

ORIGINAL RESEARCH

Functional And Radiological Outcomes Of Anterior Decompression Of Thoracic And Lumbar Spine Tuberculosis And Fusion By Bone Graft And Cage Stabilization With Pedical Screw By Posterior Approach

¹Dr. Manikaran Singh, ²Dr. Parweej Ahmed, ³Dr. Azad Khan, ⁴Dr. Vishvendra Tomar

¹Junior Resident, ²Professor and Head, ³Associate Professor, ⁴Assistant Professor, Department of Orthopaedics, Subharti Medical College and Hospital, Meerut, Uttar Pradesh, India

Corresponding Author

Dr. Manikaran Singh

Junior Resident, Department of Orthopaedics, Subharti Medical College and Hospital, Meerut, Uttar Pradesh, India

Received date: 11 August, 2024

Acceptance date: 16 September, 2024

ABSTRACT

Aim: To evaluate the efficacy & safety of decompression & stabilization via the posterior approach alone for patients with thoracic & lumbar spine TB. **Material and Methods:** The present Hospital based retrospective study was conducted in the Department of Orthopedics, CSS Hospital Subharti Medical College, Meerut, Uttar Pradesh, after approval of the research review board, including 24 patients having thoracic & lumbar TB of spine, attending OPD of Department of Orthopedics, after considering the inclusion & exclusion criteria. After enrolment into the study, patient's information regarding their age, gender & history of present illness was taken & clinical examination was done. Single-stage posterior debridement, decompression & transpedicular screw fixation with Cage or Bone Graft was performed & outcome measures were evaluated at baseline, preoperatively, & evaluation immediately post operatively, 5th day, before discharge, at 15th day, 1 month, 2 months, 3 months & 6 months. **Results:** Maximum patients were in age group 18-30 years (36%). Majority of study subjects were females (76%). There was a significant decrease ($p < 0.01$) in mean VAS pain score. There was a significant decrease in lower back pain as reported by patients, after treatment. No loss of kyphosis correction at 6 months follow-up. No complication was encountered in any of the subjects. **Conclusion:** From present findings it was inferred that both Cage & Bone Graft showed good results with good neurologic recovery, Kyphotic deformity correction & significant improvement in back pain with complete healing & no complications & high success rate, & prevents kyphosis from progressing further. To date, the functional, clinical & radiological outcomes have been positive. Of course, more research with a large increase in sample size & a longer follow-up period will be necessary.

Keywords: TB, Spine, Decompression, Stabilization, Posterior approach

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution- Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

INTRODUCTION

Since ancient times, TB (TB) has been recognised as a disease. Ancient Indian medical literature referred to it as "Yakshama" as early as 1000–600 BC.[1] The earliest known examples of spinal TB (TB) were found in Egyptian mummies that were 5,000 years old.[2] Spinal TB is still a health concern due to the rising incidence of TB in both developed & developing nations [3-5] Of all skeletal TB cases, 50% are caused by spinal TB (Pott's disease), which is also the most prevalent & fatal kind of the disease. India is the country with the biggest global TB burden, with an anticipated 2.69 million cases in

2019.[6] However, 40–50% of all spinal infections are caused by spinal TB. [7-8]

The most impacted spine regions are the thoracic, lumbar, & cervical, which lead to neurological impairment & kyphotic deformity. The most frequent cause of neurological impairments is a paravertebral abscess, kyphotic deformity, or progression that results in cord compression. Since patients with spinal TB rarely exhibit the classic TB symptoms—fever, chills, weight loss, & decreased appetite—the diagnosis of spinal TB is made on the basis of clinical suspicion. The therapy of Pott's illness has evolved recently due to advancements in spinal reconstructive

procedures & the introduction of more accurate imaging modalities.[3]

Antitubercular drugs are the gold standard for the treatment of TB in cases without spinal deformity or neurological impairment & are the first choice of treatment often resulting in fusion in 80% of cases.[9] The indication for surgery in patients with TB of the spine are severe spinal deformity, spinal instability, neurological deficits, presence of large tubercular abscess either para spinal or epidural, adequate decompression, debridement and failure of response to anti-tubercular drugs.[10-11]

