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Research article

Debridement and bone graft fusion via the lateral extracavitary approach combined with lateral and posterior screw-rod fixation in the treatment of thoracic spinal tuberculosis: A retrospective study of 38 cases

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ABSTRACT

Objectives: Thoracic spinal tuberculosis (TB) is still common, and surgical treatment can rapidly relieve pain, correct deformity, reduce bone loss and prevent further damage to neurological function. We have practiced an efficient and safe surgical method.

Methods: From January 2013 to April 2021, 38 patients with thoracic spinal TB were included in our study. Debridement and bone grafting were performed via the lateral extracavitary approach, combined with two different fixation methods. Data from these cases were analyzed retrospectively.

Results: For all cases, the C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) of all the patients decreased to normal levels at the last follow-up. The average visual analog scale (VAS) score was 7.5 ± 1.6 preoperatively and 0.6 ± 0.8 at the last follow-up, showing a significant reduction. The average angle of kyphosis correction was $6.3\pm4.7^{\circ}$, and the loss of correction was $1.4\pm1.6^{\circ}$. Neurological function was significantly improved in all cases according to the American Spinal Injury Association (ASIA) classification. Solid fusion was observed in all cases at the last follow-up.

Conclusions: Debridement and bone graft fusion via the lateral extracavitary approach combined with two fixation methods can be very effective in the treatment of thoracic spinal TB.

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Abbreviations: CRP, C-reaction protein; ESR, erythrocyte sedimentation rate; VAS, Visual Analog Scale; ASIA, American Spinal Injury Association; HIV, human immunodeficiency virus; CT, Computerized Tomography; MRI, Magnetic Resonance Imaging.

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1. Introduction

Tuberculosis (TB) is more common in underdeveloped areas, but with the prevalence of immigration and human immunodeficiency virus (HIV), the incidence of TB infection has also increased in the Western world [1-3]. The spine is the most common site of extrapulmonary TB infection [4], spinal tuberculosis occurs commonly as an extremely severe and dangerous infectious disease in the world and accounts for 50-60 percent of bone and joint tuberculosis [5]. The spinal canal of the thoracic spine is relatively narrow, which results in susceptibility to secondary neurological impairment once abscess formation and kyphosis occur here after TB infection [6]. Therefore, anti-TB treatment should be carried out as long as spinal TB is diagnosed. Most cases of spinal TB can be cured by drug treatment [7,8]. Early surgical intervention is generally recommended in cases of poor efficacy, severe vertebral bone destruction, deformity development, spinal cord compression and neurological impairment [3]. It has long been proposed that surgical treatment can rapidly relieve pain, correct deformity, reduce bone loss and prevent further damage to neurological function [9,10]. At present, the widely recognized treatment strategy for spinal TB focuses on the reconstruction of mechanical structures, thorough removal of lesions and improvement of neurological function, which is suitable for spinal TB at any segment [11]. We advocate that the thorough removal of lesions and prevention of recurrence should be the first priority of these three surgical focuses. Currently, there are many surgical approaches for thoracic TB. We selected the lateral extracavitary approach for debridement and bone grafting, through which TB lesions in front of the thoracic spine can be well exposed, followed by fairly thorough debridement. Regarding the selection of fixation methods, we chose lateral or posterior fixation according to the number of involved segments, the lesion site, the spinal stability and the vertebral bone condition and achieved good results. After screening the patients treated by our group from January 2013 to April 2021, a total of 38 patients were included in this study. The clinical data of these patients will be analyzed below to verify the efficacy and safety of this approach. For the convenience of analysis, some data will be displayed in different groups according to different fixation methods.

2. Materials and methods

2.1. Inclusion criteria

According to the following criteria, a total of 38 patients were selected from among all TB patients treated by our group from January 2013 to April 2021: (1) the surgery was completed by the same surgeon, and it was the first treatment; (2) diseased vertebrae were located from the superior margin of T1 to the inferior margin of T12, and the efficacy of conservative treatment was poor; (3) the local structure was unstable and estimated to be aggravated; and (4) the patient had or was expected to have neurological impairment.

2.2. Basic information

All patients were treated by debridement and bone grafting via the lateral extracavitary approach (Table 1). Among them, 18 patients underwent lateral single screw-rod fixation, while 20 patients underwent posterior screw-rod fixation. There were 19 males and 19 females, aged from 23 to 84 years (average, 51.0 ± 14.1 years). The follow-up time was 18–96 months, with an average of 50.8 ± 21.9 months. The involved vertebrae were distributed from T3-T12, with a single segment involved in 25 patients and multiple segments involved in 13 patients. The preoperative American Spinal Injury Association (ASIA) classification was grade B in 2 patients, grade C in 3 patients, grade D in 11 patients, and grade E in 22 patients.

