in the PRP group, and 75 patients were included in the non-PRP group. A fixed-effect model was used for meta-analysis with $I^2 = 0\%$. The outcomes indicated that there was no statistically significant difference in VAS changes between the two groups (WMD = 0.36, 95% CI: (−0.37, 1.09), $P = 0.33$) (**Figure 5**).

Estimated blood loss (excluding the amount of blood consumed for PRP preparation)

Four studies (23–25, 30) were available to merge the analysis regarding EBL, including 79 patients in the PRP group and 214 patients in the non-PRP group. A random-effects model was

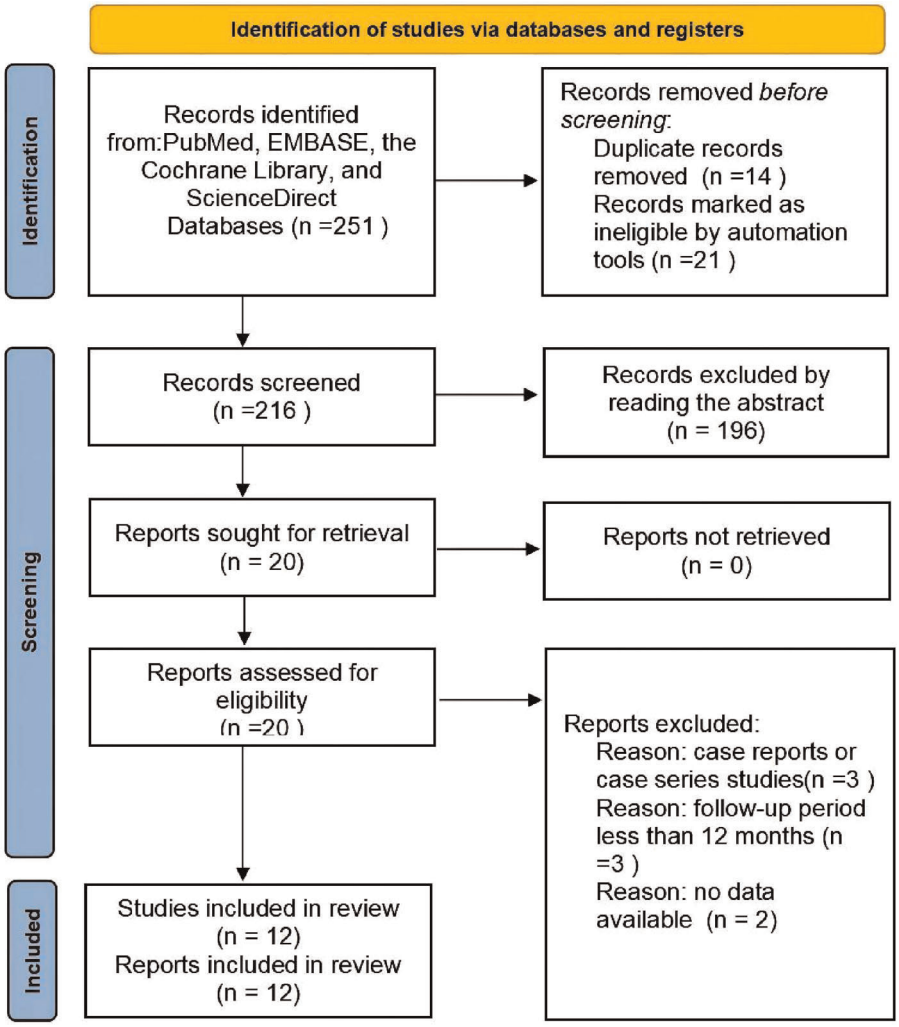

FIGURE 1
PRISMA flowchart.

used for meta-analysis with $I^2 = 65\%$. The merged data showed that there was no significant difference in EBL between the two groups (WMD = −86.03, 95% CI: (−188.23, 16.17), $P = 0.10$) (Figure 6).

Operation time

Four studies (23–25, 30) compared the operation time between the PRP group and the non-PRP group. 79 patients were in the PRP group, and 214 patients were in the non-PRP group. The random-effect model was used for meta-analysis with $I^2 = 66\%$. The outcomes indicated that there was no significant difference in operative time between the two groups (WMD = −3.74, 95% CI: (−20.53, 13.04), $P = 0.66$) (Figure 7).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by excluding a single study of each study and reanalyzing the data. None of the research findings showed significant changes after that analysis. Funnel plots indicated there was minimal to no bias for all included studies (Figure 8).

Discussion

Fusion rate is considered one of the most important factors in evaluating the clinical efficacy of PRP in lumbar fusion. The clinical use of PRP in promoting spinal fusion is currently controversial. Weiner et al. (27) reasoned that PRP must have an inhibitory effect on osseointegration because PRP may

TABLE 1 Demographic characteristics of the included studies.

PRP/non-RP

Study ID	Study type	Country	Number of participants	Fused levels	Age (Mean), year	Gender (F)	Surgical approach	Type of bone graft	Follow-up (months)
Tsai 2009	RCT	Taiwan	34/33	34/33	59.8/63.3	6:27	PLF	Autologous bone + artificial bone	28.5/27.6
Acebal 2011	Prospective non-randomized	Spain	67/40	67/40	57/59	24:16	PLF	Autologous bone + artificial bone	24
Weiner 2003	Retrospective cohort	United States	32/27	32/27	61/56	11:16	PLF	Autologous bone	24
Carreon 2005	Retrospective cohort	United States	76/76	76/76	50.6/49.9	40:36	PLF	Autologous bone	32/37
Castro 2004	Prospective cohort	United States	22/62	28/76	47/49	21:41	TLIF	Autologous bone	34/41
Hee 2003	Prospective cohort	Singapore	23/111	23/111	44.3/47.7	42:69	TLIF	Autologous bone	24
Kubota 2018	Retrospective cohort	Japan	11/9	11/9	59.4/63.3	4:5	TLIF	Autologous bone	24
Kubota 2019	RCT	Japan	25/25	32/35	65.1/65.3	14:11	PLF	Autologous bone	24
Jenis 2006	Prospective non-randomized	United States	15/22	22/32	40.3/41.4	14:8	ALIF	Autologous bone	25.7/24.3
Sys 2011	RCT	Belgium	19/19	19/19	74.9/76	12:7	PLIF	Autologous bone	24
Feiz-erfan 2007	RCT	United States	25/25	42/39	/	/	ACDF	Allogeneic bone	24
Hartmann 2009	Retrospective Cohort	Germany	15/20	15/20	43.7/39.8	13:7	ALIF	Autologous bone	12

PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; ALIF, anterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; ACDF, anterior cervical decompression and fusion.

TABLE 2 Criteria and evaluation methods for successful spinal fusion in each study.

Study ID	Imaging modalities	Criteria for successful fusion
Tsai 2009	CT/FE	FE: <5 degree of angular motion or <2 mm of translation at the operated level; CT: bridging bone remodeling occurringbetween the bilateral posterolateral intertransverse
Acebal 2011	AP	Bridging bone remodeling occurring between the bilateral posterolateral intertransverse
Weiner 2003	AP	Bridging bone remodeling occurring between the bilateral posterolateral intertransverse
Carreon 2005	CT	Bridging bone remodeling occurring between the bilateral posterolateral intertransverse
Castro 2004	AP	Bridging bone remodeling occurring between the vertebral body or bridging bone remodeling occurring between the bilateral posterolateral intertransverse
Hee 2003	AP	Bridging bone remodeling occurring between the vertebral body or bridging bone remodeling occurring between the bilateral posterolateral intertransverse
Kubota 2018	CT	Bridging bone remodeling occurring between the vertebral body
Kubota 2019	CT	Bridging bone remodeling occurring between the unilateral posterolateral intertransverse
Jenis 2006	CT	Bridging bone remodeling occurring between the vertebral body
Sys 2011	CT	Bridging bone remodeling occurring between the vertebral body
Feiz-erfan 2007	PE	No significant angular motion (no more than 2°)
Hartmann 2009	CT	Bridging bone remodeling occurring between the vertebral body

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TABLE 3 PRP preparation techniques, formulations and usage.

Study ID	Source	Preparation technology	Preparation method	Core product	Platelet concentration	Activators	Start preparation time	Drug delivery methods	Implantation site
Tsai 2009	Peripheral vein blood/NA	Gravity centrifugation	NA	NA	NA	CaCl + Thrombin	Intraoperative	Mixed with bone graft	Between the bilateral posterolateral intertransverse
Acebal 2011	Peripheral vein blood/ 100 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	NA	Thrombin	NA	Mixed with bone graft	Between the bilateral posterolateral intertransverse
Weiner 2003	Peripheral vein blood/ 450 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	6-fold	Thrombin	Intraoperative	Mixed with bone graft	Between the bilateral posterolateral intertransverse
Carreon 2005	Peripheral vein blood/ 500 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	NA	Thrombin	Intraoperative	Mixed with bone graft	Between the bilateral posterolateral intertransverse
Castro 2004	Peripheral vein blood/ 450 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	3.5 fold	Thrombin	Intraoperative	Mixed with bone graft	Between the vertebral bodies
Hee 2003	Peripheral vein blood/ 450 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	4.89 fold	CaCl + Thrombin	Intraoperative	Mixed with bone graft	Between the vertebral bodies
Kubota 2018	Peripheral vein blood/ 450 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	3–6 fold	CaCl + Thrombin	Intraoperative	Mixed with bone graft	Between the vertebral bodies
Kubota 2019	Peripheral vein blood/ 450 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	NA	CaCl + Thrombin	Intraoperative	Mixed with bone graft	Between the bilateral posterolateral intertransverse
Jenis 2006	Peripheral vein blood/ 450 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	NA	CaCl + Thrombin	Intraoperative	Mixed with bone graft	Between the vertebral bodies
Sys 2011	Peripheral vein blood/NA	Gravity centrifugation	NA	NA	3.3-fold	CaCl + Thrombin	Intraoperative	Mixed with bone graft	Between the vertebral bodies
Feiz-erfan 2007	Peripheral vein blood/NA	Gravity centrifugation	NA	NA	NA	CaCl + Thrombin	NA	Mixed with bone graft	Between the vertebral bodies
Hartmann 2009	Peripheral vein blood/ 450 ml	Gravity centrifugation	Two-step method	brownish-yellow layer	NA	Thrombin	Intraoperative	Mixed with bone graft	Between the vertebral bodies

interfere with the generation and function of the bone morphogenetic protein. Similar to Weiner, Castro, et al. (23) examined 22 patients who received TLIF with PRP and compared them to 62 patients who did not get PRP. They discovered no significant changes in the final lumbar fusion between the two groups, hence they did not recommend PRP for clinical use. Unfortunately, the reasons why PRP shows negative effects in clinical applications are inconclusive, and one possible explanation is that only anteroposterior radiographs are used to assess the fusion status of the spine. According to Jordan et al.'s systematic review of evaluation methods for lumbar and cervical spine fusion (3), CT and flexion-extension radiographs are the two preferred imaging modalities for determining the diagnosis of pseudarthrosis. In his description, anteroposterior radiographs had only a 43% to 82% probability of correlation with surgical exploration, with a high rate of false-negative, making them relatively insensitive in the diagnosis of pseudarthrosis (33–37). For this

TABLE 4 The risk of bias in non-randomized trials using risk of bias in Non-randomized studies of interventions (ROBINS-I).

Study ID	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Overall risk of bias
Acebal 2011	Serious	Low	Low	Moderate	Low	Low	Moderate	Moderate
Weiner 2003	Serious	Moderate	Low	Low	Moderate	Low	Low	Moderate
Carreon 2005	Moderate	Low	Low	Serious	Low	Serious risk	Low	Serious
Castro 2004	Serious	Moderate	Low	Low	Low	Low	Low	Moderate
Hee 2003	Moderate	Low	Serious	Moderate	Low	Moderate	Low	Moderate
Kubota 2018	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Jenis 2006	Serious	Low	Low	Serious	Low	Low	Moderate	Serious
Hartmann 2009	Moderate	Low	Moderate	Low	Serious	Low	Low	Moderate

TABLE 5 The risk of bias in randomized trials using the revised cochrane risk of bias tool (RoB-2).

Study ID	Bias arising from the randomization process	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Tsai 2009	Moderate	Low	Moderate	Low	Low	Moderate
Kubota 2019	Low	Low	Low	Low	Low	Low
Sys 2011	Moderate	Low	Low	Low	Low	Low
Feiz-erfan 2007	Low	Moderate	Low	Moderate	Low	Moderate

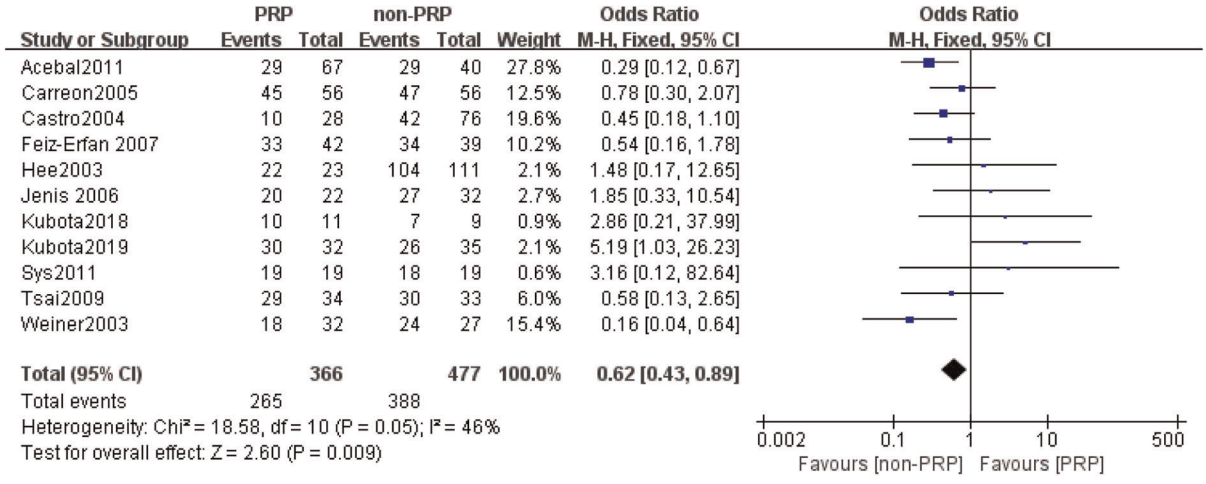

FIGURE 2
Forest plot of the final fusion rate (at least >2 years).

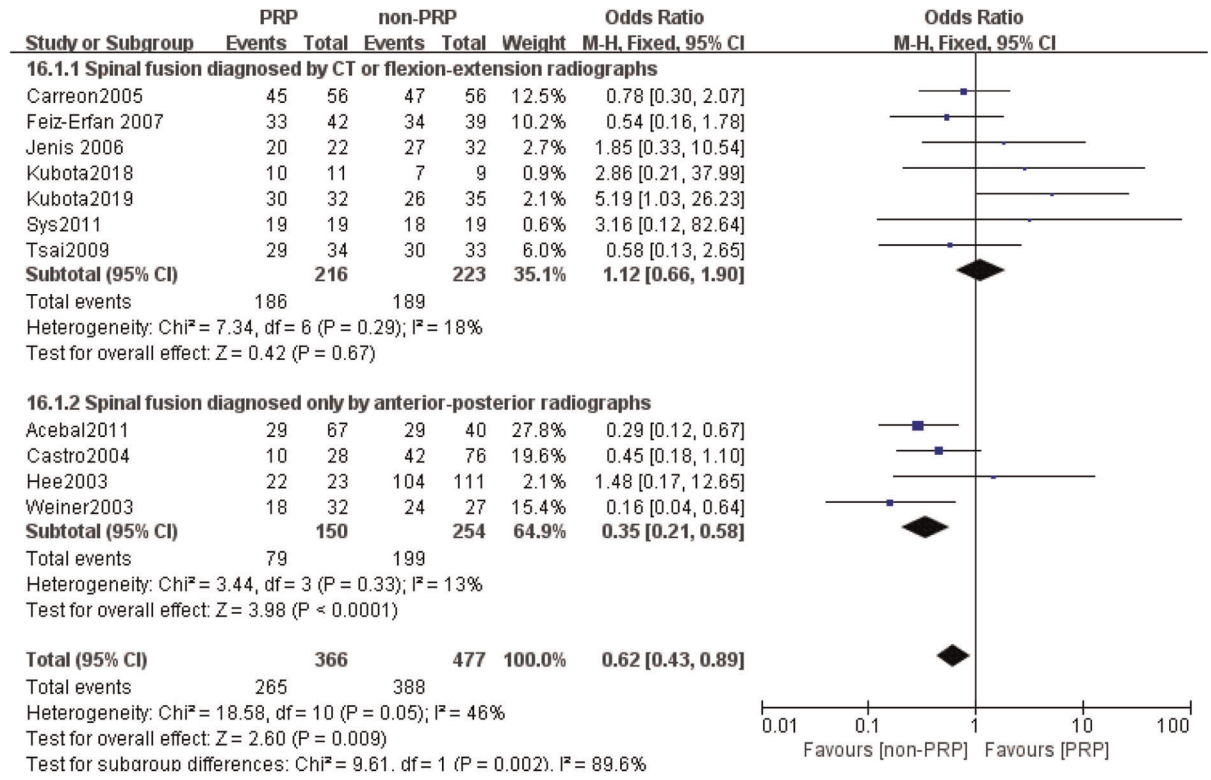

FIGURE 3
Subgroup analysis according to the spinal fusion evaluation methods.

reason, This meta-analysis performed a subgroup analysis based on the imaging modalities used to assess spinal fusion and re-evaluated the ability of PRP promoting spinal fusion. Considering the type of bone graft (autologous, artificial, or allogeneic) may affect the activity of PRP. We also performed a subgroup analysis according to the type of grafted bone. The analysis showed that the combination of autologous bone + artificial bone may decrease the rate of spinal fusion. We all know that autologous bone has excellent osteoconductivity, osteoinductivity and osteogenesis (38). However, artificial bone or allogeneic bone is not biologically active. The implanted autologous bone provides the microporous scaffold structure required for bone growth and has good vascular growth ability, and also provides a large amount of cytokines to promote the activation of osteoblasts, making it the most ideal bone grafting material for spinal fusion (39). Our analysis suggests that the rate of spinal fusion decreased when the artificial bone is mixed with the graft material. One possible explanation is that all PRPs contain high concentrations of leukocytes (according to the PRP production process) and the potential immune response triggered by this may inhibit spinal fusion. However, this requires basic experiments to further validate. Although the subgroup analysis did not reveal that the combination of allogeneic bone + PRP inhibited spinal fusion, such result is questionable due to the small sample size (only one study).

In 2006, the concept of leukocyte-rich PRP was introduced by Everts et al. (40). Therefore, PRP can be broadly classified into two types according to the number of leukocytes contained: leukocyte-poor PRP (LP-PRP) and leukocyte-rich PRP (LR-PRP). unfortunately, none of the included literature mentioned whether the prepared PRP contained leukocytes and the concentration of leukocytes. However, the PRP preparation process was the same for all studies, i.e., the use of gravity centrifugation techniques and equipment to separate the sediment brown-yellow layer from blood units containing platelets and leukocytes, and further concentrate the brown-yellow layer (40). All of the preparation processes did not de-leukocyte the brown-yellow layer, and therefore it can be concluded that the all included studies used LR-PRP. Increased leukocyte (neutrophil) increase levels of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), produce destructive proteases, induce an inflammatory environment, counteract the beneficial effects of growth factors, inhibit extracellular matrix secretion and promote degradation of bone and

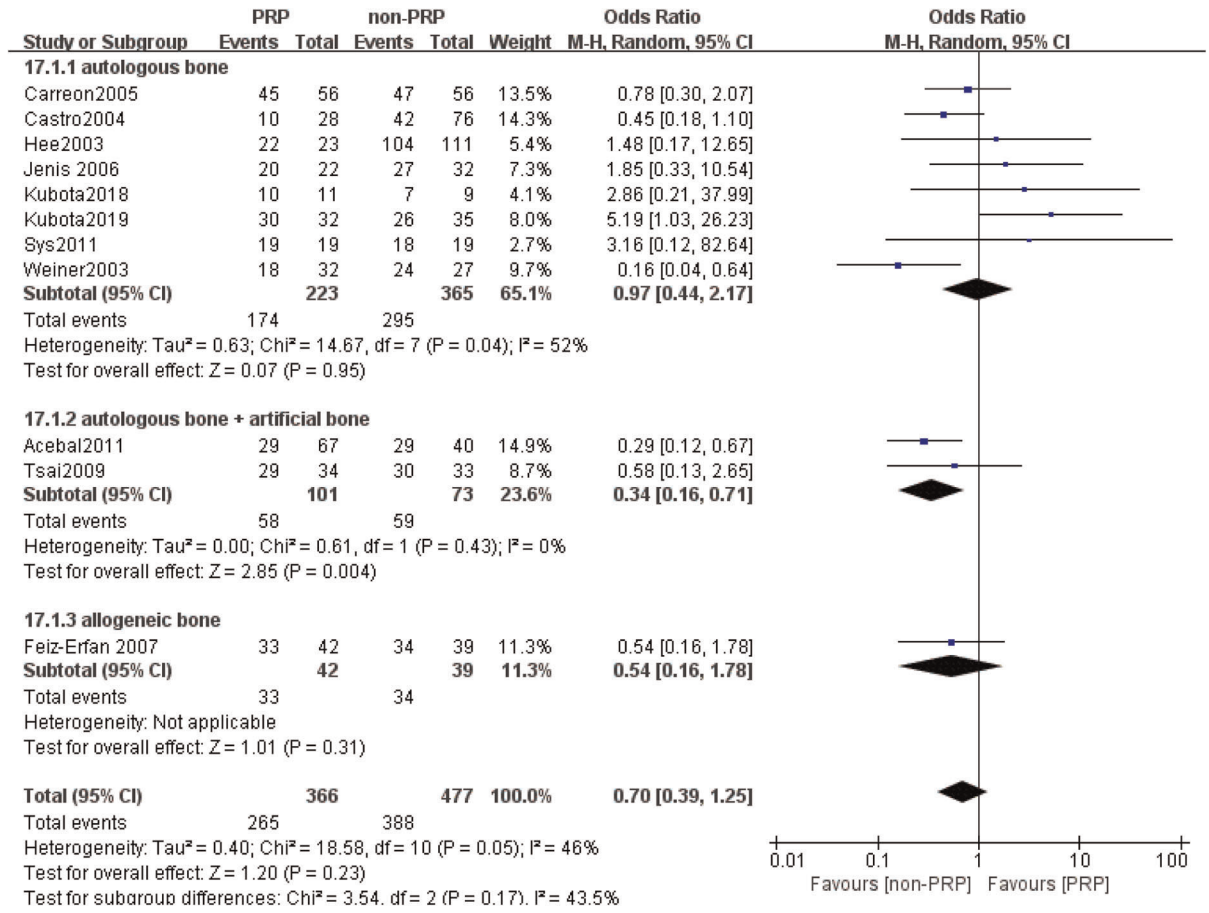

FIGURE 4
Subgroup analysis according to graft bone types.