2.3. Preoperative preparation

Preoperatively, standard anti-TB drug treatment (isoniazid 300 mg/day, rifampicin 450 mg/day, ethambutol 750 mg/day and pyrazinamide 750 mg/day) was carried out for at least 2–4 weeks, and medical diseases were actively treated to improve patients' tolerance to surgery.

Table 1 Clinical data.

	Lateral fixation	Posterior fixation	Total cases
Count	18	20	38
Months of follow-up	56.7 ± 22.6	45.5 ± 20.5	50.8 ± 21.9
Sex (Male/Female)	9/9	10/10	19/19
Age(year)	52.3 ± 18.0	49.9 ± 9.8	51.0 ± 14.1
Single/multiple segment	17/1	8/12	25/13
Surgical duration (min)	246.5 ± 23.6	342 ± 63.4	297.0 ± 68.4
Blood loss (ml)	583.3 ± 172.4	810.0 ± 267.3	702.6 ± 252.0
Hospital stay (d)	11.2 ± 3.5	10.9 ± 3.8	11.1 ± 3.6
VAS Pre/Fin	$7.3 \pm 1.7/0.4 \pm 0.8$	$7.6 \pm 1.4/0.7 \pm 0.7$	$7.5 \pm 1.6/0.6 \pm 0.8$
CRP Pre/Fin(mol/L)	$15.6 \pm 19.7/0.9 \pm 0.9$	$20.7 \pm 27.8 / 1.5 \pm 1.4$	$18.3 \pm 24.1/1.1 \pm 1.2$
ESR Pre/Fin(mm/h)	$27.3 \pm 20.2/9.1 \pm 3.2$	$33.7 \pm 26.2 / 7.5 \pm 5.2$	$30.7 \pm 23.5/8.2 \pm 4.4$

Pre = Preoperative, Fin = Final follow-up. Compared VAS, CRP and ESR before and after operation, P < 0.05.

2.4. Operative procedures

The patients who underwent lateral fixation were in the left or right lateral decubitus position according to the condition of the lesions. A paraspinous incision was made on the back, with the trapezius/latissimus dorsi separated layer by layer. Through the intermuscular space of the erector spinalis, the ribs connected with the diseased vertebrae were exposed and carefully separated from the parietal pleura. Approximately 10 cm of the ribs were cut off and removed completely. The adjacent ribs were removed in the same manner (the number of removed ribs depended on the need for debridement). Then, the intercostal vessels and nerves were ligated and severed. The transverse processes of the diseased and adjacent vertebrae were cut off, so the anterolateral surface of the thoracic vertebrae could be reached (Fig. 1). Pus, diseased intervertebral disc and bone were removed completely. If spinal canal stenosis was severe preoperatively, lateral spinal canal decompression could be performed by opening the spinal canal along the intercostal nerves. After thorough debridement, based on imaging data (preoperative CT to assess the extent of vertebral destruction, size, number, and location of necrotic bone; MRI to determine the extent of tuberculosis, whether lesion invasion into the spinal canal, and spinal cord compression), and intraoperative debridement findings, the fixation method and implantation site are determined. After that, the bone defect is shaped into a bone trough, one pedicle screw was inserted into each lateral upper and lower vertebral body, crossing the lesion site. Then, a massive iliac bone graft, rib graft or titanium mesh was implanted before the titanium rod was connected. Two grams of streptomycin was placed locally, and the incision was closed after placing a drainage tube.

The patients who underwent posterior fixation were in the prone position first. A posterior-midline incision was laterally made on the back with the diseased vertebrae as the center for exposure until reaching the vertebral plate. The pedicle screw was inserted routinely, and the screw rod on the opposite side of the approach was locked. The incision was closed temporarily, and the patients were moved to the lateral decubitus position. Both ends of the original incision were extended obliquely upward for exposure. In the same manner, exposure was performed until the anterolateral side of the thoracic vertebrae, followed by careful debridement. If there was spinal canal stenosis, lateral spinal canal decompression could also be carried out. After repairing the bone defect with an autogenous bone graft or titanium mesh, the titanium rod on the approach side was locked. Two grams of streptomycin was placed locally, and the incision was closed after placing a drainage tube.