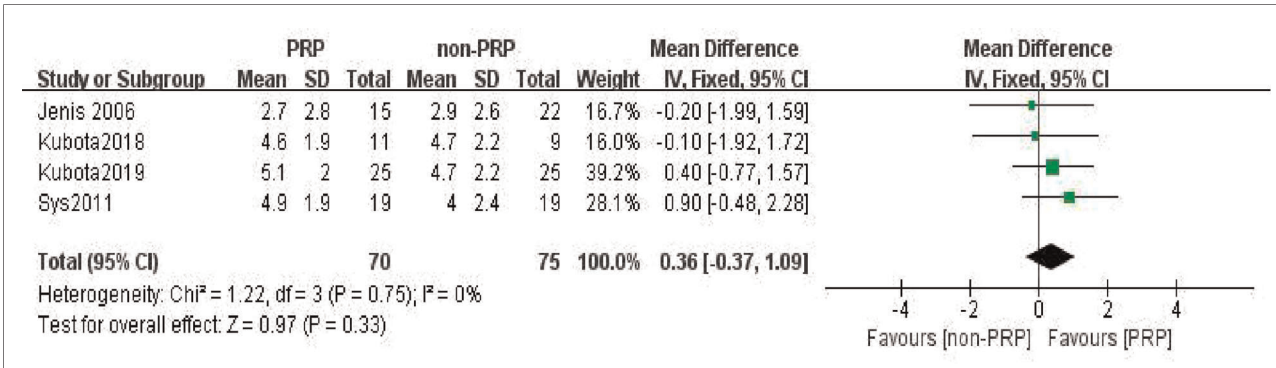

FIGURE 5
Forest plot of the VAS changes at the 24th postoperative month.

chondrocytes, impair the ability of differentiated stem cells to differentiate toward bone and cartilage, and eventually leads to degeneration of bone and cartilage tissues and aggravates the pain and swelling response (41). In contrast, the use of LP-PRP effectively reduces the concentration of inflammatory factors, decreasing the inflammatory response and accelerating

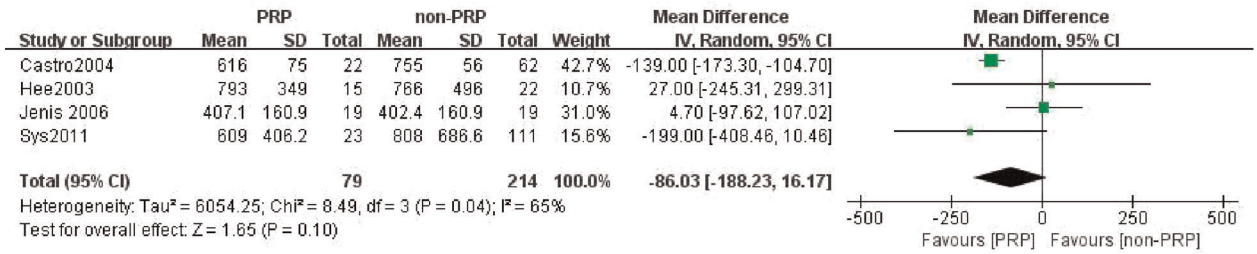

FIGURE 6
Forest plot of the EBL (excluding the amount of blood consumed for PRP preparation).

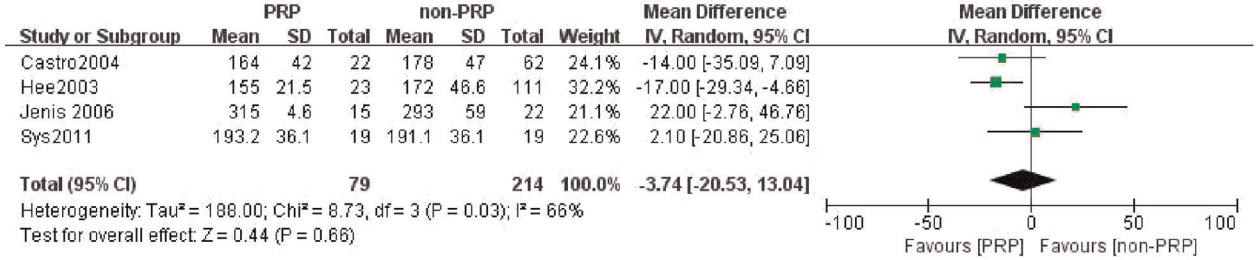

FIGURE 7
Forest plot of the operation time.

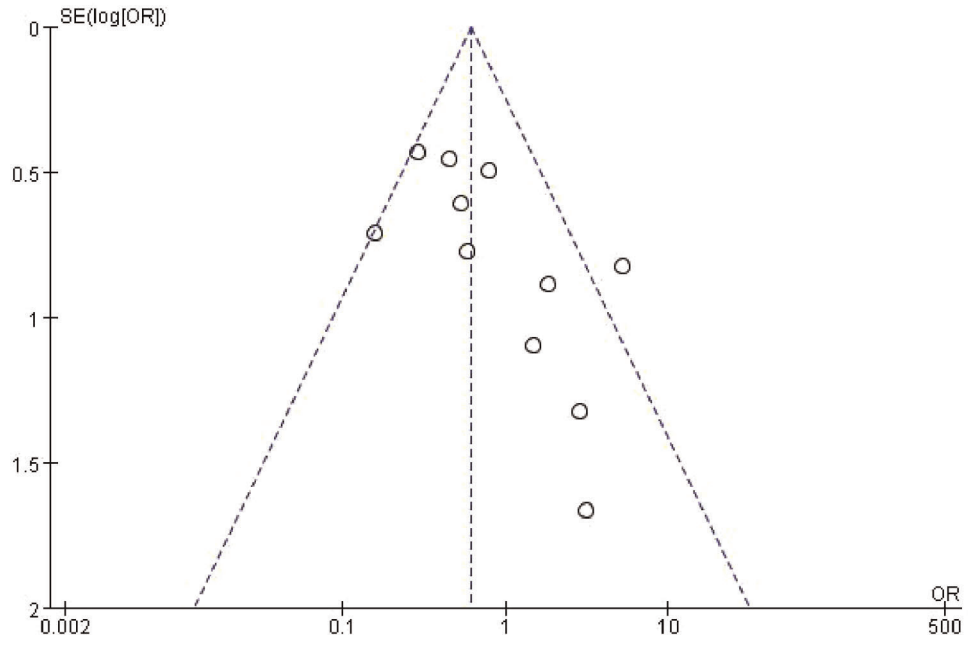

FIGURE 8
Plot of the final fusion rate.

tissue regeneration. A meta-analysis by Riboh et al. (42) comparing LP-PRP and LR-PRP in the treatment of knee osteoarthritis found that LP-PRP injection significantly improved the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and International Knee Documentation Committee (IKDC) subjective scores compared with LR-PRP or placebo. Also, the application of *P*-PRP had a lower incidence of adverse reactions compared to LR-PRP. However, there are no clinical trials assessing the efficacy of LP-PRP in promoting spinal fusion or other bone healing. Considering that currently, LR-PRP has not shown any benefit in promoting spinal fusion, LP-PRP could be a potential breakthrough.

In theory, platelet activation increases the inflammatory cascade, which may have a relieving effect on inflammatory pain. Activated platelets release many anti-inflammatory mediators that can reduce inflammation and pain. In a prospective randomized controlled trial (43), researchers evaluated the effect of applying PRP on postoperative pain reduction and functional recovery in patients who underwent open subacromial decompression, and they found patients treated with PRP demonstrated reduced visual analog scales of pain, significantly less use of pain medication, and greater shoulder range of motion compared to control patients.

Although our study did not find additional pain-relieving effects of PRP, a larger sample size is needed for further verification. Applying PRP may reduce EBL, as platelet activation is a key link in blood coagulation (25). However, our results showed that PRP can not reduce EBL. One possible explanation is that bone grafting is often the last step of spinal fusion, and most intraoperative blood loss occurs before bone grafting. It is worth noting that our estimated blood loss refers to intraoperative and postoperative blood loss and does not include the amount of blood required for PRP preparation. According to the gravity centrifugation two-step method of PRP preparation, approximately 450 ml of blood is required to make PRP; however, the concentrated red blood cell layer produced during the preparation process is perfused into the patient, so we cannot obtain the exact amount of blood loss due to PRP preparation. Given that PRP does not reduce intraoperative and postoperative blood loss, it is reasonable to believe that the total blood loss in patients in the PRP group was greater than that in the non-PRP group.

Our meta-analysis also shows that the use of PRP does not prolong the operation time ($P = 0.66$). As reported in the literature (23), anesthesia and operating room times were significantly prolonged for patients who received PRP. However, in most cases, the preparation of the PRP and its mixing with the autologous bone graft can be performed by the operating room technician, while the surgeon and his assistant can concentrate on preparing the fusion bed. therefore, the PRP preparation process does not waste too much time during the surgery.

Limitations

We admit that the current research has limitations. To begin, while some relevant trials have been published, the number of participants in some groups was modest, and some of the research were not RCTs. Second, various confounders, such as drug use, disease history, smoking history, and primary disease were not taken into account, which adds to some heterogeneous of the pooled result, but the sensitivity analysis suggested the robustness of the results. Furthermore, there was variability in terms of follow-up time among the included study. However, a minimum follow-up period of 12 months is sufficient to observe the efficacy of PRP in spinal fusion.

Conclusions

Compared with bone graft fusion alone, PRP cannot increase the rate of spinal fusion. Inappropriate methods of spinal fusion assessment or mixing PRP with artificial/allograft bone may have been responsible for the lower rate of spinal fusion in the PRP group.

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.

Author contributions

HY and TS proposed research topics and collected literatures; HY and BY drafted the manuscript; ZZ, QT and YJ corrected the English All authors reviewed this article. 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

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A predictive nomogram for intradiscal cement leakage in percutaneous kyphoplasty for osteoporotic vertebral compression fractures combined with intravertebral cleft

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Background: For patients with osteoporotic vertebral compression fractures (OVCFs) treated with percutaneous kyphoplasty (PKP), the occurrence and risk factors of intradiscal cement leakage should be characteristic of the presence of intravertebral cleft (IVC). This study aimed to identify risk factors for intradiscal leakage in individuals with OVCFs combined with IVC treated with PKP and build a powered and well-calibrated predictive nomogram.

Methods: This study retrospectively reviewed consecutive patients who underwent PKP at our center between January 2016 and May 2021. Patients diagnosed with OVCFs combined with IVC were identified, and the incidence of different types of bone cement leakage was recorded. Risk factors for intradiscal leakage among the demographic, perioperative baseline, and radiologic data were identified, following which a nomogram was developed and verified.

Results: A total of 109 eligible patients were included, and the intradiscal leakage rate was 32.1%. Compression rate (odds ratio [OR] 0.025; 95% confidence interval [CI] 0.002–0.264; $P = 0.002$) and cemented vertebral body fraction (OR 44.122; 95% CI 2.790–697.740; $P = 0.007$) were identified as independent risk factors. A predictive nomogram with good predictive power (C-statistic = 0.786) and fitness of data (Hosmer–Lemeshow goodness-of-fit test, $P = 0.092$) was established to build a quantitative relationship between the risk factors and intradiscal leakage.

Conclusion: The incidence rate of intradiscal leakage in PKP for OVCFs combined with IVC was 32.1%. Compression rate and cemented vertebral body fraction were identified as independent risk factors. A powered and well-calibrated nomogram was established to accurately predict the probability of intradiscal leakage. Further prospective and multicenter studies are required to verify and calibrate our findings.

KEYWORDS

cement leakage, intravertebral cleft, percutaneous kyphoplasty, osteoporotic vertebral compression fracture, nomogram

Introduction

Osteoporotic vertebral compression fractures (OVCFs) are common among the elderly population and are characterized by pain, dysfunction, and loss of mobility and independence (1, 2). Conservative treatments, such as bracing, early mobilization, and osteoporotic treatment, have been proven effective for pain relief and functional improvement in most cases (2, 3). However, conservative treatment can still fail in certain individuals, causing persistent back pain and low quality of life (4). Recently, minimally invasive vertebral augmentation techniques, including percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP), have been considered alternative options for the treatment of OVCFs (5–7). These procedures have the merits of partial vertebral height restoration and wedge deformity reversion (7). Although good clinical outcomes have been observed in most patients, these techniques are still associated with several complications.

Bone cement leakage (BCL) is one of the most common complications of vertebral augmentation techniques, the incidence of which varies from 7.9% to 79.9% (8–24). Traditionally, BCL is classified into three types: through the basivertebral vein (type B), through the segmental vein (type S), and through the cortical defect (type C) (25). However, a specific type, intradiscal leakage (type D), was distinguished from type C leakage by Tomé-Bermejo et al. (17). More attention should be paid to type D leakage, as it has been found associated with a higher incidence of adjacent vertebral fractures and subsequent pain (12, 26, 27).

Previous studies showed that the presence of intravertebral cleft (IVC) increases the incidence of intradiscal leakage after vertebral augmentation, which may attribute to the direct connection between the intervertebral disc space and intervertebral vacuum through endplate damage (13, 18, 20, 22). However, it still remains controversial and converse opinion was reported that the presence of IVC had no effect or even preventive effect to intradiscal leakage (12, 17, 28). A reasonable theory is that the cystic cavity in the vertebrae could promote a more homogeneous and controlled filling of the fractured vertebral body, decreasing the pressure of bone cement and risk of leakage (17).

The incidence of intradiscal leakage is low after PKP, and the reason is similar to the abovementioned theory that the inflatable balloon can create an iatrogenic cystic cavity-like space (9, 19, 29, 30). Nevertheless, there were still cases of intradiscal leakage, as high as 15.2%–22.6%, after PKP in some studies (11, 12, 24). In addition, interestingly, the preventive efficacy of intradiscal leakage seemed not to be strengthened by the presence of IVC in patients with OVCFs treated with PKP, and an even higher leakage rate was reported (11, 24). The exact reason for this remains unclear, and it is of great interest to determine whether there are specific triggers that balance these two theories.

Therefore, this study aimed to identify risk factors for intradiscal leakage and build a powered and well-calibrated predictive nomogram in individuals with OVCFs combined with IVC treated with PKP, to further explore clinical strategies to prevent intradiscal leakage in such patients.

Methods

Patient population

This study retrospectively reviewed consecutive patients who underwent PKP at our center between January 2016 and May 2021. The inclusion criteria were as follows: (1) age >55 years; (2) diagnosis of OVCFs from T7 to L5 based on evidence shown on preoperative radiography or CT and MRI (performed within 2 weeks before surgery); (3) severe back pain aligned with imaging tests; and (4) clear diagnosis of IVC. IVC was identified as a transverse, linear, or cystic region of gas-like hypointensity in the collapsed vertebral body shown on MRI T1-weighted sequences and hyperintensity on MRI T2 short-tau inversion recovery sequences (17, 28, 30). To control for confounding factors, we excluded patients who met the following exclusion criteria: (1) previous spinal surgery; (2) multilevel PKP; (3) preoperative tumor, infection, or deformity; and (4) incomplete data. This study was approved by the institutional review board.

Surgical technique

PKP was performed in the prone position under local anesthesia, and all of the procedures were conducted by a unilateral transpedicular approach. A needle and inflatable balloon (Medtronic Sofamor Danek, Memphis, TN, United States) were inserted through the working channel into the fractured vertebral body under visualization with lateral and anteroposterior fluoroscopy. Then, a kyphoplasty balloon was used to inflate and create the cavity. Subsequently, the balloon was deflated, removed, and filled with viscous polymethylmethacrylate (Mendec Spine Cement; Tecres SPA, Verona, Italy) under fluoroscopic guidance. The procedure was stopped immediately once BCLs were detected. The surgical time and cement volume were recorded.

Imaging evaluation and risk factors

BCL was assessed by postoperative radiography or CT, which were performed within three days after PKP. BCL was defined as the presence of extravertebral cement (**Figure 1**).

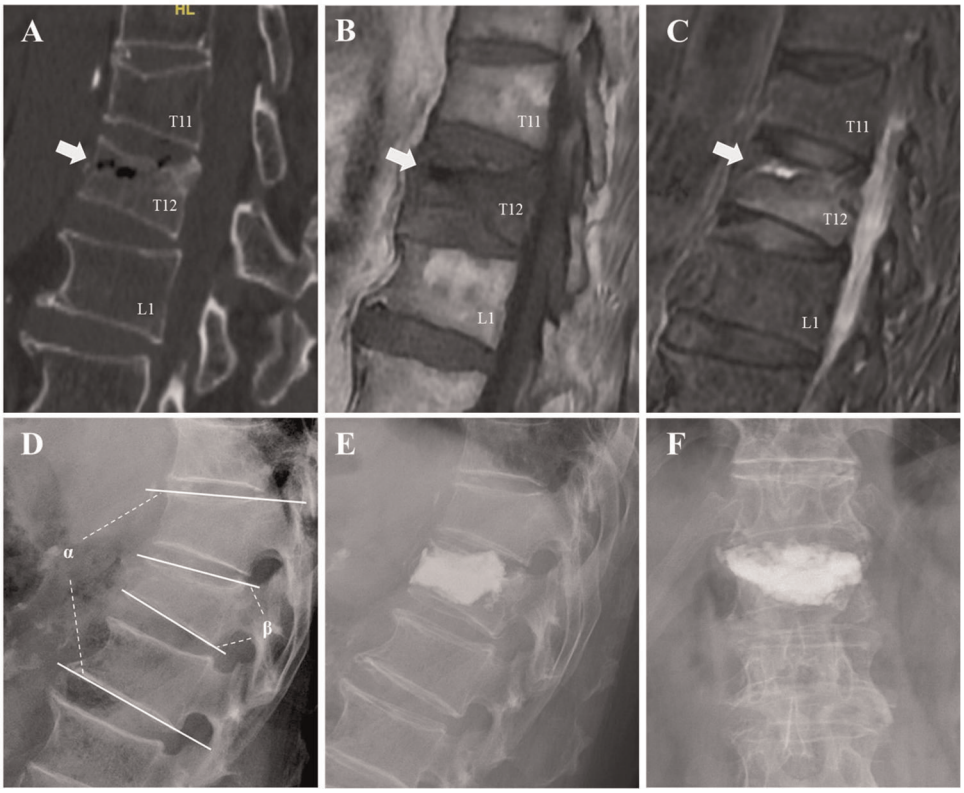

FIGURE 1
An illustrative case of an 81-year-old male patient underwent intradiscal leakage after PKP for OVCFs combined with IVC. A fracture in T12 was detected and the presence of an IVC (the white arrows) was confirmed by a gas-like density shown on preoperative CT (**A**), hypointensity shown on preoperative MRI T1-weighted sequences (**B**), and hypointensity shown on MRI T2 short-tau inversion recovery (**C**). Preoperative segmental kyphotic angle (α) and vertebral wedge angle (β) were measured on lateral radiograph (**D**). Intradiscal leakage was identified by postoperative radiographs (**E**,**F**).

Furthermore, BCL was classified into four types based on the location of the extravertebral cement according to Tomé-Bermejo et al. (17): (1) through the basivertebral vein (type B), (2) through the segmental vein (type S), (3) through the cortical defect and extraosseous non-intradiscal (type C), and (4) intradiscal leakage (type D).

Potential risk factors for intradiscal leakage in PKP for OVCFs combined with IVC were divided into two categories: First, demographic and perioperative baseline data included age, sex, weight, body mass index (BMI), overweight, obesity, time before surgery, bone mineral density (BMD), surgical level, and cement volume. Second, radiologic data included fracture type, fracture severity, presence of endplate cortical disruption, location of IVC, preoperative vertebral wedge angle, segmental kyphotic angle, minimum vertebral height, compression rate (CR), and cemented vertebral body fraction (CVBF).

Fractures were divided into three types based on a visual semiquantitative classification (31): wedge, biconcave, and crush type. According to the percentage of vertebral body collapse modified by Nieuwenhuijse et al. (18), fracture severity was graded into the following four levels: mild (20%–25%), moderate (25%–40%), severe (40%–67%), and very severe (>67%). The location of IVC was classified as follows: adjacent to the superior endplate, adjacent to the inferior endplate, and extending to both endplates (32).

All imaging parameters were evaluated on lateral radiographs. Vertebral wedge angle was measured as the angle between the superior and inferior endplates of the fractured vertebra, and segmental kyphotic angle was measured as the angle between the superior and inferior endplates of the two adjacent vertebrae. Minimum vertebral height was defined as the minimum height of the fractured vertebra. CR was calculated as fractured vertebral minimum vertebral height divided by the average vertebral heights of the two adjacent vertebrae (10). Furthermore, we measured CVBF to determine the individual efficacy of the cement injection volume. CVBF was calculated as the ratio of CV to fractured vertebral volume (33). Fractured vertebral volume was calculated by volume reconstruction of DICOM files of preoperative CT axial images using *Mimics* 21.0 (Materialize, Leuven, Belgium).