2.5. Postoperative management

The intraoperative pathological tissues were sent for pathological examination. In this study, all patients were confirmed to have TB by pathological examination. After surgery, all patients received anti-TB drug treatment for more than 18 months. The drainage tube was withdrawn when there was no extraction. Patients were discharged when the general condition was stable and the incision showed no abnormalities. All patients were asked to lie in bed for 4–8 weeks. The C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR) and computerized tomography (CT) or X-ray findings were reviewed at 3, 9, 12 and 24 months after surgery.

2.6. Evaluation

The operative duration, intraoperative blood loss volume and length of postoperative hospital stay (d) were used to assess the surgical process. Preoperative and postoperative visual analog scale (VAS) scores and preoperative ESR and CRP values were used to

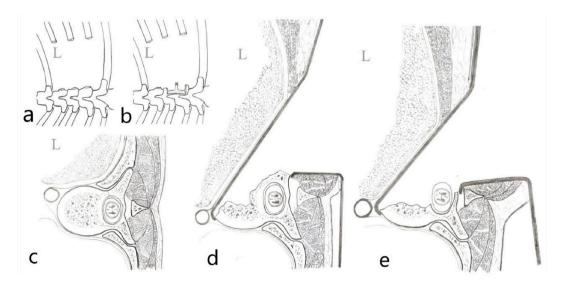


Fig. 1. Schematic of the range of excision in the right lateral decubitus position shown as an example. (a b) Dorsal view in the right decubitus position. (c) Sectional anatomy at the level of the 10th thoracic pedicle. (d) Range of excision for debridement without opening the vertebral canal. (e) Range of excision for debridement with lateral decompression of the vertebral canal.

assess postoperative recovery, and the ASIA classification was used to assess neurological function. X-ray and CT examinations were used to assess bone graft fusion and spinal deformity correction. The kyphotic angle was measured on lateral X-ray images: a horizontal line was made at the superior margin of the upper vertebral body and the inferior margin of the lower vertebral body involved in kyphosis, and the angle between the two lines was defined as the kyphotic angle [12]. The kyphotic angle was followed up to assess the correction. Additionally, complications in all patients were recorded.

2.7. Statistical analysis

The statistical analysis in this study was performed by SPSS 24.0 statistical software (IBM Corp., Armonk, NY, USA). Measurement data were expressed as mean \pm standard deviation. A paired t-test was applied to compare indices preoperatively, postoperatively, and during follow-up. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Perioperative data

The average operative duration was 297.0 ± 68.4 min, the average intraoperative blood loss volume was 702.6 ± 252.0 ml, and the average length of postoperative hospital stay was 11.1 ± 3.6 d. The average preoperative CRP and ESR values were 18.32 ± 24.1 mol/L and 30.7 ± 23.5 mm/h, respectively. At the last follow-up, the CRP and ESR values of all patients had decreased to normal levels, 1.1 ± 1.2 mol/L and 8.2 ± 4.4 mm/h, respectively. The average VAS score was 7.5 ± 1.6 preoperatively and 0.6 ± 0.8 at the last follow-up, showing a significant reduction (P<0.05) (Table 1).

3.2. Complications and neurological function

Two months after surgery, one patient treated with posterior fixation and debridement via the lateral approach showed sinus tract formation at the incision site, which was confirmed as recurrence of the original lesion and cured after debridement. Nine months after the second surgery, two screws at the lower end were withdrawn. CT confirmed that bony fusion had occurred at the bone graft site. In the other patients, the incisions healed at the first stage, with no cases of internal fixture fracture or withdrawal. Two patients presented rupture of the parietal pleura during surgery, which was repaired intraoperatively in a timely manner. There were no cases of intraoperative dural tear or large vessel injury, spinal cord injury, cerebrospinal fluid leakage or intractable intercostal neuralgia in any of the patients. Regarding neurological function, a total of 16 patients had a classification lower than grade E before surgery, and at the last follow-up, one patient was upgraded from grade B to grade D, while the rest of the patients were upgraded to grade E (Table 2).

3.3. Follow-up of imaging data

The kyphotic angle was $16.8\pm7.9^\circ$ before surgery, $10.3\pm5.6^\circ$ after surgery, and $11.6\pm5.9^\circ$ at the last follow-up. The preoperative kyphosis angle of patients with external fixation $(14.5\pm8.5^\circ)$ was significantly larger than that after operation $(8.5\pm4.5^\circ)$, P < 0.05. The preoperative kyphosis angle of patients with posterior internal fixation $(18.8\pm6.9^\circ)$ was also significantly larger than that after operation $(11.9\pm6.1^\circ)$, P < 0.05 (Fig. S1). The average angle of kyphosis correction was $6.3\pm4.7^\circ$, and the loss of correction was approximately $1.4\pm1.6^\circ$ (Table 3). All patients showed intervertebral fusion at the last follow-up, and no significant bone resorption was observed (confirmed by CT or X-ray examination).

3.4. Comparison between different internal fixation groups

In addition, comparisons were performed between groups according to the different internal fixation methods. The main

Table 2 ASIA grade of patients.

ASIA grade	$Lateral\ fixation (n=18)$	$Posterior \ fixation (n=20) \\$	
Preoperative			
A	0	0	
В	1	1	
C	2	1	
D	5	6	
E	10	12	
Final follow-up*			
A	0	0	
В	0	0	
C	0	0	
D	0	1	
E	17	20	

ASIA American Spinal Injury Association.

Table 3 Correction of spinal deformity.

	Lateral fixation	Posterior fixation	Total cases
Preoperative kyphosis angle (°)	14.5 ± 8.5	18.8 ± 6.9	16.8 ± 7.9
Postoperative kyphosis angle (°)	8.5 ± 4.5	11.9 ± 6.1	10.3 ± 5.6
Final kyphosis angle (°)	8.9 ± 5.1	14.0 ± 5.6	11.6 ± 5.9
Kyphosis angle correction (°)	6.1 ± 4.8	6.5 ± 4.6	6.3 ± 4.7
Kyphosis angle loss (°)	1.1 ± 1.2	1.8 ± 1.8	1.4 ± 1.6

Compared the kyphosis Angle preoperatively and postoperatively, P < 0.05.

differences were as follows, as shown in all tables. First, in the posterior fixation group, a total of 12 patients had multisegmental involvement, while in the lateral fixation group, only one patient showed multisegmental involvement. Second, the involved segments were distributed throughout the thoracic spine in the posterior fixation group but were only below T6 in the lateral fixation group. The preoperative kyphotic angle in the posterior fixation group was 18.8 ± 6.9 , which was larger than that in the lateral fixation group (14.5 ± 8.5) . The angle of kyphosis correction was $6.5 \pm 4.6^{\circ}$ in the posterior fixation group and $6.1 \pm 4.8^{\circ}$ in the lateral fixation group. Moreover, there were four patients in the posterior fixation group and one patient in the lateral fixation group whose preoperative ASIA grade was lower than D. Not surprisingly, the operative duration was significantly shorter and the blood loss volume was significantly less in the lateral fixation group than in the posterior fixation group.

4. Discussion

Spinal TB usually involves the thoracic vertebrae, and bone destruction often occurs in the anterior and middle columns. Therefore, the anterior column of the spine must be exposed for thorough debridement. The lateral extracavitary approach is widely used in surgery for ventral lesions of the thoracic spine, including fractures, tumors, and infections, with high efficacy [13]. At present, there are multiple surgical approaches for thoracic TB, including anterior, posterior, and combined approaches, each with their own

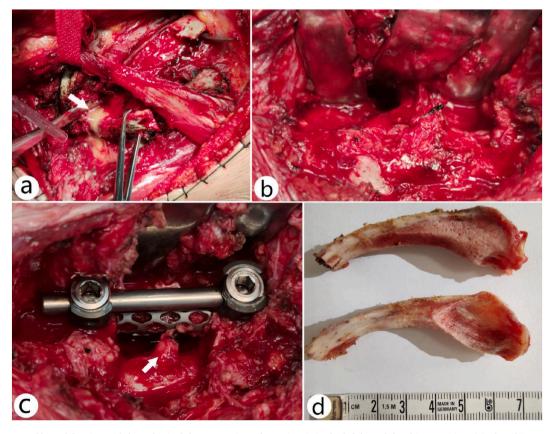


Fig. 2. A case of lateral fixation with lateral spinal decompression. The patient is in the left lateral decubitus position. (a) The white arrow shows pus emerging from the front of the eighth rib head. (b, c) After adequate debridement and lateral decompression, a titanium cage was implanted. The white arrow shows the remains of the eighth intercostal nerve root. (d) On the lower side is the 8th rib, showing a pit on the ventral side caused by tuberculosis.