Statistical analysis

Univariate and multivariate analyses were conducted using *SPSS* 24.0 (IBM, Armonk, NY, United States). Potential risk factors for intradiscal leakage were divided into demographic, perioperative baseline, and radiologic data. First, Student t-test or Mann–Whitney U test for continuous variables, and chi-square tests or Fisher exact tests for categorical variables were used for univariate analysis. Next, potential risk factors ($P < 0.10$ in univariate analysis) were included in the logistic regression model, and the stepwise forward method was performed for multivariate analysis. Statistical significance was set at a *P*-value <0.05. Finally, a nomogram was built as a predictive model based on logistic regression analysis using *R* 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Receiver operating characteristic (ROC) curves were drawn, and C-statistics were calculated to determine the predictive power of the logistic regression model and nomogram. The calibration curve and Hosmer–Lemeshow goodness-of-fit tests were used to evaluate the fitness of the data.

Results

A total of 109 eligible patients (40 men and 69 women) were included in this study. The mean age of the enrolled patients was 77.5 ± 7.9 years. The most common surgical levels were the thoracolumbar vertebrae (83.5%), followed by the lumbar vertebrae (11.0%) and thoracic vertebrae (5.5%). The median time from injury to surgery was 44 days. A total of 100 (91.7%) patients had endplate cortical disruption. Overall, 41 (37.6%) patients had BCLs, including 35 (32.1%) with type D, 7 (6.4%) with type S, 5 (4.6%) with type C, and 2 (1.8%) with type B (Table 1).

TABLE 1 Clinical baseline characters.

Clinical baseline characters ($N = 109$)	Mean ± SD or *N* (%)
Age, years	77.5 ± 7.9
Gender (female), *n*	69 (63.3%)
Surgical level, *n*	
Thoracic (upper than T10)	6 (5.5%)
Thoracolumbar (T10–L2)	91 (83.5%)
Lumbar (lower than L2)	12 (11.0%)
Endplate cortical disruption, *n*	100 (91.7%)
Time before surgery, days[a]	44 (38–60)
BLC, *n*[b]	41 (37.6%)
Type B	2 (1.8%)
Type S	7 (6.4%)
Type C	5 (4.6%)
Type D	35 (32.1%)

SD, standard deviation; BCL, bone cement leakage.
[a]Results are given as the median (interquartile range).
[b]Sum of different types is not equal to overall BLC because there are patients identified more than one type of leakage.

Among demographic and perioperative baseline data, CV (6.0 [5.5–7.5] ml vs. 4.5 [3.0–6.1] ml, $P < 0.001$) was found to be significantly higher in the intradiscal leakage group than in the control group. Age, sex, weight, BMI, overweight or obesity, time from injury to surgery, BMD, and surgical level did not significantly differ between the two groups (Table 2). In radiologic data, there were significant difference in fracture severity ($P = 0.008$), with more severe fracture and fewer mild fracture in the intradiscal leakage group. Also, we found lower minimum vertebral height (12.3 ± 3.7 vs. 15.6 ± 5.1, $P = 0.001$), lower CR (51.8 ± 18.2 vs. 66.8 ± 19.1, $P < 0.001$), and higher CVBF (35.0 ± 15.9 vs. 23.8 ± 15.3, $P = 0.001$) in the intradiscal leakage group (Table 3). Although all patients in the intradiscal leakage group had existing endplate cortical disruption, the incidence did not significantly differ from that in the control group (35/35 [100%] vs. 65/74 [87.5%], $P = 0.075$). 9 patients were found without endplate cortical disruption in the control group, including 5 combined with cortical disruption in anterior wall, 2 combined with cortical disruption in posterior wall, and 2 without any cortical disruption.

To build a logistic regression model, we selected cement volume, fracture severity, endplate cortical disruption, minimum vertebral height, CR, and CVBF as potential risk factors ($P < 0.1$). However, we excluded cement volume,

TABLE 2 Univariate analysis of demographic and perioperative baseline data for intradiscal leakage.

Variable	Intradiscal leakage group ($N = 35$)	Control group ($N = 74$)	*P* value
Age, year	78.0 ± 9.0	77.3 ± 7.3	0.635
Gender (female), *n*	22 (62.9%)	47 (63.5%)	0.947
Weight, kg	62.6 ± 12.8	62.5 ± 12.1	0.972
BMI, kg/m^2	24.4 ± 4.7	23.4 ± 3.7	0.209
Overweight (BMI 25–30), *n*	15 (42.9%)	23 (31.1%)	0.228
Obesity (BMI ≥ 30), *n*	4 (11.4%)	2 (2.7%)	0.157
Time before surgery, days*	50 (39–80)	43 (38–60)	0.128
BMD, T-score	−3.2 ± 0.6	−3.0 ± 0.7	0.587
Surgical level, *n*			0.855
Thoracic (upper than T10)	2 (5.7%)	4 (5.4%)	
Thoracolumbar (T10–L2)	30 (85.7%)	61 (82.4%)	
Lumbar (lower than L2)	3 (8.6%)	9 (12.2%)	
CV, ml*	6.0 (5.5–7.5)	4.5 (3.0–6.1)	**<0.001**

BMI, body mass index; BMD, bone mineral density; CV, cement volume.
Bold values indicate statistical significance ($P < 0.05$).
**P* values were calculated *via* the Mann–Whitney *U* test and results are given as the median (interquartile range).

TABLE 3 Univariate analysis of radiologic data for intradiscal leakage.

Variable	Intradiscal leakage group ($N = 35$)	Control group ($N = 74$)	P value
Fracture type, n			0.102
Wedge	13 (37.1%)	31 (41.9%)	
Biconcave	22 (62.9%)	38 (51.4%)	
Crush	0 (0)	5 (6.8%)	
Fracture severity, n*			**0.008**
Mild**	0 (0)	9 (12.2%)	
Moderate	9 (25.7%)	25 (33.8%)	
Severe**	18 (51.4%)	21 (28.4%)	
Very severe	5 (14.3%)	5 (6.8%)	
Endplate cortical disruption, n	35 (100%)	65 (87.8%)	0.075
Location of ICV, n			
Adjacent to superior endplate	17 (48.6%)	34 (45.9%)	0.798
Adjacent to inferior endplate	3 (8.6%)	11 (14.9%)	0.542
Extending to both endplates	12 (34.3%)	20 (27.0%)	0.437
VWA, °	13.3 ± 6.6	12.1 ± 7.4	0.397
SKA, °	17.6 ± 13.5	16.2 ± 15.4	0.657
VHmin, cm	12.3 ± 3.7	15.6 ± 5.1	**0.001**
CR, %	51.8 ± 18.2	66.8 ± 19.1	**<0.001**
CVBF, %	35.0 ± 15.9	23.8 ± 15.3	**0.001**

IVC, intravertebral cleft; VWA, vertebral wedge angle; SKA, segmental kyphotic angle; VHmin, minimum vertebral height; CR, compression rate; CVBF, cemented vertebral body fraction.
Bold values indicate statistical significance ($P < 0.05$).
*17 patients were excluded because their vertebral body collapses were less than 20%.
**Indicates significant difference between pairwise comparison (Bonferonni adjusted $P < 0.05$).

TABLE 4 Multivariate logistic analysis for intradiscal leakage.

Variable	OR	95% confidence interval	P value
Endplate cortical disruption	–	–	0.099
CR	0.025	0.002–0.264	**0.002**
CVBF	44.122	2.790–697.740	**0.007**

OR, odds ratio; CR, compression rate; CVBF, cemented vertebral body fraction.
Bold values indicate statistical significance ($P < 0.05$).

fracture severity, and minimum vertebral height as they showed significant collinearity with others and had negative effects on model prediction. Stepwise forward binary logistic analysis revealed that CR (odds ratio [OR] 0.025; 95% confidence interval [CI] 0.002–0.264; $P = 0.002$) and CVBF (OR 44.122; 95% CI 2.790–697.740; $P = 0.007$) were independent risk factors (Table 4).

Based on the results of the multivariate logistic analysis, a predictive nomogram was established (Figure 2). CR and CVBF, as independent risk factors, were scored, and a quantitative relationship with intradiscal leakage was built in patients with OVCFs combined with IVC treated with PKP. Then, the ROC curves of CR, CVBF, and overall predicted probability were drawn and showed good predictive power (C-statistic = 0.786) for the multivariate logistic model and nomogram (Figure 3). The calibration curve showed good fitness of the data and a well-calibrated predictive model (Hosmer–Lemeshow goodness-of-fit test $P = 0.092$; Figure 4).

Discussion

For patients with OVCFs treated with PKP, the occurrence and risk factors of intradiscal cement leakage should be characteristic of the presence of IVC. However, to the best of our knowledge, the present study is the first to provide a unique insight into identifying risk factors for intradiscal leakage among such specific individuals. Our results revealed that the incidence of overall BCLs was 37.6%, whereas intradiscal leakage was the most common type, which developed in 32.1% of patients. CR and CVBF were identified as independent risk factors, and a powered and well-calibrated predictive nomogram was established to further explore the clinical strategies to prevent intradiscal leakage in such patients.

The presence of IVC may have conflicting effects on the different types of BCLs. Several studies have indicated that IVC decreases the risk of leakage through the veins (types B and S) (17, 28, 34, 35), and the effects may be multifactorial. First, IVC is caused by avascular osteonecrosis, and the area is surrounded by a fibrocartilaginous membrane, which makes the cement hard to extrude into the paravertebral veins (28). Moreover, pathological evidence showed that the occlusion of segmental arteries caused by fracture fragments and poor vascular supply beneath the superior endplate, where most IVCs occur, both contributed to a lower probability of venous leakage (36). In contrast, previous studies have recognized that the presence of IVC increases the risk of discal leakage, mainly because most clefts are connected directly between the intravertebral cavity and intradiscal area through the disrupted endplate, providing a low stress approach for cement distribution (13, 18, 20, 22, 31, 37, 38). In agreement with these findings, this study also found a lower incidence of 8.3% in venous leakage compared to as high as 32.1% in discal leakage in OVCFs combined with IVC.

Interestingly, in a recent study on BCLs after PVP (34), although a similar conclusion was drawn that IVC had opposite impacts on leakage through the vein and bone cortex, we noticed that the overall incidence of venous leakage was still higher than that of discal leakage (37.4% vs. 16.5%), contrary to our results. The authors believe that this is mainly because PKP exacerbates this contradiction. On the one hand, the inflated balloon may cause more occlusion or damage to

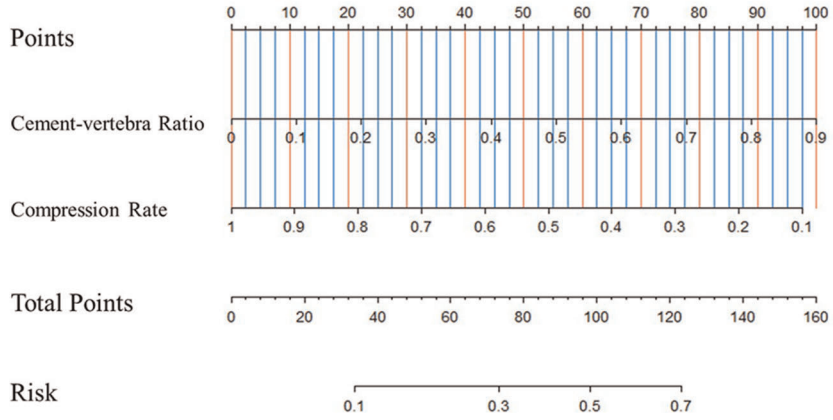

FIGURE 2
Predictive nomogram for intradiscal leakage in osteoporotic vertebral compression fractures combined with intravertebral cleft treated by percutaneous kyphoplasty.

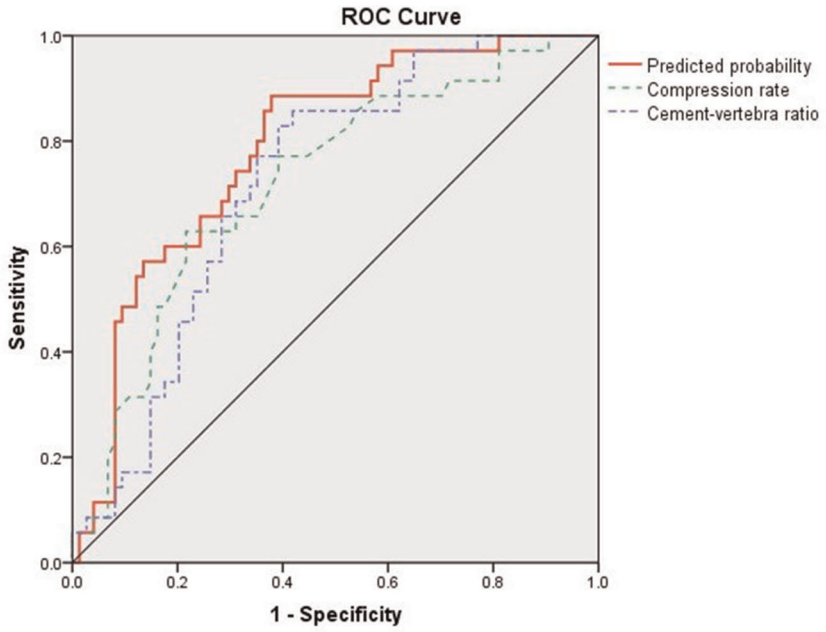

FIGURE 3
Receiver operating characteristic (ROC) curve of compression rate, cemented vertebral body fraction, and overall predicted probability, C-statistic = 0.786.

the vascular system, leading to less cement leakage into the veins. On the other hand, the ballooning procedure may play a jack-like role when IVC is present, which results in pushing the normal bone apart to aggravate the cleft instead of compressing the bone (39). Together with the presence of a fibrocartilaginous membrane, the cement will not form an interdigitated but a crumby distribution and will leak into the disc through the increased cleft when filling the vacuum. However, these findings should be verified in further anatomical and pathophysiological studies.

In this study, the incidence of type D leakage was higher than 3.7%–18.0% reported by previous studies of PKP for treatment of OVCFs with IVC (11, 24, 29). We believe that there are two main reasons for this. First, cortical disruption has generally been identified as a risk factor for intradiscal leakage (10, 12, 13, 18, 37). Of the patients enrolled in our

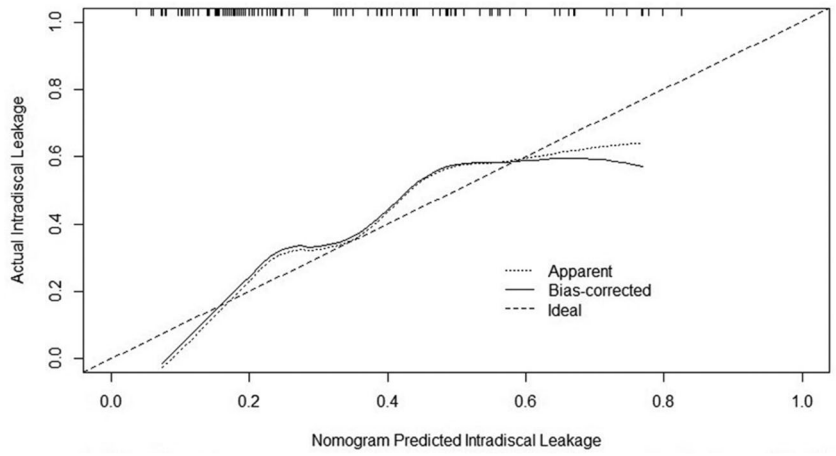

FIGURE 4
Calibration curve of the nomogram showed a well-calibrated predictive model, Hosmer–Lemeshow goodness-of-fit test $P = 0.092$.

study, 91.7% had endplate cortical disruption and 97.0% were found to communicate with the IVCs. Second, approximately 45.0% of patients had severe or very severe fractures, yet the mean CV (5.5 ± 2.8 ml) was relatively large, which may account for the high incidence of intradiscal leakage. Wang et al. suggested that meticulous expansion of the balloon and filling with cement could prevent the risk of cement leakage to some extent (30). However, these procedures were difficult to perform in our experience, especially for patients with severe fractures, as we should balance well between the maximum restoration of vertebral height and prevention of BCLs for better prognosis, and the threshold was difficult to identify. Therefore, further identification of quantitative predictors of intradiscal leakage is of great benefit and requirement.

Previous studies have evaluated the relationship between fracture severity and intradiscal leakage after vertebral augmentation techniques (10, 12–14, 17, 18). Generally, the measurements of the severity of OVCFs can be divided into semiquantitative methods (17, 31) and quantitative parameters, such as fractured vertebral height and CR. In a retrospective study of 283 vertebrae in 239 patients with OVCFs, fracture severity was not recognized as a risk factor for intradiscal leakage (12). However, most studies have identified severe fracture as an independent risk factor (10, 13, 14, 17, 18). Similarly, the present study comprehensively evaluated semiquantitative and quantitative parameters of fracture severity and found that CR was the only independent risk factor. This can be explained by more severe vertebral fractures aligned with more endplate destruction, which may shorten the path between the IVC cavity and the destroyed endplate. In addition, severe vertebral fractures result in a less volume of vertebra, which limits the potential of filling the cement and increases the risk of cement leakage (10).

The role of the injected cement volume in intradiscal leakage remains conflicting and unclear (10, 12, 14, 26, 40). Chen et al. found that a greater amount of injected cement resulted in a higher tendency for cement leakage in the disc during PVP (26). Similarly, in a 10-year retrospective study of 485 patients, Zhu et al. identified that lower cement volume had a protective effect against intradiscal leakage in PVP (14). However, an association between cement volume and intradiscal leakage has not been found in other studies (10, 12, 40). The authors believe that the inconsistency may partly be attributed to the fact that these studies did not adjust cement volume to a specific vertebral volume in different individuals. For instance, an amount of 4.5 ml cement volume has different effects among different vertebral sizes, as a small and severely fractured vertebra was not likely to contain such a cement volume, thus leading to cement leakage. Therefore, the present study used CVBF, a vertebral volume-adjusted parameter, in the risk factor analysis and identified it as an independent risk factor for intradiscal leakage. The cavity area of the IVC and inflated balloon was limited by vertebral volume. When the cement fills a finite space, it tends to leak through the path from the IVC to the destroyed endplate, causing intradiscal leakage.

It is generally believed that endplate cortical disruption is a crucial risk factor for intradiscal leakage (10, 12, 13). However, although slightly more endplate cortical disruptions were found in intradiscal leakage group in this study, the difference did not reach statistical significance (35/35 [100%] vs. 65/74 [87.8%], $P = 0.075$). The main reason for this may because all patients enrolled in this study was with IVC, while IVC were found to be communicated with the endplate cortical disruption in 89.0% patients. This resulted in a high incidence of endplate cortical disruption, which may weaken its effect on contributing to the discrepancy in the two groups. Moreover,

Tang et al. demonstrated that all intradiscal cement leaks were occurred through the cortical disruption at the endplates (35). This was confirmed by this study, and we also found all endplate cortical disruptions were communicated with IVC in intradiscal leakage group. Therefore, we inferred that endplate cortical disruption may be a requisite for intradiscal leakage in patients with IVC, rather than just a risk factor. However, we cannot draw an arbitrary conclusion, and further pathophysiological studies were required.

The present study attempted to build a novel nomogram to quantitatively predict the risk of discal leakage of PKP for the treatment of OVCFs with IVC. Our nomogram, containing CR and CVBF, showed a good predictive value (C-statistic = 0.786) and good fitness of data (Hosmer–Lemeshow goodness-of-fit test $P = 0.092$). Among the two independent risk factors, CR is an intrinsic risk factor that is non-modifiable since injury, whereas CVBF is a modifiable risk factor. This allows surgeons to calculate the most suitable threshold of injected cement volume according to CR to further reduce the risk of discal leakage in such individuals.

This study has some limitations. First, this was a retrospective and single-center study, which may have led to a selection bias. Second, the study had a relatively small sample size and the outcome of the intradiscal leakage group was limited to an even smaller sample size of 35 patients. However, the number of events per variable included in the logistic regression model should be greater than 10, which indicates that the multivariate model was sufficiently stable in this study. Moreover, several potential risk factors, including cement viscosity, multilevel OVCFs, and surgeon experience, were not analyzed. Further prospective, multicenter studies with large population and comprehensive predictors are required to verify and calibrate our findings.

Conclusion

The incidence of overall BCLs in PKP for OVCFs combined with IVC was 37.6%, whereas intradiscal leakage was the most common type, developed in 32.1% of patients. CR and CVBF were identified as independent risk factors. A powered and well-calibrated predictive nomogram was established to accurately predict the probability of intradiscal leakage and further explore clinical strategies to prevent intradiscal leakage in such patients. Further prospective and multicenter studies are required to verify and calibrate our findings.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement

The research conducted has been performed in accordance with the Declaration of Helsinki. Approval for the study was obtained from the ethics committees of the Beijing Chaoyang Hospital (2021-KE-479).

Author contributions

NF and TW contributed equally to this work. NF and TW designed and wrote this manuscript; WZ, JL, LZ conducted manuscript review and editing; NF, TW, AW, SY, PD, FS participated in data collection. All authors were involved in writing 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.

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RBC, HB, HCT, CRP, and ESR at different postoperative periods after the application of intravenous unit dose transient acid in PLIF: A case control study

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Background: Tranexamic acid (TXA) has been used in posterior lumbar interbody fusion (PLIF) and reduces blood loss. However, it has not been reported whether it will continue to affect postoperative red blood cells (RBC), hemoglobin (HB), hematocrit (HCT), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The purpose of this study was to observed the above indicators at different time after PLIF with unit dose intravenous (iv) TXA.

Methods: The data of 44 patients treated by single-segment PLIF from 2020.11 to 2022.3 were retrospectively analyzed. Observation group was given a unit dose of ivTXA (1 g/100 mL) 15 min before skin incision after general anesthesia. Patients without TXA were recorded as control group. Main observation indicators include RBC, HB, HCT, CRP and ESR on the 1st, 4th, 7th and last tested day after surgery. Secondary observation indicators include postoperative activated partial thrombin time (APTT), prothrombin time (PT), thrombin time (TT), and fibrinogen (FIB); and operation time, intraoperative blood loss, postoperative drainage volume, incision healing, postoperative deep vein thrombosis and postoperative hospital stay.