advantages [14]. Anterior approaches require entry through the thoracic/abdominal cavity and were first reported by Hodgson et al. [15]. Anterior approaches can be used for debridement, precise bone grafting and spinal reconstruction in one stage, with high efficacy. Combined anterior and posterior approaches are also widely used and can achieve 360° spinal reconstruction. Based on thorough debridement and nerve decompression, these approaches offer better orthopedic ability and stability [16]. Hirakawa, Liu et al. [17,18] reported that the treatment of thoracic TB via a combined approach yielded good results. Wang, Guzey et al. [19,20] reported that the treatment of thoracic TB via a posterior-only approach achieved high efficacy. Debridement, bone grafting and internal fixation were completed in one stage; the debridement was thorough, and the fixation was reliable. They also compared the advantages and disadvantages of the three types of surgical approaches and concluded that a posterior approach alone should be the first choice for the treatment of thoracic TB. In addition, Yin et al. [21] reported that the lateral extracavitary approach for the treatment of thoracic TB involving multiple segments achieved high efficacy, which is in line with the results of our study. Combined with our practical experience and data, it is concluded that the lateral extracavitary approach has the following advantages: (1) it provides a wide field of view and allows both thorough debridement and precise bone grafting. A window can be made by resecting the ribs and the transverse processes connected with the diseased vertebrae. If multiple segments are affected, several adjacent ribs can be resected to enlarge the window. Through this window, the anterolateral side of the thoracic spine can be reached. Under direct vision, the abscess and necrotic tissues in front of every affected vertebra can be removed. Moreover, in the lateral decubitus position, the lesion on the opposite side of the thoracic vertebra can be reached after gradual debridement via this approach, allowing more thorough debridement. After debridement, the amputated rib or ipsilateral iliac bone can be used for structural bone grafting, or it can be crushed and filled into a titanium cage and then implanted [22,23]. (2) Whether the spinal canal should be opened can be determined according to the demand (Fig. 1). When the anterior lesion is cleared preliminary, if the spinal canal stenosis is confirmed by preoperative imaging data, the spinal canal can be opened laterally at the lesion site for decompression (Fig. 2). In some cases, the anterior vertebral bone destruction is severe, but the spinal canal is not involved, and there is no need for decompression, only debridement. The resection range only involves the transverse processes, ribs and pathological bone. The integrity of the spinal canal can be preserved, while the remaining support of the spine can be retained as much as possible, and the risk of spinal cord injury can be reduced. The obvious disadvantages of this approach include the extensive trauma and the necessary damage to intercostal nerves and



Fig. 3. A case of lateral fixation. A 23-year-old male patient was admitted to the hospital with back pain for more than 2 months, accompanied by a gradually growing dorsal mass without any neurological impairment. (a b c d) Preoperative MRI and CT showed bone destruction at T8 and T9; the damage was concentrated in the middle column and accompanied by a large amount of pus in front and on both sides of almost all of the thoracic vertebrae and connected with the dorsal mass. (e f) Debridement, bone grafting and internal fixation were performed by the lateral extracavitary approach in one stage. (g h) CT reexamination one year after the operation showed that the ribs used for structural bone grafting had fused with the surrounding bone. (i j) X-rays two and a half years after surgery.

blood vessels due to rib resection, which results in postoperative chest wall paresthesia in some patients. Furthermore, if posterior fixation is selected, the position needs to be changed during surgery, which also increases the operative duration and the risk of infection.

In spinal tuberculosis, significant bone destruction often occurs, accompanied by mild to moderate spinal kyphotic deformity, frequently necessitating internal fixation support. The pedicle screw technique, commonly employed in spinal fusion and deformity correction, offers advantages such as three-column fixation, immediate stability, and high fusion rates. Its widespread application in spinal surgery has demonstrated favorable outcomes [24,25]. Consequently, in this study, we selected the pedicle screw technique to enhance spinal stability, correct spinal deformity, and promote bone fusion in the grafting area.