Results: The operation was successfully completed without related complications. At term of main observation indicators, RBC, HB and HCT remained relatively stable, while CRP and ESR fluctuated to some extent after PLIF. The RBC, HB and HCT in the observation group were higher than those in the control group with statistically significant ($p < 0.05$). Except the CRP of 7th postoperative day of the observation group was significantly lower than that of the control group ($p < 0.05$), there was no difference in other CRP and ESR between the two groups ($p > 0.05$). At term of secondary observation indicators, the intraoperative blood loss and postoperative drainage volume of the observation group were lower than those of the control group with statistically significant ($p < 0.05$). There was no significant difference in postoperative APTT, PT, TT, FIB, and operation time and postoperative hospital stay between the two groups ($p > 0.05$).

Conclusion: The application of unit dose of ivTXA in PLIF can safely and effectively reduce blood loss. Meanwhile, it can also maintain higher RBC, HB, HCT levels without disturbing CRP and ESR levels after surgery.

KEYWORDS

lumbar degenerative disease, posterior lumbar interbody fusion, tranexamic acid, anemia index, inflammatory response index

Background

With the continuous increase of the elderly population and the improvement of patients' awareness of healthy life, the number of patients undergoing surgeries for lumbar degenerative diseases such as lumbar disc herniation, lumbar spinal stenosis, and lumbar spondylolisthesis has increased sharply in recent years (1, 2). Posterior lumbar interbody fusion (PLIF) is a common and effective operation for the treatment of lumbar degenerative diseases (3, 4). However, it faces the challenge of large perioperative blood loss (5). That can lead to anemia often requiring transfusion, which increases the risk of transfusion-related adverse events (6). Besides, PLIF is one of the major orthopaedic operations, which is also prone to infection after surgery, as a disaster.

Tranexamic acid (TXA), as a synthetic derivative of lysine, was discovered in 1962 and the chemical term was trans-4-aminomethylcyclohexanecarboxylic acid (7). It, as a synthetic antifibrinolytic drug, can reduce surgical bleeding by inhibiting fibrinolysis and stabilizing blood clots (8). Studies have reported that intravenous (iv)TXA can effectively reduce perioperative blood loss in PLIF (9–12). Red blood cell (RBC), hemoglobin (HB) and hematocrit (HCT) are commonly used clinical indicators to monitor the course of anemia. The current research basically focuses on HB, and only observed the value at a time point after surgery, such as the pioneer researcher Kushioka et al. (13). Therefore, this study plans to simultaneously and continuously observe the three indicators of RBC, HB, and HCT, in addition to intraoperative and posteperative blood loss.

The disaster that worries doctors the most after PLIF is infection. The commonly used indicators in inflammation monitoring after lumbar spine surgery are Serum procalcitonin, white blood cell count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), among which CRP has the highest specificity of 90.27%, and ESR has the highest sensitivity of 88.50% (14). Combined monitoring of CRP and ESR after lumbar spine surgery is important for monitoring infectious events (15). However, there are few reports on postoperative CRP and ESR monitoring with TXA in PLIF, and these are different for a single time point comparison (16, 17). Therefore, continuous monitoring of CRP and ESR after surgery may provide more information to know whether the ivTXA affects the judgment of inflammation after surgery.

There are various schemes for perioperative application of TXA, such as single preoperative intravenous administration, continuous intravenous infusion, topical administration, and intravenous combined topical administration (18, 19). Among them, the most used way is ivTXA (20). After about 15 min of ivTXA, it can reach and accumulate in the surgical field to exert hemostatic effect (21). Besides, this medication method is also the main recommendation for the application of TXA in the 2019 Chinese Expert Consensus, which has the advantage of not interfering with other intraoperative intravenous drugs (22). Single-level PLIF is one of the most common types of surgery. Therefore, in this study, the single-segment PLIF cases with ivTXA applied 15 min before surgery were selected as the research sample. This study mainly discusses two questions: (1) Describe the RBC, HB, HCT, CRP, and ESR after PLIF without TXA, and try to find out its characteristics. (2) Find out whether the above indexes are significantly affected after PLIF with TXA.

Method

Study design

As a case control study, the time frame for case collection was from 2020.11 to 2022.3, and the location was General Hospital of Pingmei Shenma Medical Group. The inclusion criteria included American Society of Anesthesiologists classification was grade II, anesthesia mode was general anesthesia, the surgical segment was single-segment PLIF, and there was no previous history of lumbar spine surgery. The exclusion criteria included those with deep venous thrombosis (DVT) before surgery, and those who received anticoagulation in coming 2 weeks before surgery, and those who had cerebrospinal fluid leakage or dural damage during surgery. In the end, 44 cases data was retrospectively collected, including 26 males and 18 females, with an average age of (55.57 ± 10.38) years old. Grouping was based on whether or not ivTXA was applied. Patients who started applying unit dose of ivTXA (1 g/100 mL) 15 min before skin incision after general anesthesia were included in the observation group. Patients who without applied TXA were included in the control group. The PLIF operation steps were the same and two drainage tubes were placed. When the patient returns to the ward after

the operation, some conventional treatment measures are given. They included the application of cephalosporin antibiotics to prevent infection, glucocorticoids to reduce spinal cord stress response, glycerol drugs to reduce edema response, non-steroidal drugs to relieve pain, and low molecular weight heparin drugs to prevent DVT. The vital signs, surgical incision, sensation and movement of both lower extremities were observed. When the drainage volume is less than 50 mL/24 h, the drainage tubes will be removed. Meanwhile, preoperative general information of patients was collected as baseline data, including age, gender, body mass index (BMI), disease type, coexisting diabetes, coexisting high blood pressure, activated partial prothrombin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), RBC, HB, HCT, CRP and ESR.

Outcome indicators

Main observation indicators include RBC, HB, HCT, CRP and ESR on the 1st, 4th, 7th and last tested day after surgery. Secondary observation indicators include APTT, PT, TT, FIB of the first postoperative day, and operation time, intraoperative blood loss, postoperative drainage volume, incision healing, postoperative DVT and postoperative hospital stay.

Statistical methods

Data analysis was performed *via* SPSS statistical software (version 22.0). The measurement data conforming to the normal distribution is expressed by mean ± standard deviation, and the comparison between groups is by t test. The measurement data that is not normally distributed is expressed by M [P25; P75], and the comparison between groups is by the Mann-Whitney U nonparametric test. The enumeration data were described in the form of the number of cases (percentage), and the chi-square test was used for comparison between groups. $p < 0.05$ was considered statistically significant.

Results

The comparison results of preoperative baseline data between the two groups

There was no significant difference in baseline data between the two groups, including age, gender, BMI, disease type, coexisting diabetes, coexisting high blood pressure, APTT, PT, TT, FIB, RBC, HB, HCT, CRP and ESR ($p > 0.05$) in Table 1.

TABLE 1 Comparison of preoperative baseline data between the two groups.

Groups	Observation group ($n = 23$)	Control group ($n = 21$)	$t/\chi^2/Z$	p
Age, year	55.39 ± 10.95	55.76 ± 9.98	−0.117	0.907
Sex, *n* (%)			0.063	0.802
Male	14 (60.90)	12 (57.10)		
Female	9 (39.10)	9 (42.90)		
BMI, kg/m^2	24.68 ± 2.09	25.81 ± 3.55	−1.299	0.201
Disease type, *n* (%)			1.001	0.606
Lumbar disc herniation	3 (13.04)	4 (19.05)		
Lumbar spinal stenosis	11 (47.83)	7 (33.33)		
Lumbar spondylolisthesis	9 (39.13)	10 (47.62)		
Coexisting diabetes, *n* (%)	2 (8.70)	3 (14.29)	0.341	0.658
Coexisting high blood pressure, *n* (%)	3 (13.04)	7 (33.33)	2.573	0.155
APTT, s	30.90 ± 2.07	30.85 ± 3.35	0.052	0.959
PT, s	11.29 ± 0.88	11.11 ± 0.78	0.724	0.473
TT, s	15.00 [13.90; 15.60]	15.35 [14.50; 15.81]	−1.458	0.145
FIB, g/L	2.72 [2.52; 3.14]	2.68 [2.36; 3.15]	−0.529	0.597
RBC, $10^{12}/L$	4.47 [4.10; 4.70]	4.36 [4.16; 4.57]	−0.035	0.972
HB, g/L	143.57 ± 11.33	141.00 ± 10.91	0.763	0.449
HCT, L/L	0.42 [0.38; 0.44]	0.41 [0.38; 0.44]	−0.343	0.731
CRP, mg/L	0 [0; 0.32]	0 [0; 1.03]	−0.597	0.551
ESR, mm/h	12 [4; 29]	11 [5; 22]	−0.494	0.621

The comparison results of the main observation indicators between the two groups after surgery

RBC, HB and HCT in both groups remained relatively stable after PLIF. The RBC, HB and HCT in the observation group were higher than those in the control group with statistically significant ($p < 0.05$). CRP and ESR in both groups fluctuated to some extent after PLIF. Except the CRP of the observation group on the 7th day after operation was significantly lower than that of the control group ($p < 0.05$), there was no difference in other CRP and ESR between the two groups ($p > 0.05$) in Table 2.

The comparison results of the secondary observation indicators between the two groups after surgery

All patients successfully completed the operation, the incision healed well, and there was no DVT after operation.

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TABLE 2 Comparison of the main observation indicators between the two groups after surgery.

Groups	Observation group ($n = 23$)	Control group ($n = 21$)	t/Z	p
RBC, 10^{12}/L				
1st day	3.99 ± 0.43	3.64 ± 0.35	3.039	0.004
4th day	3.87 ± 0.49	3.55 ± 0.44	−2.303	0.021
7th day	4.12 [3.85; 4.29]	3.59 [3.25; 3.72]	−3.278	0.001
Last tested day	4.16 [3.85; 4.26]	3.51 [3.36; 3.98]	−3.325	0.001
HB, g/L				
1st day	128.22 ± 13.03	116.86 ± 10.48	3.199	0.003
4th day	124.65 ± 14.59	114.05 ± 13.50	2.504	0.016
7th day	130 [121; 139]	117 [103; 123]	−3.163	0.002
Last tested day	128.26 ± 13.17	115.33 ± 10.41	3.627	0.001
HCT, L/L				
1st day	0.37 ± 0.04	0.34 ± 0.03	3.045	0.004
4th day	0.37 [0.33; 0.4]	0.34 [0.29; 0.36]	−2.415	0.016
7th day	0.37 [0.35; 0.4]	0.33 [0.29; 0.35]	−3.537	0.000
Last tested day	0.37 ± 0.04	0.33 ± 0.04	3.821	0.000
CRP, mg/L				
1st day	13.21 ± 7.98	17.68 ± 9.31	−1.715	0.094
4th day	4.79 [1.86; 15.29]	6.89 [3.43; 31.86]	−1.668	0.095
7th day	1.35 [0; 7.19]	9.87 [1.88; 24.31]	−2.58	0.010
Last tested day	2.8 [0.55; 7.68]	6.58 [2.08; 14.16]	−1.635	0.102
ESR, mm/h				
1st day	8 [3; 14]	5 [2; 13]	−1.088	0.277
4th day	18 [8; 44]	26 [9; 40]	−0.564	0.573
7th day	21 [7; 40]	32 [15; 44]	−1.07	0.290
Last tested day	31 [18; 43]	39 [17; 48]	−0.682	0.495

TABLE 3 Comparison of secondary observation indicators between the two groups after surgery.

Groups	Observation group ($n = 23$)	Control group ($n = 21$)	t/Z	p
Operation time, min	150.52 ± 24.79	155.48 ± 36.02	−0.535	0.595
Intraoperative blood loss, mL	300 [200; 300]	300 [300; 500]	−2.391	0.017
Postoperative drainage volume, mL	200 [190; 250]	330 [290; 350]	−4.475	0.000
APTT, s	28.78 ± 2.49	28.60 ± 2.71	0.233	0.817
PT, s	12.37 ± 0.99	12.34 ± 0.79	0.115	0.909
TT, s	14.55 ± 1.21	14.61 ± 1.03	−0.169	0.867
FIB, g/L	2.87 [2.55; 3.23]	2.87 [2.61; 3.23]	−0.223	0.823
Postoperative hospital stay, day	13 [10; 14]	14 [8; 15]	−0.024	0.981

The intraoperative blood loss and postoperative drainage volume of the observation group were lower than those of the control group with statistically significant ($p < 0.05$). There was no significant difference in APTT, PT, TT, FIB of the first postoperative day, and operation time and postoperative hospital stay between the two groups ($p > 0.05$) in **Table 3**.

Discussion

Surgical safety is the premise of PLIF. Some scholars worried about that TXA may lead to systemic fibrinolytic system inhibition, relative insufficiency of plasmin system activity, reduced thrombolysis and increased DVT, and even death of patients (23, 24). Moreover, the elderly face a higher risk of DVT after surgery (25). Therefore, it is necessary to study the safety of ivTXA in PLIF. Therefore, the study observed preoperative and postoperative coagulation markers (including APTT, PT, TT, FIB) and DVT. The results found that ivTXA in PLIF had no effect on coagulation markers and did not produce DVT. This illustrates the feasibility and safety of our study.

Studies found that ivTXA can reduce perioperative blood loss in PILF (26–28). This study similarly found that a unit dose of ivTXA was effective in reducing intraoperative blood loss and postoperative drainage in PILF. It was reported that the application of TXA in PILF can also reduce the operation time (29). But this study did not yield such results, which is similar to the study of Wang et al. (30). There are two possible reasons for the different outcomes. Firstly, in the present study, cases are all single-segment, and the operation is relatively less difficult, so that the operation time will not be significantly affected. Secondly, the study data is a small sample, which may produce bias.

The study showed that RBC, HB and HCT in both groups remained relatively stable after surgery, but those of the observation group were significantly higher than those of the control group at different times after surgery. It shows that the application of ivTXA can play a role in protecting postoperative blood volume. In addition, elderly patients have poor hematopoietic function, and their ability to correct anemia is relatively weak. Therefore, when there is malnutrition after the operation, the patient is difficult to recover. Studies have shown that due to the influence of surgical trauma, inflammatory reaction, and pain stimulation, patients often suffer from lack of energy, poor appetite, and insufficient intake after surgery, which is not conducive to the correction of postoperative anemia. Meanwhile the anemia and hypoproteinemia can also cause and aggravate gastrointestinal mucosal edema, anorexia and other problems

which further aggravates anemia and hypoproteinemia, leading to a vicious circle eventually (31).

The disaster that worries doctors the most after PLIF is infection. Once infection occurs, it challenges the effect of treatment. Clinically, CRP and ESR are important indicators which are commonly used to monitor and predict lumbar postoperative infection (32). CRP is an acute, non-specific phase protein with a half-life of 15 h and it is less than 10 mg/L in 99% of healthy individuals (33). The elevated CRP is not related to the amount of bleeding, operation time, drugs, age and gender, but is related to the bacterial infection, the type and degree of tissue damage (34). CRP generally peaks in 2 or 3 days after surgery and returns to normal within 2 weeks after surgery, and the magnitude and duration of elevated CRP is proportional to the severity of the injury, which can be 10 to 60 times higher than the normal value (35).

ESR, a relatively sensitive indicator, lacks specificity for the diagnosis of infection, but has high sensitivity in the occurrence and development of inflammation (36). The elevated ESR is not related to age, disease type, or blood transfusion, but is related to gender, surgical site, and surgical time (35). ESR will increase within 1 week after lumbar spine surgery, peak on the 4th day, and return to the baseline level in 2 or 3 weeks, but it is more than 25 mm/h in most cases (36). However, ESR has a certain false-positive rate, a positive result does not indicate infection, and its positive predictive value is low, which makes it not valuable for early detection of infection, so it is not appropriate to use ESR alone to monitor postoperative infection (35).

Therefore, continuously observation of CRP and ESR after PLIF can accurately determine whether infection occurs, which is conducive to timely detection and treatment of infection. However, there are few studies on postoperative CRP and ESR when TXA is used clinically in PLIF. In addition, different studies hold different viewpoints. Peng Zhao et al. (16) observed the CRP and ESR on the 3rd day after PLIF with ivTXA, and found that they were no different from the group without TXA. Jianru Yuan et al. (17) found that ivTXA could reduce CRP on the 3rd day after PLIF, which may be related to the ability of TXA to relieve postoperative inflammatory response, but the specific mechanism is still unclear. The present study found that CRP and ESR after PLIF with or without ivTXA both fluctuated to some extent. And only the CRP of the observation group was significantly lower than that of the control group only on the 7th day after operation, and there was no difference between the two groups at other time points, which was in line with the general change regulation of CRP and ESR after operation. The possible reason is that the control group continued to have low levels of anemia indicators after surgery, resulting in a weaker ability to fight inflammatory responses, manifested as high CRP on the 7th day after surgery. Therefore, it was possible to speculate that a unit dose of ivTXA in PLIF does not affect the post-operative inflammatory response process.

Enhanced recovery after surgery (ERAS) is a good strategy for patients (37), and studies have shown that the application of TXA is beneficial to ERAS (22). Reducing perioperative blood loss can promote wound healing and early postoperative recovery (38). Theoretically, the postoperative hospital stay should be shortened in patients receiving TXA. However, this study did not yield the similar result, which is similar to the research results of some scholars (39, 40). There are two possible reasons for this. First, the hospital adopts standardized treatment and high-quality nursing measures, which may make no difference in the postoperative hospital stay of patients. Second, the sample size of the study is small, which may cause bias, which cannot be ignored.

Conclusion

There are some deficiencies in this study, one is the retrospective analysis of medical records, and the other is the small sample size, so the reliability of the conclusions is inevitably affected to some extent. In sum, we believe that the application of unit dose of ivTXA in PLIF has the characteristics of simple operation, safe and effective in reducing blood loss. Our previous questions in introduction are solved, and it can maintain higher levels of postoperative RBC, HB, and HCT, and does not significantly interfere with the levels of CRP and ESR.

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

The studies involving human participants were reviewed and approved by the Ethics Committee of the General Hospital of Pingmei Shenma Group (No. 2021004). 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

HS had been involved in drafting the manuscript. DS assisted in revising the manuscript. WP, MS, LH and LS diagnosed and treated the patients. WX and YZ had made substantial contributions to the conception and designed of the manuscript. ZR followed up the patients. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that this study received funding from China Pingmei Shenma Energy and Chemical Group Co., Ltd. The funder had the following involvement in the study: the study design, data collection and analysis, decision to publish, and preparation of the manuscript.

Publisher's note

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Will the adjustment of insertional pedicle screw positions affect the risk of adjacent segment diseases biomechanically? An in-silico study

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Background: The fixation-induced biomechanical deterioration will increase the risk of adjacent segment diseases (ASD) after lumbar interbody fusion with Bilateral pedicle screw (BPS) fixation. The accurate adjustment of insertional pedicle screw positions is possible, and published studies have reported its mechanical effects. However, no studies clarified that adjusting insertional screw positions would affect the postoperative biomechanical environment and the risk of ASD. The objective of this study was to identify this issue and provide theoretical references for the optimization of insertional pedicle screw position selections.

Methods: The oblique lumbar interbody fusion fixed by BPS with different insertional positions has been simulated in the L4-L5 segment of our previously constructed and validated lumbosacral model. Biomechanical indicators related to ASD have been computed and recorded under flexion, extension, bending, and axial rotation loading conditions.

Results: The change of screw insertional positions has more apparent biomechanical effects on the cranial than the caudal segment. Positive collections can be observed between the reduction of the fixation length and the alleviation of motility compensation and stress concentration on facet cartilages. By contrast, no pronounced tendency of stress distribution on the intervertebral discs can be observed with the change of screw positions.

Conclusions: Reducing the fixation stiffness by adjusting the insertional screw positions could alleviate the biomechanical deterioration and be an effective method to reduce the risk of ASD caused by BPS.

KEYWORDS

adjacent segment diseases, biomechanical deterioration, insertional screw positions, arm of force, pedicle screw fixation

Abbreviations

ASD, Adjacent segment diseases; BEP, Bony endplate; BPS, Bilateral pedicle screw; CBT, Cortical bone trajectory; CEP, Cartilage endplate; DC, Disc compression; FCF, Facet contact force; IDP, Intradiscal pressure; IVD, Intervertebral disc; LIF, Lumbar interbody fusion; OLIF, Oblique lumbar interbody fusion; ROM, Range of motion; ZJ, Zygapophyseal joint.

Introduction

The bilateral pedicle screw (BPS) is extensively used in spinal operations to restore physiological alignment, maintain stability, and correct hypermotility (1, 2). During the lumbar interbody fusion surgery (LIF), BPS could construct three-column instant stability by transpedicular fixation (2, 3). Although BPS is the gold standard of additional fixation technique in LIF surgery, the stiffness-increasing mechanism of BPS will lead to the fixation-induced pathological load transmission pattern (e.g., stress concentration and motility compensation in adjacent segments) and resulting adjacent segment diseases (ASD) (2–4).

Surgeons advocate removing BPS after solid interbody fusion, and its positive biomechanical effects on adjacent segments have been reported by in-silico mechanical simulations (2, 3). But this method has not been widely promoted in clinical practice, for it is difficult for patients without severe symptoms to accept a second surgical trauma. Additionally, low stiffness material connection rods (e.g., Polyether ether ketone rod) have been designed to alleviate postoperative biomechanical deterioration and reduce the risk of ASD. Their biomechanical advantages have also been proved by in-silico and in-vitro mechanical studies (4–8). However, a higher incidence rate of fixator failure and revision surgery inhibits the promotion of these instrumentations (8, 9). Hence, BPS is still the gold standard of the additional fixation device in LIF at the present stage. The optimization of surgical procedures during the use of BPS, rather than the replacement of BPS, may have a better clinical application prospect. During the modification of the screw trajectory, studies reported that the shift of the screw insertion point medially in the coronal plane could alleviate biomechanical deterioration and reduce the risk of ASD (10, 11); the biomechanical mechanism behind the relation between these screw insertion techniques and the risk of ASD should include not only biomechanical changes caused by different grades of the violation of zygapophyseal joints (ZJ) (12, 13), but also the change of fusion segmental stiffness and resulting overall lumbar biomechanical changes (2, 14).