The orthopedic efficacy and stability of posterior fixation are significantly better than those of lateral single screw-rod fixation [26]. However, our data showed that lateral single screw-rod fixation could achieve the same orthopedic effect as posterior fixation, and the loss of kyphosis correction was not obvious. The reason for this result is that the choice of the internal fixation method was not random during our diagnosis and treatment processes. In the cases of single screw-rod fixation, the lesions were relatively simple, and the stability was not poor. In contrast, posterior fixation was selected for patients with more severe conditions, more bone destruction, more complex lesions and poorer spinal stability after debridement. Additionally, the affected segments in the 18 patients treated with lateral single screw-rod fixation in our study were all below T6. Lateral screw-rod fixation is not suitable for the upper thoracic spine (T1-T5). The lateral side of the upper thoracic spine is covered by the scapula, the curvature of the ribs is greater, and the pleura is tenser, which makes lateral screw placement more inconvenient. Therefore, for lesions in the upper thoracic spine (above T6), we chose posterior fixation. Combined with practice and data, we preliminarily explored the indications for the two fixation methods. Based on debridement via the posterolateral approach, posterior fixation should be selected for patients with multisegment involvement, complex lesions, severe deformity and poor stability. In the case of single-segment lesions in the lower thoracic spine, good stability and no serious deformity, lateral single screw-rod fixation can be selected (Fig. 3). The specific characteristics of these methods are as follows: Posterior fixation offers good holding force and a good support capacity, with high strength, high stability and a wider application range [27,28]. Lateral single screw-rod fixation can be completed with debridement and bone grafting in one stage. It is characterized by relatively little trauma, a short operative duration, less blood loss and a simple operative procedure but provides less strength. In addition, Mycobacterium tuberculosis will not form a biofilm on the surface of the internal fixation instrumentation [29], so it is not improper to directly implant the screw rod or titanium cage into the lesion.

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) was first published by the American Spinal Injury Association (ASIA) in 1982. The seventh edition of this international classification system remains widely used as the standard reference for classifying sensory and motor impairments following spinal cord injury [30]. At the last follow-up, one patient was upgraded from grade B to grade D, while the rest of the patients were upgraded to grade E. Neurological function was significantly improved in all cases according to the American Spinal Injury Association (ASIA) classification. In addition, the preoperative kyphotic angle in the posterior fixation group was larger than that in the lateral fixation group. Confirmed by postoperative follow-up CT and X-ray imaging of the patients, the angle of kyphosis correction was $6.5 \pm 4.6^{\circ}$ in the posterior fixation group and $6.1 \pm 4.8^{\circ}$ in the lateral fixation group. All patients showed intervertebral fusion at the last follow-up. The experimental results indicate that using lateral extracavitary approach for debridement and bone grafting of tuberculosis lesions, combined with the selection of lateral or posterior screw-rod fixation based on the lesion location, extent, and severity of vertebral destruction, can achieve satisfactory repair outcomes.

Overall, since spinal tuberculosis primarily damages the anterior and middle columns, selecting anterior approach allows for direct visualization and removal of necrotic bone and tissue, facilitating thorough debridement of the lesion and anterior decompression of the spinal canal, while clearly exposing the dura mater and minimizing spinal cord injury. Additionally, anterior column bone grafting can provide a better graft bed and a larger fusion area, avoiding damage to the stability of the posterior column. However, the anterior approach requires high technical proficiency due to the extensive exposure and necessary dissection. The posterior approach for debridement may be suitable in cases where the vertebral body has already fused, there is bony bridging at the anterior edge of the vertebra, or the tuberculosis lesion is located in the posterior structures.

Finally, any surgical method should be selected based on the patients' condition combined with the surgeons' expertise to achieve individualized treatment. Anti-TB drugs are the basis of the treatment of TB [31]. While paying attention to surgical treatment, drug treatment should be given sufficient attention. The follow-up duration of this study was relatively short, and the complications merit more long-term observation.

5. Conclusions

Debridement and bone graft fusion via the posterolateral extracavitary approach combined with two fixation methods can both achieve high efficacy in the treatment of thoracic TB. Lateral single screw-rod fixation is more suitable for patients with single-segment lower thoracic lesions and high stability, with less blood loss and shorter surgical duration. Posterior pedicle screw fixation has higher strength, and is more suitable for patients with multi-segment lesions, poor stability and complex conditions.

CRediT authorship contribution statement

Shuanhu Lei: Conceptualization. Jianwei Zhou: Data curation. Li Guo: Formal analysis. Xiaoli Guan: Investigation. Mingtao Zhang: Methodology. Haiyuan Yue: Supervision. Xuewen Kang: Supervision.

Ethical approval statement

Approval was obtained from the ethics committee of Lanzhou University second Hospital (Project No.2019A-031). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

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Declaration of competing interest

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

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39435.

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