The percutaneous BPS insertion technique is widely promoted (15, 16). Its insertional screw positions can be accurately adjusted under the guidance of the C-arm, but no studies were elucidating the biomechanical changes with the adjustment of screw insertion positions in the sagittal plane. Adjusting screw insertion positions will affect the BPS's fixation length and locally biomechanical impacts on adjacent segments (2, 14). Considering long segment LIF with the expansion of fixation length has been proven a risk factor of ASD (17, 18), we believe that optimizing screw insertion positions in the sagittal plane (i.e., reducing the fixation length) may be an effective method to reduce the risk of ASD biomechanically. The objective of this study was to identify the biomechanical significance of insertional pedicle screw positions on the risk of ASD. Published literature has not adequately clarified this issue to the best of our knowledge.

Methods

Model construction

We simulate oblique lumbar interbody fusion (OLIF) fixed by BPS with different insertional positions in a previously constructed and well-validated lumbosacral model (19, 20). Bone structures include cortical, cancellous, and bony endplates (BEP), the thickness and morphology of BEPs were defined according to the measurement of large sample imaging data (21, 22). Nonbony components include the intervertebral disc (IVD) and ZJ cartilages. IVD consists of the nucleus core, the surrounding annulus, and cartilage endplates (CEP) on the cranial and caudal sides of the nucleus and inner part of the annulus (23, 24).

Boundary and loading conditions

Models were computed under identical loading conditions, including flexion, extension, bending, and rotation. Sizes of the moment in the mechanical indicators computation process were consistent with the validation of the range of motion (ROM). They were set to be symmetric in the sagittal plane to increase their computational efficiency by allowing the unilateral calculation of the bending and axial rotation loading conditions (19, 20). Hybrid elements (including tetrahedron and hexahedron) with different mesh sizes were established in different components, and smaller mesh sizes were used in structures with low thickness and large deformation (20, 25).

In the definition of material properties, cortical and cancellous bone were set as anisotropic materials (26, 27), other parts of the model were defined by isotropic law (26, 27). The annulus was assumed to be hypoelastic (26, 28), and the nucleus was set as an incompressible "semi-fluid pad" (25, 29). Ligaments structures and capsules of ZJ were defined as cable elements in the pre-processing step of FEA (**Table 1**) (25, 29–31). Contact elements defined facet cartilages of ZJ, and its frictional coefficient was set as zero (29, 32).

Model calibration and validation

All freedom degrees were fixed under the inferior surfaces of current models, and moments were applied on their superior surfaces (5, 29). The stiffness of ligaments under different loading conditions was calibrated to reduce the difference

TABLE 1 Material properties of components in current models.

Components	Elastic modulus (MPa)	Poisson's ratio	Cross-section (mm^2)
Cortical	E_{xx} = 11,300 E_{yy} = 11,300 E_{zz} = 22,000 G_{xy} = 3,800 G_{yz} = 5,400 G_{xz} = 5,400	V_{xy} = 0.484 V_{yz} = 0.203 V_{xz} = 0.203	/
Cancellous	E_{xx} = 140 E_{yy} = 140 E_{zz} = 200 G_{xy} = 48.3 G_{yz} = 48.3 G_{xz} = 48.3	V_{xy} = 0.45 V_{yz} = 0.315 V_{xz} = 0.315	/
Bony endplates	12,000	0.3	/
Annulus	Hypoelastic material		/
Nucleus	1	0.49	/
Cartilage endplates	10	0.4	/
Anterior longitudinal ligaments	Calibrated load-deformation curved under different loading conditions	0.3	60
Posterior longitudinal ligaments	Calibrated load-deformation curved under different loading conditions	0.3	21
Ligamentum flavum	Calibrated load-deformation curved under different loading conditions	0.3	60
Interspinous ligaments	Calibrated load-deformation curved under different loading conditions	0.3	40
Supraspinous ligaments	Calibrated load-deformation curved under different loading conditions	0.3	30
Intertransverse ligaments	Calibrated load-deformation curved under different loading conditions	0.3	10
Capsular	7.5 (\25%) 32.9 ([25%)	0.3	67.5
PEEK	3,500	0.3	/
Titanium alloy	110,000	0.3	/

between the computed ROM in the L4-L5 segment and in-vitro studies (33, 34). A mesh convergency test on the intact model was performed by evaluating intradiscal pressure (IDP) change with different mesh sizes. The model was considered converged if the change of computed IDP was less than 3% (35, 36), multi-indicators model validation has been accomplished by comparing the computed ROM, IDP, the disc compression (DC), and the facet contact force with values from in-vitro studies under different sizes and directions load to ensure computational credibility (37, 38).

Surgical simulations and ASD's risk evaluation

The L4-L5 segment has been selected to simulate the oblique lumbar interbody fusion (OLIF) fixed by BPS with different insertional positions for the incidence rate of lumbar degenerative diseases in this segment was higher than that of the L3-L4 segment, and the L5-S1 segment was not suitable for OLIF generally (15, 16). Lateral parts of the annulus, all of the nucleus, and CEPs in the surgical segment were removed, and a PEEK OLIF cage (18 mm long and 50 mm wide) filled with grafted bony material was inserted into interbody space (15, 39). It was assumed that the disc height and lordotic angle of disc space were not affected by cage insertion, and the outline between cage and BEP was assumed to be perfectly matched (3, 30, 40). Considering ASD was a typical long-term complication, the boundary conditions have been defined to simulate solid interbody fusion. In which, the contact type between grafted bone and BEP was set to be "bounded" (completely constrains the motion under all degrees of freedom), and the frictional coefficient in surfaces between cage and BEP was 0.8 (41, 42).

During the simulation of titanium alloy (Ti6Al4V) BPS fixation with different insertion positions, bilateral pedicle screws (were inserted into L4 and L5 vertebral bodies. The axes of screws on the cross-section were parallel to the pedicle axis, and the screw axis was parallel to which of corresponding cranial BEP (5, 16). The connection between the screw tulip and the nut was simplified to reduce the computational burden (2, 5). Five postoperative models with different insertional screw positions have been constructed, and the screw compaction effect was simulated by adjusting the material property of bony tissue around the screw thread (43, 44). Motility parameters, stress distribution in IVD, and ZJ in both cranial and caudal sides of functional units were recorded to evaluate the risk of ASD.

Results

Multi-indicators model validation

Well-validated computational results can be recorded in the intact model. Specifically, the values of computed ROM and DC under were compared with which in in-vitro studies reported by Renner et al (38), values of IDP were compared with the study published by Schilling et al (7), and which of FCF were also compared with Wilson et al.'s study (37). These indicators computed by the intact model were within ±1 standard deviation of the average values reported by the above-mentioned in-vitro studies, proving that current models could make a good representation of real biomechanical situations (**Figure 1**).

Changes in mechanical indicators related to ASD

Overall ROM, ROM in different segments (including the surgical and adjacent segments), and the proportion of different segmental ROM to the overall value have been computed and recorded to evaluate the motility compensation. Except for the axial rotation condition, positive relations between BPS's fixation length and fixational stiffness can be observed. Specifically, the change of fixation length will slightly affect the overall ROM (the variation range was smaller than 5% except for model 2 (model with shortest fixation length) under the flexion loading condition). By contrast, the change of ROM in the fusion segment was dramatically under most loading conditions. Meanwhile, pathological motility compensation could be amplified and alleviated by increasing and decreasing the arm of force in these segments, especially under the flexion condition in the cranial and bending in the caudal segment (**Figures 2**, **3**).

FCF was not recorded under the flexion loading condition for ZJ cartilages that were not in contact. For the same reason, FCF on the opposite side to the bending condition and the rotation side could not be recorded. In other words, FCF under left lateral bending is observed on left-side cartilages, while FCF under left axial rotation is observed on right-side cartilages. The change of insertional screw positions can lead to the change of FCF. Generally, reducing the arm of force in adjacent segments will decrease FCF and vice versa (**Figure 4**). The variation tendency of the cranial side was more pronounced than the caudal one. To investigate the risk of disc degeneration, we calculate IDP, maximum values of annulus shear and equivalent stress (**Figure 5**). Inconsistent with the variation tendency of ROM and FCF, no apparent tendency of these mechanical indicators can be observed with the change of insertional screw positions, especially under the rotation condition.

Discussion

This work evaluated biomechanical deterioration and the related risk of ASD after OLIF fixed by BPS with different insertional screw positions. An intact lumbosacral model and corresponding OLIF models were constructed, and biomechanical indicators closely related to ASD were computed and evaluated. The importance of the biomechanical environment for achieving positive postoperative clinical outcomes has been repeatedly demonstrated (2, 17, 29). Thus, investigations on the biomechanical effects of different insertional screw positions are of great significance for optimal operative strategy and reducing the risk of ASD.

OLIF, rather than other LIF operations, has been selected for the following reasons. The percutaneous pedicle screw insertion was accomplished under C-arm fluoroscopy in OLIF, and the adjustment of insertion positions is feasible in this operation (**Figure 6**). By contrast, selecting screw insertion positions in other lumbar fusion operations (e.g., transforaminal and posterior lumbar interbody fusion) was based on identifying anatomic structures (10, 11). Considering the prevalence of anatomic variations and the hypertrophy of the articular process during the pathological process of spinal stenosis (45, 46), it is difficult to accurately judge and adjust the exact insertional screw position under the freehand pedicle insertion process. Furthermore, for the same reason, the promotion of the optimized insertional screw positions elucidated by this study may also be limited in LIF fixed by percutaneous pedicle screw.

The deterioration of the biomechanical environment caused by inappropriate surgery may be continuously amplified and lead to a devastating prognosis (17, 19, 47). Therefore, optimizing a surgical technique based on a biomechanical study is significant. There are three common pathological changes of ASD: disc degeneration, ZJ degenerative osteoarthritis, spinal stenosis, and segmental instability (17, 48). The annulus-driven phenotype is the most common reason for disc degeneration in the lower lumbar spine (49, 50). Stress concentration on the annulus, especially on the post and post-lateral parts of the annulus, were related to different types of annulus tears (34, 51). Meanwhile, the aberrant increase of IDP could also increase the risk of annulus failure (26, 52); therefore, annulus stress distribution and IDP are critical indicators in related mechanical studies (26, 53). Simultaneously annulus tears and increased intradiscal pressure would promote disc herniation. The in-growth of blood vessels along annulus tears will promote the inflammatory response, leading to extracellular matrix catabolism and further disc degeneration (50, 54). The in-growth of pain-sensing nerve fibers is also the primary reason for postoperative pain recurrence in ASD (54, 55).

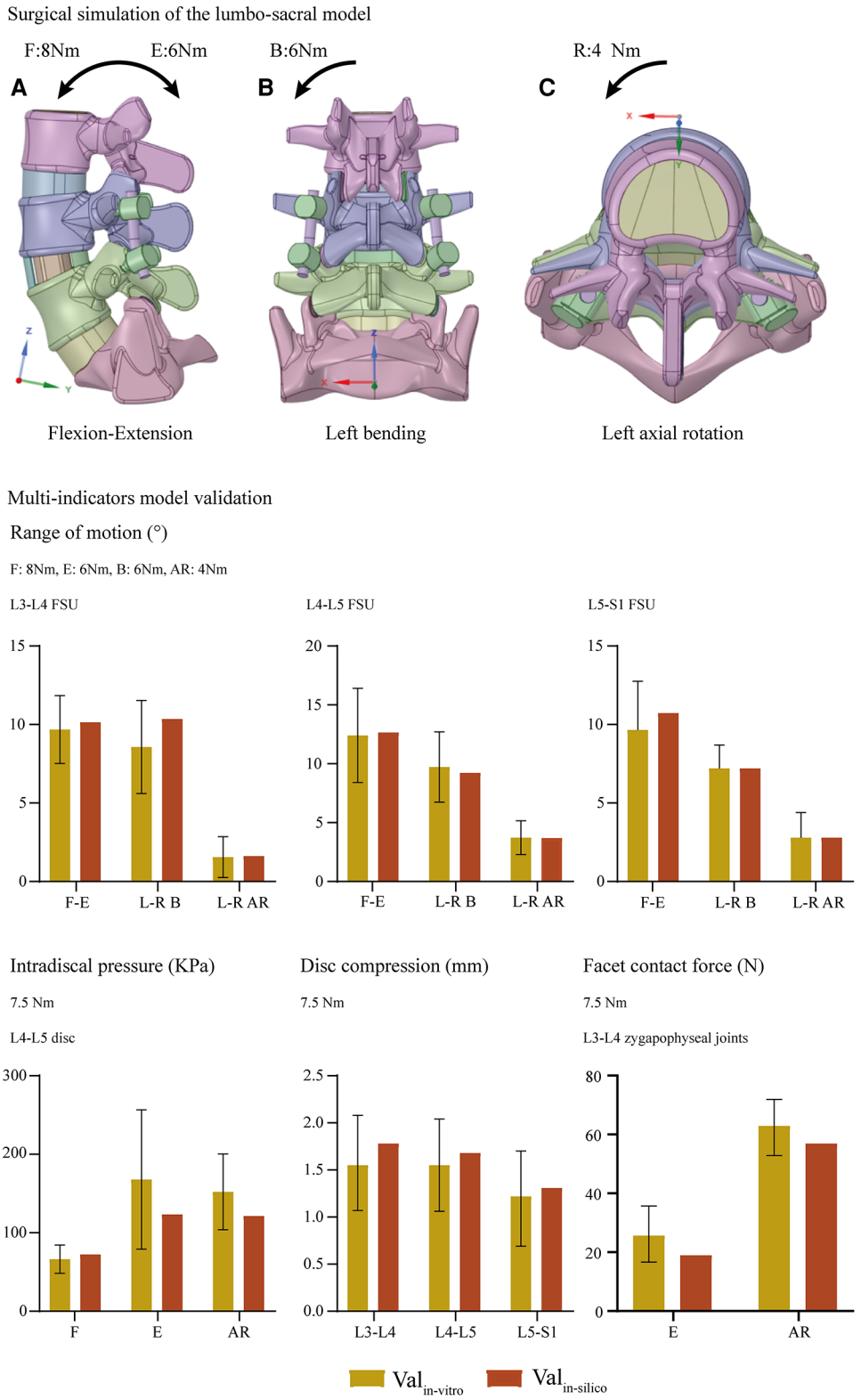

FIGURE 1
Surgical simulations and multi indicators model validation: $Val_{in-vitro}$, indicators measured by published in-vitro studies; $Val_{in-silico}$, indicators computed by the current in-silico study; F-E, flexion-extension; L-R, left-lateral; B, bending; AR, axial rotation.

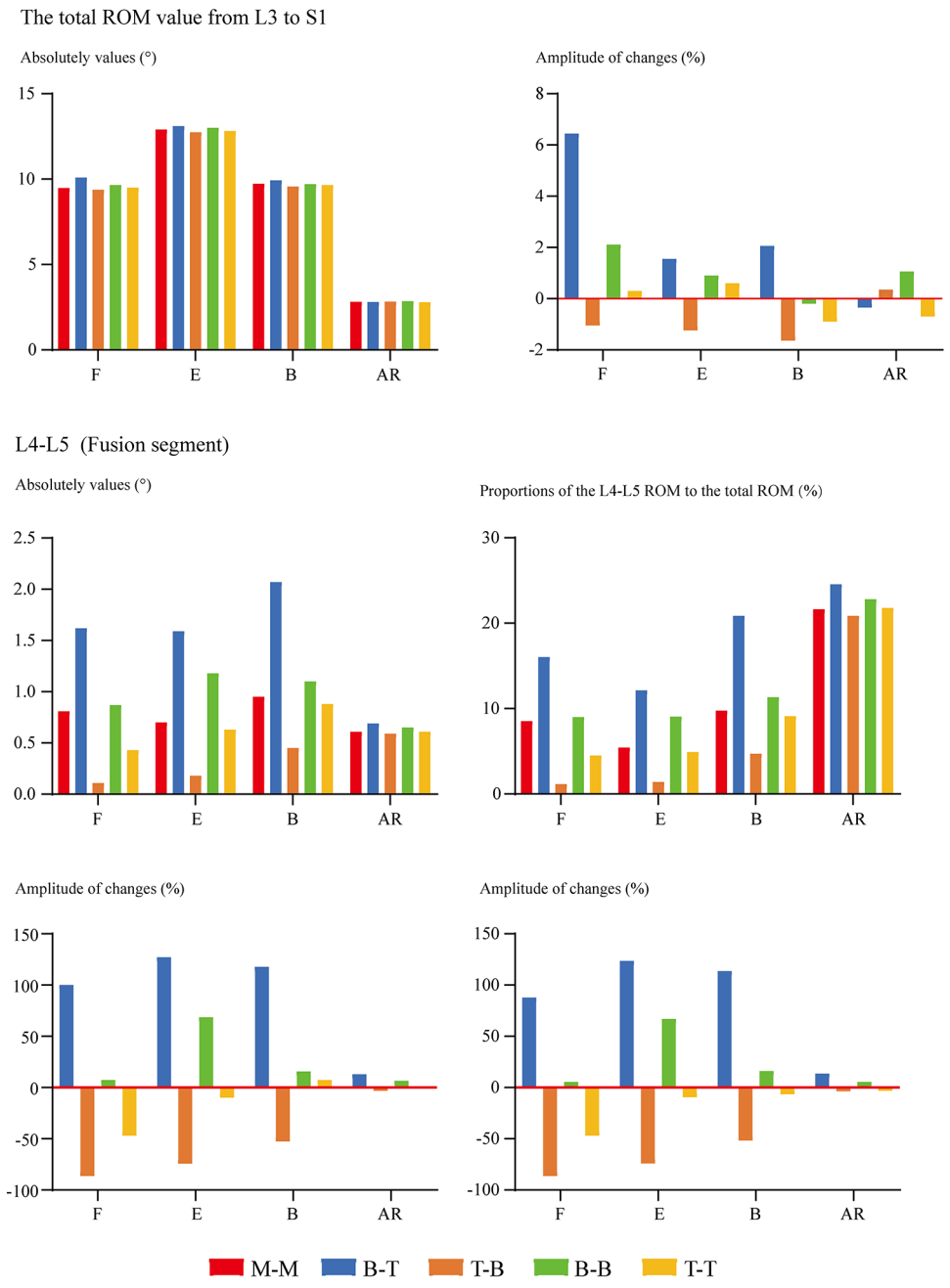

FIGURE 2
Comparison of overall and surgical segment's ROM between surgical models with different insertional screw positions. F, Flexion; E, Extension; B, Bending; AR, Axial rotation.

The pathological change in ASD was not limited to IVD. The degenerative osteoarthritis, hypertrophy of the articular process, and resulting spinal canal stenosis were also essential triggers symptoms recurrence (42, 56). Therefore, ZJ degeneration should also be considered in ASD, which can be well reflected by evaluating the FCF (19, 26) Additionally, as mentioned above, postoperative pathological motility compensation and resulting spinal instability is also a basic form of ASD (17, 42), which could be reflected by the variation of ROM and its proportion (5, 47). Therefore, ROM can be used as an indicator for model calibration and validation, and assess ASD's risk. Moreover, the interaction between segmental instability and spinal canal stenosis was also clearly elucidated, reactive hyperplasia of the articular process and ligamentum structures caused by segmental instability was the main reason for spinal stenosis over a long

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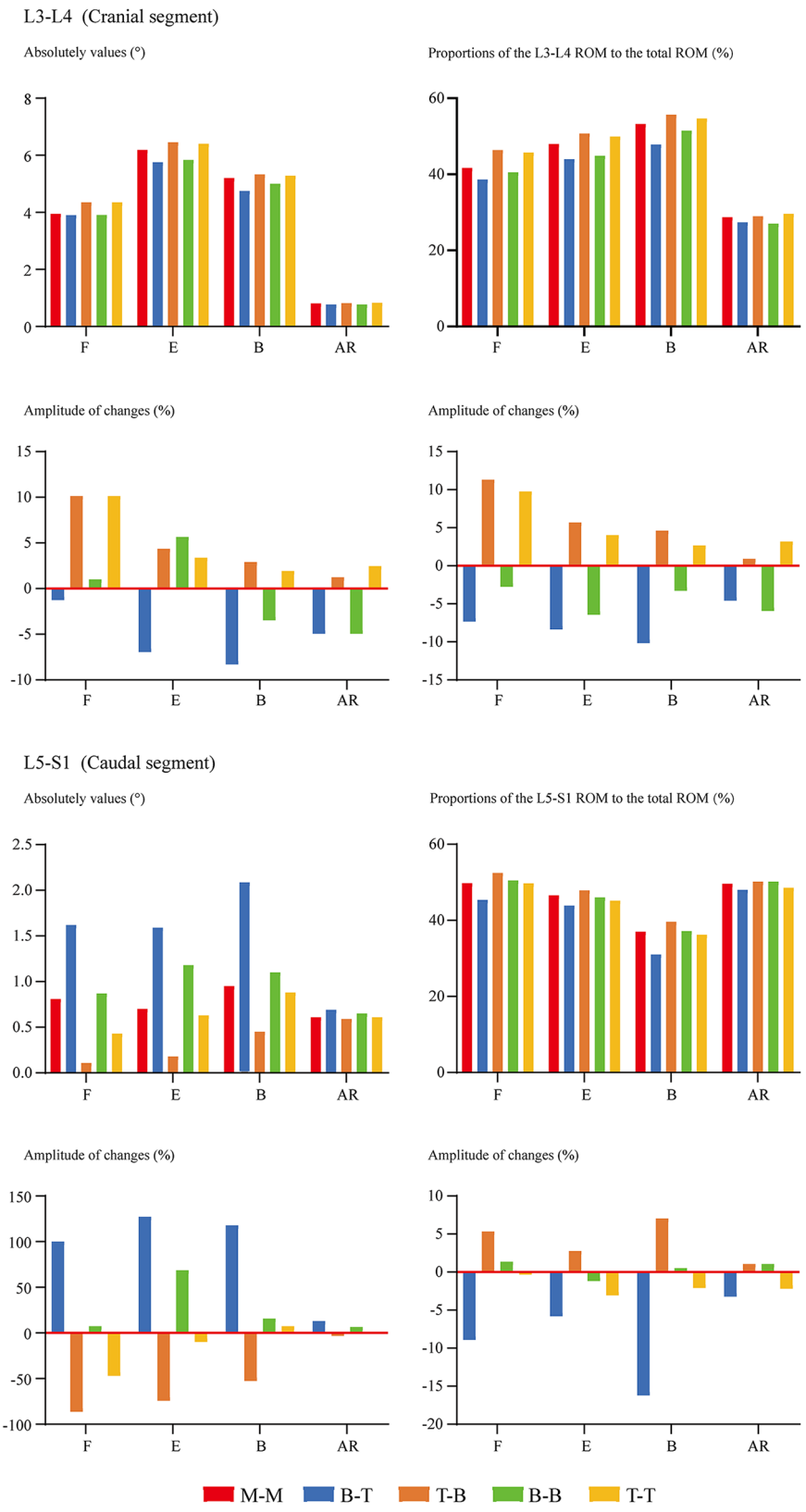

FIGURE 3
Comparison of cranial and caudal adjacent segments' ROM between surgical models with different insertional screw positions. F, Flexion; E, Extension; B, Bending; AR, Axial rotation.

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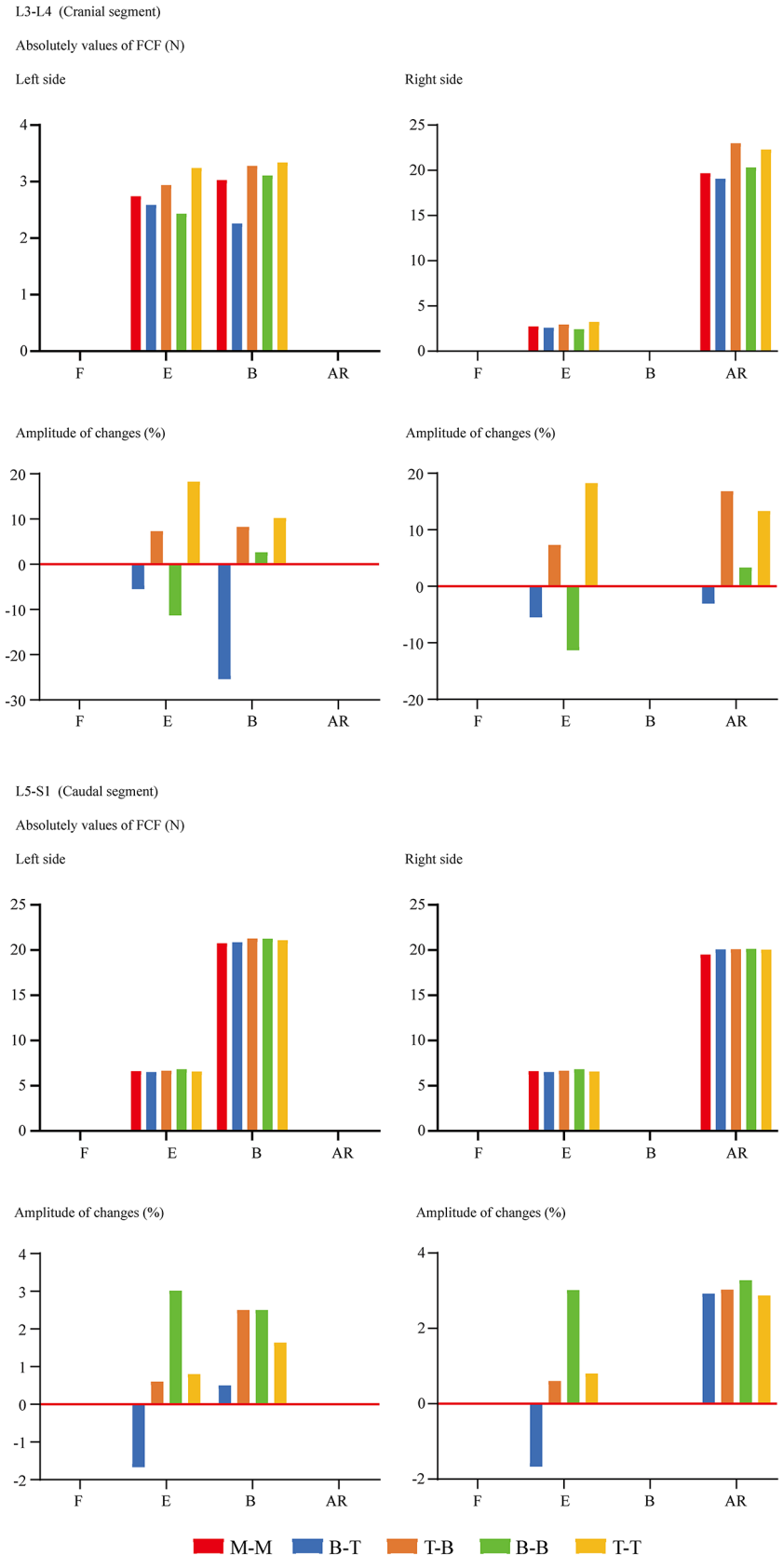

FIGURE 4
Comparison of FCF between surgical models with different insertional screw positions. F, Flexion; E, Extension; B, Bending; AR, Axial rotation.

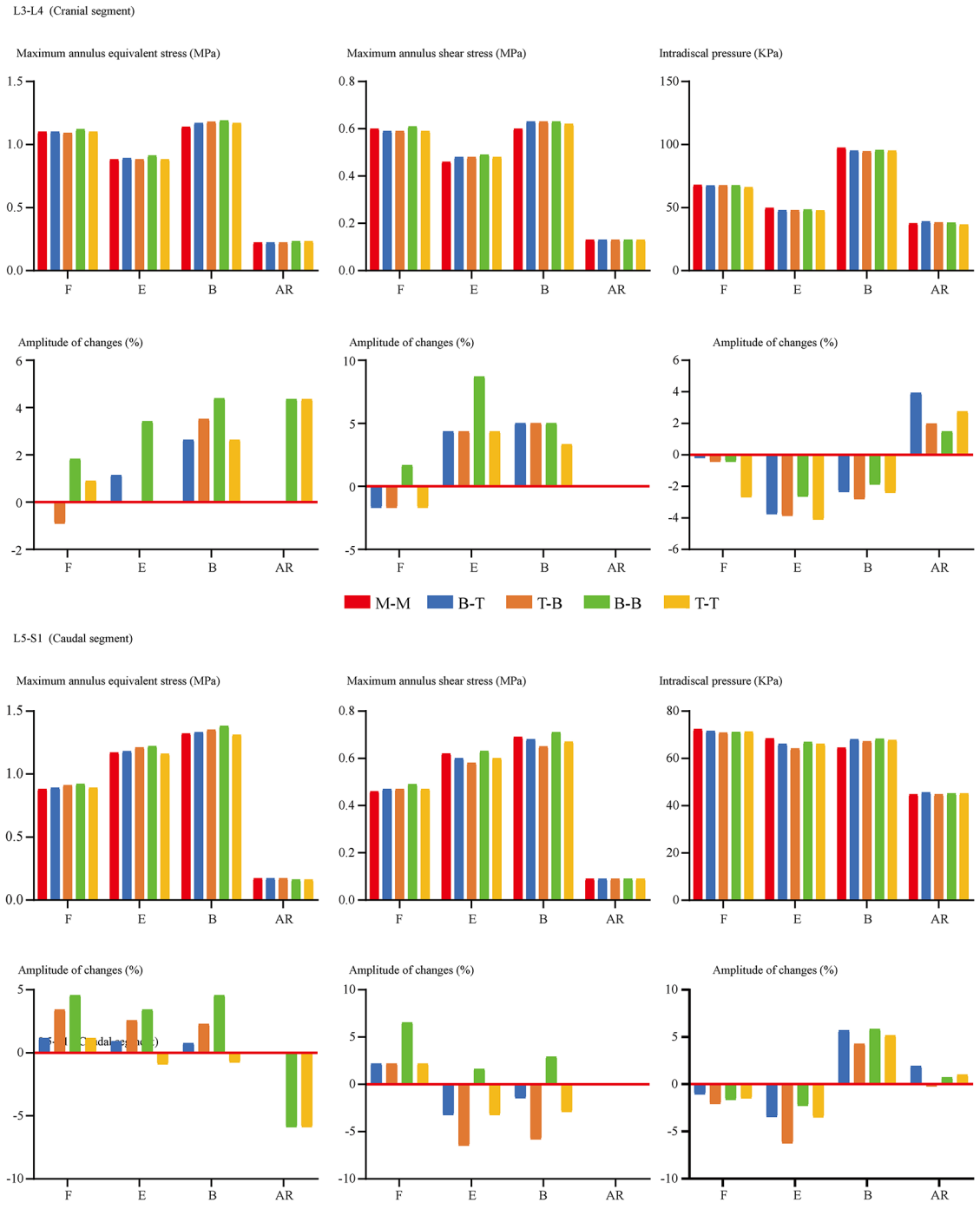

FIGURE 5
Comparison of indicators related to the cranial and caudal disc degeneration between surgical models with different insertional screw positions. F, Flexion; E, Extension; B, Bending; AR, Axial rotation.

period (45, 57). In a word, by computing these biomechanical indicators, the risk of ASD could be investigated systematically.

Based on the current computational results, slight changes in stress concentration on the disc can be observed in cranial and caudal IVDs. Therefore, we can deduce that the tendency of disc degeneration acceleration may not be changed obviously with the change of arm of force. By contrast, the fixation stiffness in the surgical segment and motility compensation in adjacent segments could be distinctly affected by the change of fixation length. Pronounced motility

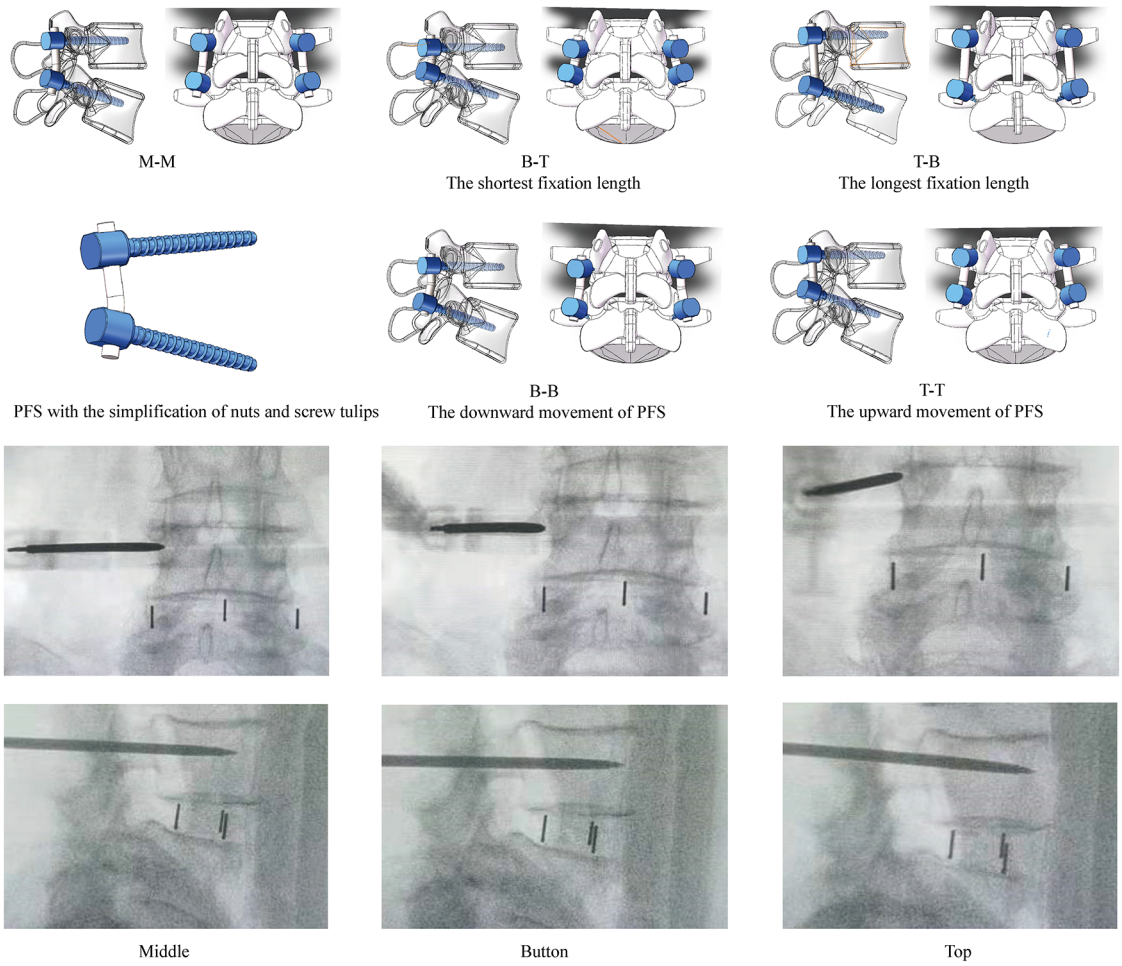

FIGURE 6
Diagrams of OLIF fixed by PFS with different insertional screw positions, and the highly adjustable of percutaneous BPS insertion. M-M: Screws were inserted into the middle positions of both cranial and caudal vertebral bodies; B-T: Screws were inserted into the bottom of the cranial and the top of the caudal vertebral bodies (Shortest fixation length of PFS); T-B: Screws were inserted into the top of the cranial and the bottom of the caudal vertebral bodies (Longest fixation length of PFS); BB: Screws were inserted into the bottom of both cranial and caudal vertebral bodies (The downward movement of PFS); TT: Screws were inserted into the top of both cranial and caudal vertebral bodies (The upward movement of PFS).

compensation can be recorded when the fixation length increases and the BPS shift towards the measured side. Meanwhile, although the range of variations is higher in the cranial than the caudal segment, the overall variation tendency of FCF is still consistent with which of the motility compensation. Considering above mentioned interaction between segmental instability and spinal canal stenosis (45, 57), the reduction of BPS's fixation length by adjusting the percutaneous BPS's positions could optimize the local biomechanical environment and reduce the risk of adjacent segmental instability in the short term and spinal stenosis in the long term in both cranial and caudal motion segments adjacent to the surgical segment with percutaneous BPS fixation.

Admittedly, the current study results should be interpreted within the context of the following-mentioned limitations. Firstly, the mechanical effect of ligaments can only be acted on artificially selected positions rather than their entire original surfaces. We defined these ligaments as cable elements, and the potential risk of mechanical indicators distortions should be considered. However, we believe that the computational results elucidated by current models are still reliable for the following reasons. The definition of cable ligaments has been widely used in the same kind of in-silico spinal studies (25, 29, 51), and the multi-indicators model validation has guaranteed the credibility of the current models. Additionally, no attach positions of cable elements are defined on structures with computed indicators (e.g., annulus, CEPs, and facet cartilages of ZJ); this determines that even if there is computational distortion, it can be excluded from the indicator's computation. The definition of ligaments should still be optimized in future in-silico studies. Meanwhile, the damage to facet joint capsule and facet cartilages were not

simulated in this study. That's because current FEA studies never research this topic, so it is not easy to find a widely accepted standard to simulate this topic in our models. But the simulation of this topic may be necessary and should be performed in our future studies. Moreover, we could not provide clinical evidence to verify the computed biomechanical changes in the current study. We admit that corresponding clinical evidence is of great significance to this topic, and we will try to provide clinical evidence in our future studies.

Conclusion

Collectively, computed indicators in this study elucidated that during LIF operations fixed by percutaneous BPS, reducing the fixation stiffness by adjusting the insertional screw positions on the sagittal plane could alleviate motility compensation and stress concentration on ZJ cartilages, especially on the cranial segment. Thus, this mechanical effect may be an effective method to reduce the risk of ASD (adjacent segmental instability in the short term and spinal stenosis in the long term).

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 Approval for the current study protocol (including the lumbar CT scan) was obtained from the ethics committees of Jiangsu Province Hospital on Integration of Chinese and Western Medicine (2019LWKY015). We confirm that the subject signed the informed consent and submitted it to the ethics committee for review before the examination, and all methods were carried out in accordance with relevant guidelines and regulations.. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conception and design: JL, PC, and CH; Model construction and finite element analysis: JL, ZF and PC; Analysis and interpretation of data: CH, ZL and JL; Figures preparation: CH, ZW, ZF, and ZX; Manuscript Preparation and modification: CYH, ZL, PC and JL. 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

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Artificial lamina after laminectomy: Progress, applications, and future perspectives

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In clinical practice, laminectomy is a commonly used procedure for spinal decompression in patients suffering from spinal disorders such as ossification of ligamentum flavum, lumbar stenosis, severe spinal fracture, and intraspinal tumors. However, the loss of posterior column bony support, the extensive proliferation of fibroblasts and scar formation after laminectomy, and other complications (such as postoperative epidural fibrosis and iatrogenic instability) may cause new symptoms requiring revision surgery. Implantation of an artificial lamina prosthesis is one of the most important methods to avoid post-laminectomy complications. Artificial lamina is a type of synthetic lamina tissue made of various materials and shapes designed to replace the resected autologous lamina. Artificial laminae can provide a barrier between the dural sac and posterior soft tissues to prevent postoperative epidural fibrosis and paravertebral muscle compression and provide mechanical support to maintain spinal alignment. In this paper, we briefly review the complications of laminectomy and the necessity of artificial lamina, then we review various artificial laminae from clinical practice and laboratory research perspectives. Based on a combination of additive manufacturing technology and finite element analysis for spine surgery, we propose a new designing perspective of artificial lamina for potential use in clinical practice.

KEYWORDS
laminectomy, artificial lamina, epidural fibrosis (EF), finite element analysis, additive manufacturing (3D printing)

Introduction

Laminectomy is a widely-applied technique in clinical practice. Lumbar disorders, such as ossification of ligamentum flavum, lumbar stenosis, severe burst fracture, and intraspinal tumor, can cause various spinal compressive symptoms, often requiring spinal canal decompression (1–8). Despite the utility of minimal invasive spinal surgeries, which cause less damage to the posterior part of the spinal column, studies have shown open-door decompressive laminectomy is still an effective method to treat lumbar spinal stenosis (4, 9). Laminectomy can offer adequate space for the spinal cord and provide instant decompression. However, postoperative complications related to laminectomy may cause recurrent symptoms and necessitate secondary surgery. Such complications include iatrogenic spinal instability, epidural fibrosis, and back muscle injury, all of which may cause fail back surgery syndrome (FBSS) (10). The inevitable complications result from lamina resection. Removal of the lamina may lead to lordosis or spondylolisthesis because of biomechanical instability of the spine. In the traditional posterior lumbar approach, paravertebral soft tissues are sutured directly above the dura mater, lack of mechanical barrier between the dura mater and posterior structure can cause proliferation of fibroblast into the spinal cord and result in epidural adhesion/fibrosis. Losing attachment sites for paravertebral muscles/ligaments leads

to muscle weakness. Artificial lamina, a synthetic lamina tissue made of various materials and shapes, is intended to replace the resected autologous lamina. Artificial lamina implantation is a straightforward solution to prevent laminectomy-related complications for vertebral reestablishment. Firstly, an artificial lamina is instant structural support to the spine and is an osteogenesis "bridge" for a bony reunion, which is the ultimate purpose of an implant prosthesis (11, 12). Secondly, artificial lamina can be a mechanical barrier between the dura sac and posterior structures, especially those hyperplasia fibroblasts, which can prevent epidural adhesion/fibrosis (13, 14). Finally, artificial lamina can provide attachment sites for paravertebral muscles/ligaments to enhance muscle strength (15).

Clinical practitioners have used various titanium-made prostheses as artificial lamina to reconstruct the posterior column, which provided an instant lamina structure for the stability of the spinal column and protection of the neural elements (16, 17). At the same time, the orthopedic doctors sought to use polymer material to form artificial lamina to prevent epidural fibrosis and found well results. The artificial lamina positively affects epidural fibrosis, but the mechanism of preventing dural adhesion is unclear. Meanwhile, the artificial lamina not only serves as a barrier between the dura and the posterior tissue but also needs to provide mechanical support to the spinal column (18). However, the stress distribution of these artificial laminae remains unclear, considering various materials present different mechanical properties.

With the rapid development of material science and tissue engineering, many researchers have focused on designing materials to prevent epidural fibrosis and induce osteogenesis. Inorganic materials such as alpha-tricalcium phosphates (α-TCP), β-tricalcium phosphate (β-TCP), hydroxyapatite (HA), and mesoporous bioactive glass (MBG) have been incorporated with organic materials to develop inorganic or organic composites. On the one hand, polymeric materials can be used as the physical barrier; on the other hand, polymeric materials can be used as the carrier in the controlled release of chemical drugs (19). Stem cells are seeded on scaffolds as a "bridge" for osteogenesis induction and bony reconstruction of the posterior column (20). To explore the biomechanical effect of the artificial lamina, interdisciplinary medical engineering, such as finite element analysis (FEA) and additive manufacturing (AM), have been introduced. FEA can simulate the real stress situation and predict the biomechanics of implant and bone tissue. Based on FEA, a basic structure composed of finite elements is established in the design space, and then the elements in the designed space are determined according to the algorithm (21–24). The introduction of AM can facilitate customization and better bony reconstruction (25).

This paper briefly introduces the complications of open laminectomy and the necessity of artificial lamina in clinical practice. Then we review the different types of artificial laminae which have already been applied clinically and those still under research. Finally, the advances in the field of additive manufacturing technology and finite element analysis in spine surgery are reviewed, and the future perspective of 3D printing artificial lamina is proposed. This review aims to provide an elementary basis for future artificial lamina investigation and design.

Complications of laminectomy

Facet-preserving laminectomy is the current gold standard surgical technique for posterior laminectomy. This technique involves a midline lumbar incision and extensive resection of the posterior bone, posterior ligaments, and local muscular structures (26). Despite the prevalence of laminectomy, it may cause several postoperative complications. These complications include iatrogenic instability, epidural fibrosis, and back muscle injury resulting from missing autologous lamina. If treated improperly, some complications may lead to FBSS, persistent radicular and/or lumbar pain and lower extremity pain after spine surgery, which is used to describe a large and diverse group of patients who have undergone a variety of lumbar surgeries with unsatisfactory outcomes (27).

Iatrogenic spinal instability is an instability secondary to direct surgical and/or medical intervention. It is radiographically defined as the translational motion of a spinal segment over an adjacent segment at the level of a previous decompression (28). Postoperative iatrogenic instability has been reported at different spine levels, from cervical laminectomy to lumbar spine fusion (29–32). Furthermore, laminectomy for lumbar stenosis can disrupt spinal stability and result in iatrogenic spondylolisthesis in patients with no overt pre-existing instability. Therefore, a substitute for the decompressed bony support can be implanted to preserve spinal integrity and maintain spinal stability. Instead of the rigid lumbar spine after pedicle screw instrumentation, the artificial lamina can provide instant support by sharing the load to help stabilize the spine column.

Epidural fibrosis is a common cause of pain after lumbar spine surgery, such as laminectomy, and has been implicated in 8% to over 60% of cases of FBSS (33–36). The exact mechanism of epidural fibrosis is complex and remains unclear. After many years of research, the ventral originated (37)/dorsal originated (38) theory was published. However, the current consensus is the three-dimensional fibrosis formation theory (39). The pathophysiological mechanisms of epidural fibrosis include excessive deposition of extracellular matrix, which includes collagen, fibronectin, and dermatan sulfate, and a decrease in tissue cellularity (40–42). While extensive research on FBSS and epidural fibrosis has been performed in recent years, the best strategy to reduce its incidence and the associated morbidity is to focus on prevention (43). A mechanical barrier between the dural sac and the posterior tissue is an effective method. Artificial lamina made of a specific material can prevent the extensive proliferation of fibroblasts and scar formation.

Back muscle injury occurs in all patients who undergo laminectomy because of the incision of the posterior ligaments and muscular structures in the area. The sequelae of posterior surgery include atrophy, loss of cross-sectional area (CSA), fat infiltration, and reduced strength of back muscles (44). Progression of the impairment and disability can lead to severe low back pain, which is an essential cause of FBSS (10, 45). Furthermore, the paraspinal muscles of the lumbar spine may play an important role in the etiology of adjacent segment changes besides a spinal fusion, and this effect is independent of spinal instrumentation (23). Therefore, paraspinal muscle injury may lead to adjacent segment disorder (ASD). Reconstruction of the paravertebral muscles requires a structure for posterior muscle attachment, along with the posterior

ramus of the spinal nerve (46). Artificial lamina can provide muscle/ligament attachment sites for paravertebral muscle reconstruction.

Complications of laminectomy have greatly restrained its application in patients requiring posterior decompression. The invention of the artificial lamina is an applicable method. Some artificial laminae have been used in clinical practice, while many are still in the phase of experimental research.

Artificial lamina applied in clinical practice

Clinical practitioners focused on instant stabilization of the posterior spinal column by different novel types of artificial laminae. Most artificial laminae were applied to associate with posterior lumbar instrumentation fusion (PLIF), while the others were designed to prevent epidural fibrosis simultaneously. Therefore, biomaterial and non-biomaterial have been used to fabricate artificial laminae.

Artificial lamina made of biomaterial is mainly designed to prevent epidural fibrosis. This artificial lamina normally consists of the inorganic element, which provides mechanical support, and the organic element, which prevents scar tissue formation. Zhao et al. (47). designed and fabricated a novel composite artificial lamina made of nano-hydroxyapatite/polyamide66 (n-HA/PA66) in spinal decompression surgery. The n-HA/PA66 composite was developed with a bioactive ceramic (n-HA) and an organic polymer (PA) to mimic natural bone. The n-HA/PA66 material was molded into the hump shape of the lumbar spinal lamina. Eight different scales were designed with 20–35 mm width, 10.6–12.4 mm height, and 4-mm thickness (**Figure 1A**). After receiving posterior laminectomy and discectomy, patients were implanted with an n-HA/PA66 artificial lamina of appropriate size, which was used to cover the opened spinal canal (**Figures 1B, C**). The artificial lamina was fixed by titanium rods (**Figures 1D, E**). At an average follow-up of 5.2 years, the patients showed improved clinical symptoms and significantly improved Japanese Orthopedic Association (JOA) scores. After surgery, the vertebral canal was noticeably enlarged, from 16.7 ± 4.7 mm to 32.9 ± 2.2 mm, and well maintained to 32.1 ± 1.8 mm. The lumbar lordosis was well maintained after surgery. Magnetic resonance imaging (MRI) showed normal spinal canal morphology, with no signs of stenosis, obvious scar formation, or compression of nerve roots or epidural sac. However, the bony union between the host bone and the artificial lamina was not detected, which may lead to the loosening of the pedicle screw and rods. Moreover, the artificial laminae provided limited size options, which hindered its matching with patients' autologous reserved bony structure.

Compared to artificial lamina made of biomaterial composite, clinical practitioners are more likely to use titanium alloy as implanted prostheses because of its high strength and

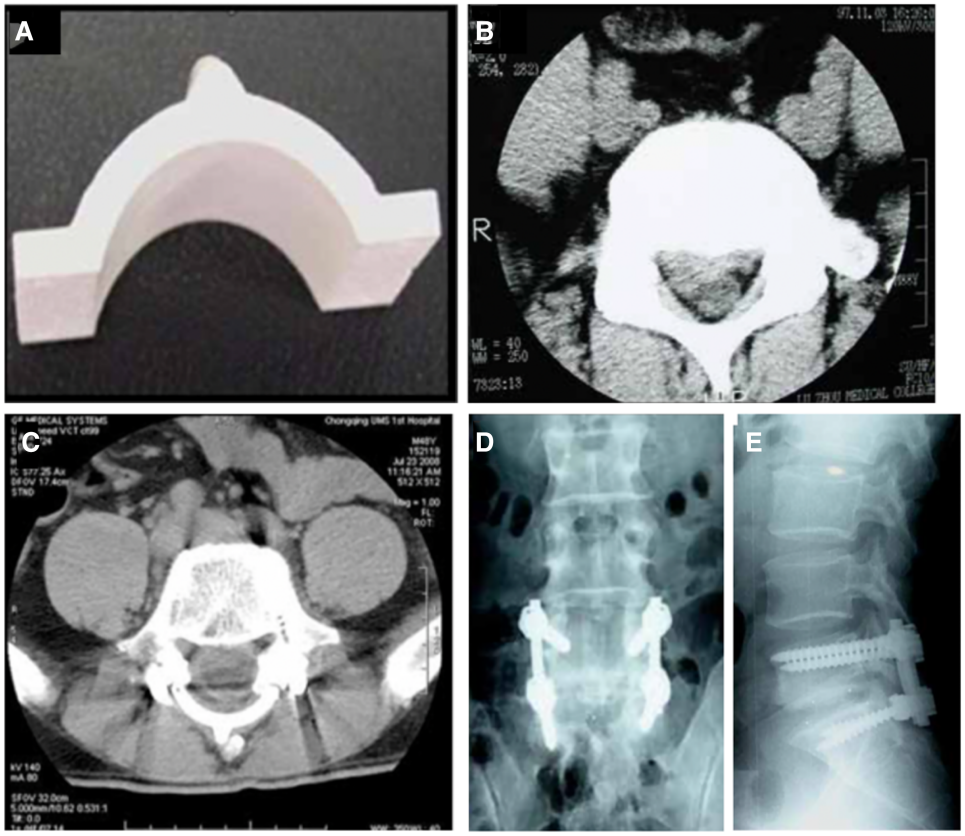

FIGURE 1
The appearance of the artificial vertebral lamina of n-HA/PA66 composites. Front view (**A**); preoperative CT images showing lumbar disc herniation compressing the nerve root on the right side (**B**). The postoperative CT and radiographs films show good internal fixation with good spinal alignment (**C**–**E**) (47).

biocompatibility. It is feasible to obtain postoperative early stability reinforcement, sufficient space and protection for the posterior neural structure, prevention of epidural adhesion, and permanent stability from the new lamina reconstruction after the union of the bone graft. Before the prototype of contemporary artificial laminae used in patients, prostheses used in clinical practice for laminae reconstruction were mainly for laminoplasty. Fornari et al. (16) introduced artificial titanium laminae in 7 patients with progressive and severe myelopathy. Those 7 patients received modified double-door laminoplasty. The double-door laminoplasty procedure was modified by using two artificial titanium laminae which obtained from a simple surgical 0.5-mm Ti-mesh. The sagittal diameter of the cervical spinal canal was reduced (<10 mm) in all cases, and further severe spinal cord compression resulted from osteophytes bars and calcified ligamentum flava at different levels. No abnormal alignment, pathological movements, or instability was present. Postoperative imageological examination demonstrated complete spinal cord decompression and preservation of the patency of the subarachnoid spaces. The proposed laminae have the advantages of achieving immediate stabilization of the spine through a bridge-like mechanism and protection from the possible compression to the dural sac from paravertebral muscles. In another cervical laminoplasty approach, Park et al. (48) introduced a novel titanium plate to maintain canal expansion in multilevel cord compression and cervical myelopathy. The plate afforded an elementary resistance to misplacing the plate or the lamina as the "mouth" of the plate, which accepted the cut edge of the laminae. Moreover, the ventral crotch on the plate's lateral part caught the lamina's cut edge along with it. There were drilling holes and screw insertion facilitated. This novel laminoplasty plate could help minimize the problems with loss of canal expansion and allow the patient to engage in a more aggressive rehabilitation protocol. Furthermore, it could also decrease the incidence of postoperative complications during neck rotation after laminoplasty. To explore the bony reunion effect of artificial titanium lamina in lumbar spine surgery, Chung et al. (12) investigated a new titanium lamina mesh for posterior column reconstruction in patients who underwent total *en bloc* spondylectomy. The prosthesis was an unfolded 1-mm thick titanium mesh. After removing the vertebra body on the posterior side, the surgeon inserted a titanium cage filled with bone graft. Then, the titanium lamina mesh was cut to size according to the resected vertebra level's interlaminar space length and width. The appropriately sized titanium mesh was fixed on vertebral laminae of both upper and lower levels of the spine, along with the autogenous bone (**Figure 2**). At postoperative 6-month follow-up, there were bony connections between the titanium mesh in both upper and lower adjacent laminae in all cases, except for one with infection. None of the patients had

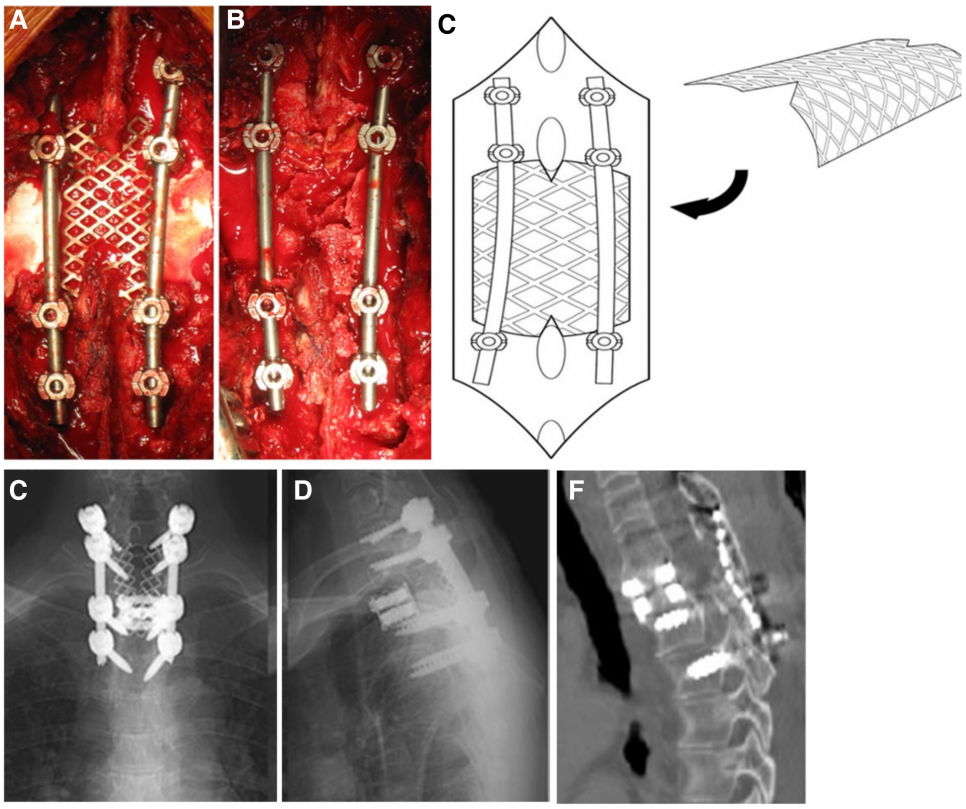

FIGURE 2
A 55-year-old female with primary T2 vertebra spine tumor (aneurysmal bone cyst) received total *en bloc* spondylectomy. Intraoperative images of the appropriately sized titanium mesh fixed between the upper and lower lamina of total *en bloc* vertebra (**A**). Image of autogenous bone placed on the titanium lamina mesh (**B**). The schematic diagram demonstrated the insertion and fixation of the titanium lamina mesh (**C**). At 28 months of follow-up, radiographs showed no evidence for collapse or displacement of titanium lamina mesh nor instability/malalignment of the spinal column (**D**,**E**). Postoperative CT image showed complete bony union above the lamina mesh and inside of the titanium MESH cage (**F**) (12).

developed collapse or displacement of the implanted lamina or instability/malalignment of the spinal column. The outcome of the titanium artificial lamina implant is encouraging despite the small sample size and short follow-up time. However, this type of artificial lamina could only be used in laminoplasty and could provide no muscle/ligaments attachment; whether it is suitable for lumbar laminectomy remains unclear.

To evaluate the clinical efficacy of different types of artificial lamina, Li et al. (49) compared the clinical efficacy of the simple expansion of the spinal canal decompression, decompression plus hydroxyapatite/polyamide artificial lamina reconstruction, and decompression plus titanium mesh reconstruction in treating spinal canal stenosis. The study found that patients who received artificial lamina reconstruction, hydroxyapatite/polyamide and titanium mesh had better JOA scores than those who underwent a simple decompression procedure in a 12-month follow-up. Despite the small number of studies reported, the authors offered potential and encouraging method to achieve instant and permanent stability of the spine after unionizing the bone graft by artificial lamina implantation. Nevertheless, these artificial laminae have a limited anti-adhesion effect and the biomechanical characteristic remain unclear. Exploring the anti-adhesion mechanism can make the best use of artificial lamina in future clinical practice.

The progress for the artificial lamina

To prevent postoperative FBSS caused by epidural fibrosis, iatrogenic spinal instability, and muscle weakness, researchers have conducted a lot of research to improve the biomechanical effect and anti-adhesion ability of artificial lamina. Compared to few artificial lamina applications in clinical practice, researchers have undergone many attempts in the laboratory. Because an ideal artificial lamina should offer a mechanical barrier between the dura and the posterior tissue while inducing bony union, which is the ultimate purpose of an artificial lamina prosthesis (**Figure 3**). Furthermore, the artificial lamina with clarified biomechanical characteristics can stabilize the spine column. Finally, customized prosthesis would have more contact area and better bony union possibility.

Artificial lamina for epidural fibrosis prevention

Based on the "3-dimensional fibrosis formation theory" proposed by Songer and Ghosh Spencer (39), fibroblast migration from paravertebral muscles and/or movement *via* fluid circulation into the surgical area to form epidural fibrosis, which mechanically tethers and compresses the spinal roots and the neural sac (50). local application of different materials to separate epidural mater from local tissue to prevent fibrosis can be an effective method. Along with the rapid development of materials science and tissue engineering techniques, strategies to prevent post-laminectomy complications are a contemporary research hotspot.

Calcium phosphate has bioinert, good biocompatibility, and mechanical properties, which is currently a significant material for bone tissue reconstruction. Porous calcium phosphate can be fabricated as a scaffold to carry various anti-adhesion components to prevent scar formation (51). Ran et al. (52) used a biodegradable α-TCP/poly (amino acid) composite artificial lamina in goats for the prevention of intraspinal scar adhesion. The results indicated that α-TCP/poly (amino acid) composite artificial lamina

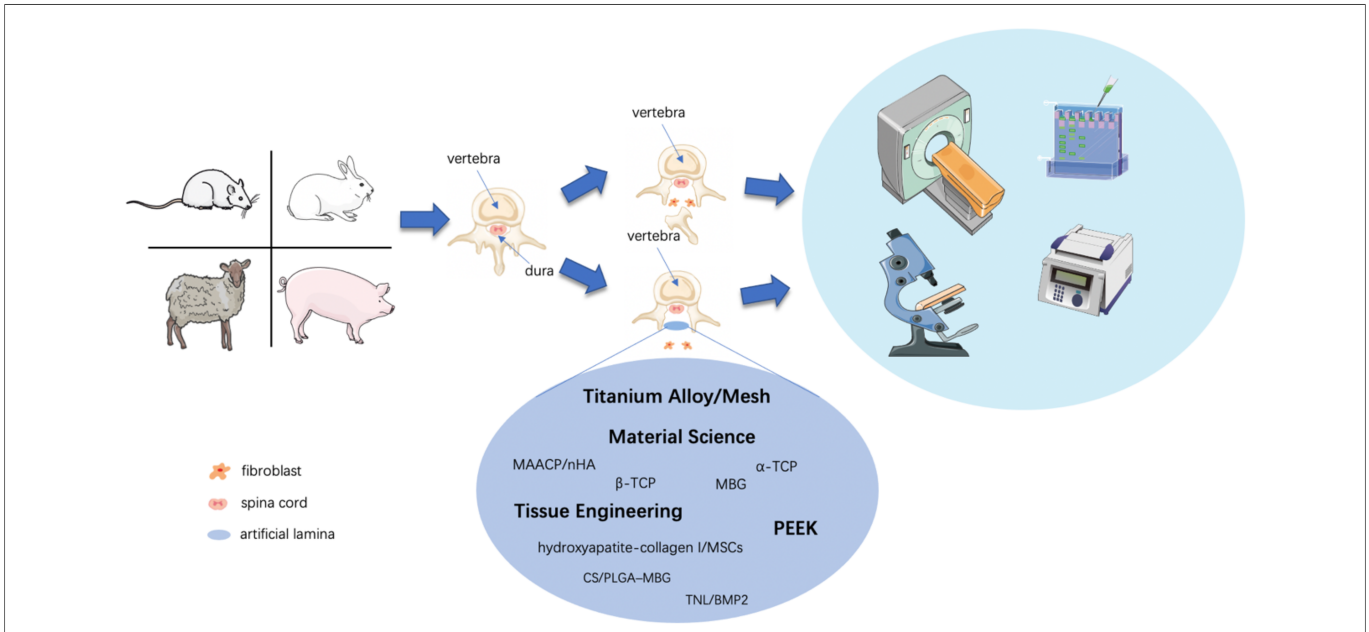

FIGURE 3
Schematic diagram of techniques investigating artificial lamina in laboratory research. Rats, rabbits, goats, and pigs were sacrificed to form a laminectomy model by lumbar or cervical laminectomy, while the artificial lamina implant model by implantation of various shapes and textures of the artificial lamina. Experimental animals would receive tests, including imageological examinations, histological examinations, western blot, PCR, etc. for biological verification of the artificial laminae.

might prevent potential scar tissue infiltration into the spinal canal. Wang et al. (53) designed a biphasic calcium phosphate (70% hydroxyapatite/30% tricalcium phosphate) (HA-TCP) ceramic (CVL) implant to evaluate the biological effect after laminectomy in experimental animals. The study showed that fibrous connective tissues and blood vessels had grown into the porous structures of the CVL substitutes rather than into the epidural space, and macrophages were found on the macropore surfaces. After up to 1-year follow-up, CVL could realize the fusion with the natural spine, improve the spinal stability and protect the spinal cord. The study indicates that inorganic material as calcium phosphate and hydroxyapatite were suitable to be a clinical substitute for human vertebral laminae.

Hydroxyapatite (HA), a good biocompatibility and osteoinductivity materials, has been widely used to treat in bone and tooth defects (54–56). Wu et al. (14) discovered that different hydroxyapatite ceramics surface microstructures could prevent the hyperplastic fibrous tissue from penetrating the spinal canal area and inhibited the formation of scar-like tissue in laminectomy sites both *in vitro* and *in vivo* experiments. The artificial laminae were prepared by HA powders with cold isostatic pressing (CIP) and slip casting (SC) technique. Both types of laminae were cut into discs (Φ 9 × 2 mm^3) and Y-shaped vertebral lamina (10 mm in length, 5 mm in width, and 2 mm in thickness), respectively. *In vitro*, HA ceramics could potentially inhibit the proliferation of the cells and stimulate the CCNI secretion to induce the senescence of human skin fibroblast (HSF) cells. *In vivo*, a dense HA-CIP lamina implant had a better anti fibrosis/adhesion effect, including a thinner layer of fibrous tissue and a smaller gap between the implant surface and paravertebral muscles, than HA-SC in rabbits under laminectomy. These artificial laminae could prevent epidural fibrosis by directly blocking the spinal cord's posterior structure and adjusting the micro-structure to depress the proliferation of fibroblasts.

Most of the artificial laminae in the laboratory were designed using various inorganic materials, tissue-engineered artificial laminae with added cellular components may be able to act as a better barrier. Li et al. (20, 57, 58) conducted consecutive studies about cerebrospinal fluid pulsation (CSFP) remodeling artificial laminae formation. For the preparation of the artificial lamina, MSCs were obtained from rabbit umbilical cord Wharton's Jelly and their differentiation into osteogenic MSCs was induced using a hydroxyapatite-collagen I scaffold. The tissue-engineered lamina (TEL) scaffold was cut into the size of 10 mm × 8 mm × 20 mm (57). The experimental CSFP rabbits received open posterior lumbar 5 laminectomies under anesthesia. Then, the TEL was placed on a 10 mm × 8 mm × 2 mm bone defect and fixed and sutured. The spinous processes of non-CSFP rabbits were removed from the top of the process to the cancellous bone end while preserving the dura surface cortex of the laminae (**Figure 4B**). The

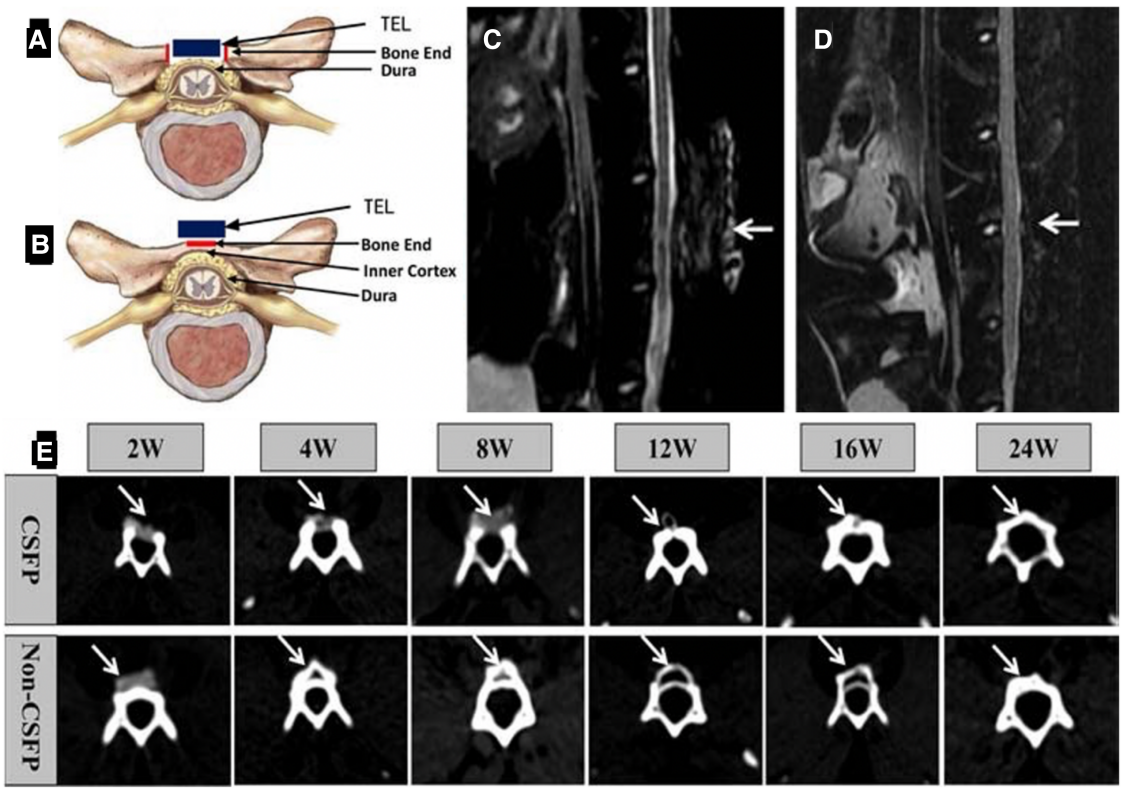

FIGURE 4
Construction of animal models. (**A**) Diagrammatic sketch of orthotopic laminae animal model. The red square shows the two bone ends, and its length was 2 mm. The blue square shows the tissue-engineered laminae (TEL). (**B**) The diagrammatic sketch of ectopic laminae animal model. The red square shows the bone end, and its length was 4 mm. The blue square shows the tissue-engineered laminae (TEL). MRI scanning of the lumbar spine, 2 weeks after the operation (**C**), 8 weeks after the operation (**D**); white arrow: the targeted vertebrate. (**E**) CT scan of the targeted vertebrate in the 2nd, 4th, 8th, 12th, 16th, and 24th weeks. White arrow: the newborn laminae (57).

TEL was then fixed onto the native laminae (20). MRI examination showed no signs of epidural scar adhesion, spinal cord compression, or intervertebral disc herniation in the targeted vertebrae or adjacent segments in both CSFP and Non-CSFP groups (**Figure 4**). Similar to the studies mentioned above, these studies did not perform the osteogenesis effect of the artificial lamina. Therefore, it is not certain that the structure will remain stable between the regeneration of the new bone and the degradation of the implanted composite. The artificial lamina could have a promising effect in dealing with the epidural fibrosis problem. On the other hand, the osteoinductive effect of the artificial lamina is determinant since bony reconstruction is the most stable structure for the long term.

Artificial lamina for osteogenesis induction

Artificial lamina could be implanted not only as a barrier to prevent epidural fibrosis but also as a "bridge" for osteogenesis induction and bony reconstruction of the posterior column. Many materials with osteoinductivity are used to fabricate artificial lamina. Nowadays, calcium phosphates are mainly used to induce the repair or regeneration of damaged bone tissue (51). β-TCP had been applied as a supplement lamina autograft to perform posterolateral lumbar-instrumented arthrodesis before being fabricated as a lamina shape, (11). Calcium phosphates can be implanted alone and serve as a scaffold for other bio-materials. Dong et al. (59) used bone marrow mesenchymal stem cells (BMSCs) to reconstruct laminae in rabbits. The BMSCs were seeded into porous β-TCP bio-ceramics and cultivated with osteogenic supplements for less than 3 weeks. Rabbits received L5/L6 laminectomy with a bone defect measuring approximately 20 mm × 8 mm. After 8 weeks' observation, rabbits that received β-TCP bio-ceramics implanted with BMSCs showed signs of regeneration of the lamina of the vertebral arch. Imaging examinations (CT and MRI) at 16 weeks showed the successful formation of the artificial lamina of the vertebral arch. In another research conducted by Dong et al. (60), the authors induced osteoblastic differentiation of BMSCs, which were then transplanted into collagen sponges to construct the tissue-engineering bone. After receiving laminectomy and implanted with collagen sponge and tissue-engineered bone, the rabbits were found to successfully artificial laminae of the vertebral arch formation 4 weeks after the operation. This tissue engineering designed artificial lamina seems a promising method for future mass production.

The porous HA is another important material as a scaffold for bone tissue regeneration. It may act as a solid matrix for adsorption, storage and controlled release of circulating or locally produced bone morphogenetic proteins, which locally initiate bone formation (55). In a study related to the utilization of hydroxyapatite, Lv et al. (61) introduced a novel biodegradable artificial lamina, which was made of multi-amino acid copolymer/nanohydroxyapatite (MAACP/nHA) copolymer composite. This artificial lamina was designed to prevent epidural adhesion surrounding the bony defect and promote bone tissue repair. This artificial lamina composite was a hard nHA material (strength: 257.53 MPa, yield strength: 42.77 MPa, and modulus: 350 MPa), which could provide enough strength to prevent dural compression by the posterior tissue. The artificial lamina was a smooth rectangular plate (28 mm × 16 mm × 4 mm) with a natural lamina-like spinous process (**Figure 5A**). In the experimental study, cervical 4 laminae of goats were removed to create 27 mm × 9 mm bone defects without damaging the small facet joints. Then, the biodegradable composite artificial laminae were implanted to cover the dura before fixation on the pedicle cervical 4 *via* 2 screws. Postoperative images showed no displacement of the composite or dural adhesion compression (**Figures 5B, C**). An imaging examination performed 24 weeks after the operation showed new cervical natural bone in the defect forming the reconstructed bony spinal canal (**Figure 5D**). This study has put the mechanic module of artificial lamina into practice. However, no analysis of the biomechanical test between these cervical composite laminae and autologous bone was performed.

CS/PLGA–MBG is widely used as a porous scaffold in tissue engineering applications. For one, the porous structure of the scaffold can load organic material, such as MSCs, to induce osteogenesis; on the other hand, new bone tissue can grow into porous structure to

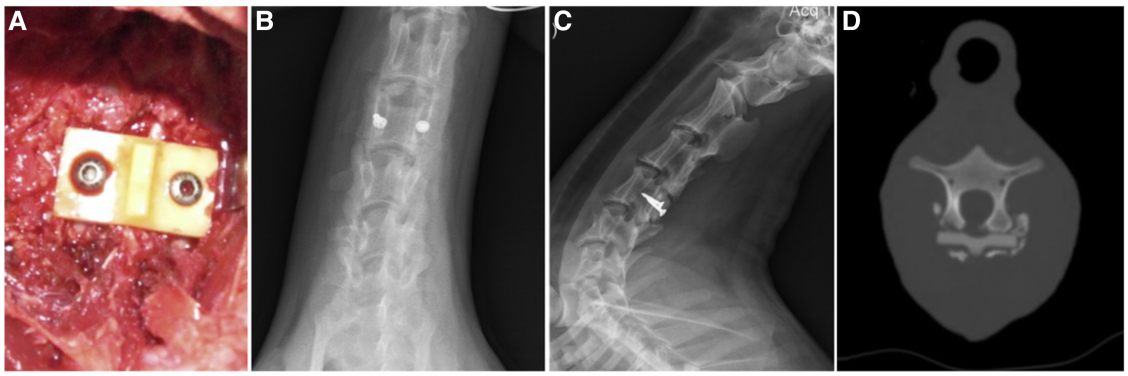

FIGURE 5
A biodegradable MAACP/nHA composite artificial lamina was implanted to cover the dura before fixing it on the pedicle cervical 4 *via* 2 screws. Insertion of the lamina (**A**). Radiograph and CT images of goat cervical from the test group received biodegradable MAACP/nHA composite artificial laminae after 24 weeks. (**B–D**) The artificial lamina was used to cover a defect, and no artificial lamina displacement was found in the test group. (**B**) longitudinal proliferation along the edge of the artificial lamina is observed without the C4 spinous process. (**C**) CT image shows new bone formation above the artificial lamina. (**D**) (61).

promote bone fusion. In another study of artificial lamina developed by tissue engineering, Han et al. (14) designed a Chitosan (CS)/poly lactide-co-glycolide (PLGA) bilayer membrane loaded with tranilast (TNL) and BMP-2. TNL is an oral anti-allergic drug that has been shown to be highly effective in various fibrotic disorders by inhibiting collagen deposition and fibroblast proliferation. MBG, which has a mass of porosity and interconnected pore network, has been shown to enhance human MSCs infiltration, attachment, and proliferation and promote osteogenic differentiation. This bilayer composite was implanted as an artificial lamina into the rabbit with an L5 lamina bony defect. Compared to the control group, there was no fibrous tissue formation or invasion in the TNL/BMP-2 experimental group. Moreover, the new bone formation in the experimental group at the laminectomy site was loaded with TNL/BMP-2. This multifunctional bilayer composite seems to be an ideal artificial lamina. Nevertheless, the complex methodology for preparing the bilayer membrane hinders its mass production for clinical application.

Different artificial laminae's biological effects have been reviewed, including epidural fibrosis prevention and osteoinductivity. However, the human spine column is a load-bearing system, and the biomechanical effect is also very important.

Artificial lamina with biomechanical effect

Despite the wide application of biomaterials and drugs for the prevention of epidural fibrosis (62–65), the beneficial effects are not sustained, and the effect decreases over time. Some of the artificial laminae mentioned above have a biomechanical effect, but none of them have clarified the stress distribution of the implant and the spine. The artificial laminae applied in clinical practice merely provides mechanical support, for which no biomechanical analysis was performed. Therefore, the postoperative stress on the spine and the prostheses is unknown, which may lead to further complications. To explore the artificial lamina's biomechanical effect, interdisciplinary medical engineering, such as finite element analysis (FEA) and topological optimization (TO), have been introduced. By using finite element analysis, the biomechanical effect of the whole postoperative spine complex can be analyzed, and the artificial lamina can be topologically re-designed to a perfect state.

Compared to many FEA studies on vertebral bodies and intervertebral discs, fewer vertebra lamina FEA studies have been conducted. Most of them focused on analyzing various surgical approaches for posterior decompression. Spina et al. (66) investigated the effect of graded pars interarticularis (PI) resection in a three-dimensional manner on PI stress to provide surgical guidelines to avoid iatrogenic instability following lumbar laminectomy using a biomechanical finite element method. Based on a series of finite element analyses, the authors concluded that PI resection exceeding 50% bone resection greatly reduces the spine's stability for all laminectomies and may increase the incidence of iatrogenic spondylolisthesis. The study demonstrates that the biomechanical properties of vertebral lamina is very important, and it is necessary to reconstruct the mechanical function of lamina.

In a recent artificial lamina designing study developed by FEA, Liu et al. (67) used poly-ether-ether-ketone (PEEK) to establish the system, which could stabilize the lumbar spine and prevent postoperative spine malfunctions such as ASD and iatrogenic lumbar deformities. The researchers derived a finite element model of L3–5 from computed tomography images (**Figure 6A**). Apart from the intact human spine model, 4 surgical models, including laminectomy, artificial lamina alone, ligament reconstruction, and osteointegration, were constructed (**Figure 6B**). The 4 surgical models were used to simulate 4 different stages of L4 artificial lamina implantation. FEA of the artificial lamina showed that the artificial lamina could stabilize the lumbar isthmus and share the

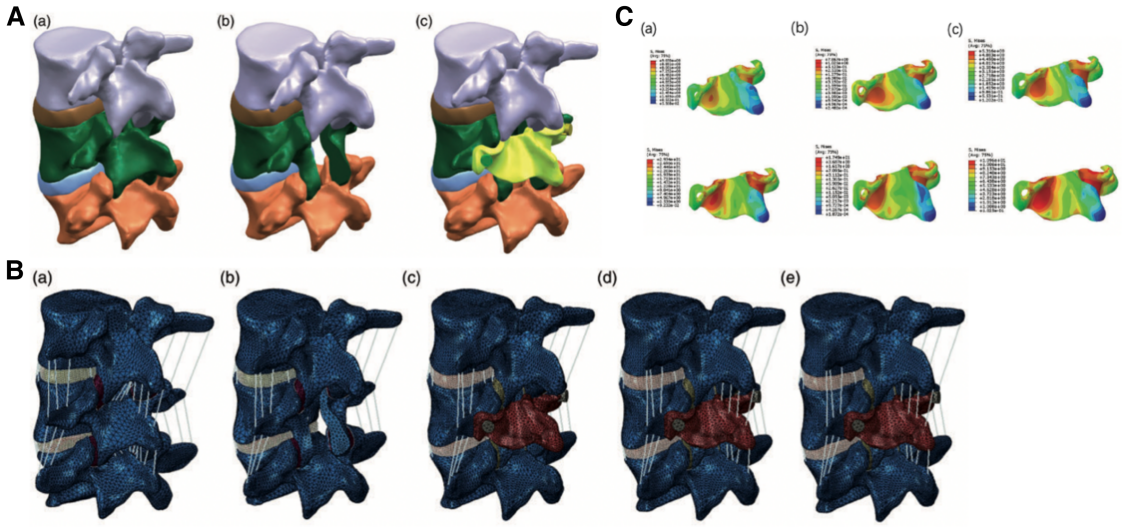

FIGURE 6
(**A**) the artificial lamina model of L4. (**a**) Intact lumbar spine; (**b**) Laminectomy model; (**c**) Laminectomy model with artificial lamina (yellow part). (**B**) The finite element model of different surgical stages. (**a**) Intact lumbar model; (**b**) Laminectomy model (LN); (**c**) Artificial lamina alone model (ALA); (**d**) Artificial lamina with ligament reconstruction model (ALR); (**e**) Artificial lamina with osseointegration model (ALO). (**C**) Stress distributions in the PEEK artificial lamina in all motions. Stress concentration in the area corresponding to the in-situ lumbar isthmus. (**a**) flexion and extension stress distribution in the ALA model; (**b**) flexion and extension stress distribution in the ALR model; (**c**) flexion and extension stress distribution in the ALO model (68).

stress after laminectomy (**Figure 6C**). These findings suggested that the PEEK artificial lamina may have the potential to stabilize the post-laminectomy lumbar spine and prevent related complications.

FEA can clarify the mechanical contribution of the artificial lamina and demonstrate the mechanical distribution between the prosthesis and the autologous spine, which guide the artificial lamina design for posterior column reconstruction of the spine.

Artificial laminae for personal customization

Lumbar spine after laminectomy should be biomechanically stable, especially multi-level laminectomy requires artificial lamina reconstruction. Additive manufacture (AM), also known as 3D printing, can provide a viable alternative for producing artificial lamina. 3D printing is based on computer-generated three-dimensional images, which can accurately manufacture a variety of physical structures. This technology has been applied to industrial design, architecture, engineering, automotive, and aerospace fields. In medicine, 3D printing is applied for preoperative planning and design of surgical instruments and individualization of prostheses, etc. (69–71). The application of 3D printing technology in the field of spine surgery had obtained enormous and substantial progress. Among which, vertebral skeleton model (including lesion model) printing has been widely used in clinical application due to its relatively simple technology and low cost (72). The part with full expectation is undoubtedly the clinical application of 3D printing microporous metal implant and personalized implant as well as the clinical application of 3D printing biological materials in the future (73). Many bio-and/or non-biomaterials have been used to make artificial laminae, as described above. Among those materials, titanium (Ti) alloy has favorable mechanical property features and is widely used in clinical fields (74–77).

The combination of computational design optimization with 3DP technologies allows for the realization of architecture optimized custom-designed implants and opens the way to promising future surgical solutions (78). A recent study yielded encouraging results of 3D printing for artificial lamina design. Li et al. (79) designed an individualized titanium alloy spine lamina using 3D printing technology and evaluated its effectiveness by implantation in human cadaveric spines. The authors used computed tomography (CT) to reconstruct the lumbar vertebrae and simulating lumbar laminectomy. Then an artificial lamina was designed to fill the post-laminectomy bone defect. The lamina made of titanium alloy was fabricated by 3D printing in the shape of the native lamina, which included edge passivation, thinning of the lamina thickness of the spinous process root, and increasing the curvature of the ventral lamina to increase the spinal canal volume. This artificial lamina also involved attachment holes to fix paravertebral muscles at the spinous process. One advantage of this lamina was the statistically significant enlargement of the bony canal after laminectomy compared to before surgery (356.17 ± 43.11 mm^2 vs. 311.23 ± 38.17 mm^2). In a further study conducted by the same team (25), a novel type of 3D-printed bionic titanium alloy artificial lamina was fabricated and implanted into a pig laminectomy model. *In vitro* and *in vivo* tests have shown good biomechanical effect and well fixation of bionic titanium alloy artificial lamina and screws 10 weeks after laminectomy. This 3D printed artificial lamina can prevent epidural adhesion while restoring the structural stability of the posterior complex, suggesting the potential of lamina substitutes for adhesion prevention after laminectomy.

Artificial lamina under AM is accurately manufactured as a variety of physical structures accordance with the native lamina functional parts. This prosthesis not only has biological characteristics, but also can improve the biomechanical structure according to the results of mechanical analysis. Some barriers of 3D printing artificial lamina in widespread adoption include financial burden (both on the hospital and the patients) and time consuming. And only very few specialists can apply this method in clinical practice (80). Despite the limitations of 3D printing in clinical adoption, patients would benefit more when 3D printing technologically develops and the cost reduces. Therefore, as clinical practitioners, we should do better designing and demonstrating, preparing for future mass adoption.

Complications of artificial lamina and limitations

Complications of artificial lamina include infection, bone nonunion and the unparralled of osteogenesis and biomaterial degradation.

Postoperative infection is a major complication of artificial lamina implantation. Jae-Yoon Chung et al. (12) investigated a new titanium lamina mesh for posterior column reconstruction in patients who underwent total *en bloc* spondylectomy. The prosthesis was an unfolded 1 millimeter thick, titanium mesh. One of the eight patients suffered postoperative infection at the surgical site. To solve this complication, Liu et al. investigated a surface-modified 3D printed porous Ti6Al4V possesses balanced antibacterial and osteogenic functions and found well outcome (73). Bone nonunion is another major complication in prosthesis implant surgeries. To prevent nonunion and promote bony reunion, artificial laminae for osteogenesis induction have been investigated, which were described above. Finally, despite the widely application of biomaterials and drugs for prevention of epidural fibrosis and promote osteogenesis, the duration of effect is unstable and the effect is decreasing over time. The proportion of osteogenesis contained and the speed of its release need more experimental and further study. The unparalleled of osteogenesis and biomaterial degradation is another risk factor of bone nonunion (81).

We have reviewed different types of artificial lamina with various functions, yet clinical trials or randomized control tests (RCTs) are not available to prove the clinical evidence of artificial lamina, further studies are necessary for these issues.

Discussion

Lumbar laminectomy is a commonly used procedure for spinal decompression in routine clinical practice. In patients with spinal disorders, laminectomy is often performed as a spinal decompressive intervention. However, the loss of posterior column bony support, the extensive proliferation of fibroblasts and scar formation after

laminectomy, and other complications (such as postoperative epidural fibrosis and iatrogenic instability) may cause new symptoms requiring revision surgery. Given the inevitable surgical intervention of posterior open decompression procedure in some critical spine disorders, artificial lamina prosthesis implantation is one of the most important methods to avoid post-laminectomy complications. An ideal artificial lamina should not only serve as a physical barrier between the dura mater and the posterior tissue but also provide mechanical support to the posterior spinal column. The combined use of FEA and 3D printing can improve the practicability and clinical application of artificial lamina. However, the accuracy of the algorithm and the 3D printed material needs to be demonstrated. Using FEA and topology optimization for titanium 3D printing, the stress distribution of lumbar vertebrae can be analyzed, and the real stress can be simulated. 3D printing technology allows the design and manufacture of microporous structures with low elastic modulus. Finite element analysis of the individualized anatomical shape lumbar lamina has been carried out to verify the macro biomechanical advantages of the individualized anatomical bionic shape lumbar artificial lamina. Customized titanium artificial lamina has the potential to prevent epidural fibrosis and can reconstruct biomechanical structure, providing adequate dynamic support.

Author contributions

JY contributed to original draft writing. QH, JW, MW provided funding acquisition. HC reviewed the manuscript. AZ, YL conducted the software. XG, YW performed the methodology. MW conceptualized the manuscript. All authors contributed to manuscript revision, read, 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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