Surgical management helps regain motor function & ameliorates disability. Currently, the selection of an optimal surgical approach for treating thoracolumbar TB remains controversial. The anterior approach was traditionally preferred because it enabled direct access to the infected focus & provided easier access for debridement & reconstruction of defects. Unfortunately, concomitant osteoporosis associated with the infection prevented adequate fixation in the thoracic & lumbar region. [12-13] A combined anterior & posterior approach helped overcome stability-related drawbacks of an anterior approach, although it had its own drawbacks.[13] Posterior or posterolateral approaches have gained popularity in the last decade. Via the posterior extrapleural approach, both the anterior & lateral columns can be accessed,[13] thereby providing excellent exposure for circumferential spinal cord decompression & enabling extension to multiple levels above & below the pathology level,[12] with less morbidity & short operation time, as well as reduced blood loss, compared with the combined anterior & posterior approach.[13] Moon et al.[13] concluded that posterior spinal stabilization & anterior interbody fusion were helpful for preventing the disease early, providing an early fusion, & correcting & preventing kyphosis progression.

There has been limited research regarding the incorporation of a posterior approach for surgically treating thoracolumbar TB. This study aimed to evaluate the efficacy & safety of decompression & stabilization via the posterior approach alone for patients with thoracic & lumbar spine TB. The objectives of the study was as follows:

1. To evaluate the clinical & functional outcomes of the patient after procedures.
2. To evaluate the healing & deformity correction of spine.
3. To evaluate the surgical time, blood loss & level of vertebral fixation and postoperative rehabilitation.
4. To evaluate the graft & implant related problem.

MATERIAL & METHODS

The present hospital based prospective study was conducted among patients having thoracic & lumbar TB of spine, of either gender were recruited for the study at Department of Orthopedics, CSS Hospital

Subharti Medical College, Meerut, U.P. during September 2022 to October 2023. The ethical clearance for study was taken by the IRB for Ethical Clearance of CSS Hospital Subharti Medical College, Meerut, Uttar Pradesh. All consenting patients /attendants were asked to sign a written informed consent form (in the language best understood by them).

Sample size: During the surgery; 24 patients were recruited.

Inclusion criteria

- Patients aged >14 years who had thoracic & Thoracolumbar Pott's disease.
- The diagnosis was confirmed in all patients by clinico-radiological & histopathological methods.
- Neurological signs not improving or worsening within 4 weeks of adequate conservative treatment.
- Progressive neurological deficit in spite of conservative treatment.
- Reoccurrence of the neurological symptoms.
- Rapid onset paraplegia
- Late onset paraplegia
- Spinal instability & a spine with a risk sign of $\geq 2/4$ (Kumar's classification)

Exclusion criteria: Subjects having following characteristics were excluded from the study:

- Patients who have not given written informed consent,
- Patients histology consistent with another diagnosis,
- Patient with cervical or sacral TB,
- Patients with severe co morbidities & deemed unfit for operation.

Surgical Technique: The procedure was carried out while under general anaesthesia. In order to allow the abdomen to hang freely, the patient was placed prone with one bolster under the chest & another beneath the pelvis, protecting the eyes & head. The pedicle screws were placed in the unaffected vertebrae (1 to 3 levels above & below the afflicted location) after a midline incision & paravertebral muscle stripping. Following preoperative imaging evaluation, decompression & pedicle fixation were performed in the lumbar spine, & a pedicle screw & extrapedicular fixation were placed in the thoracic spine. The primary site of infection was chosen, & the thoracic spine underwent unilateral & bilateral facetectomies, laminectomy up to the medial pedicle edge, & possible sacrifice of the local site's thoracic nerve root for improved exposure. The operating table was tilted 30 degrees towards the opposite site to provide a better view & enable complete lesion removal & 360 degrees of cord decompression. Dead tissue, granulation tissue, pus, & consecutive bone were removed. An autograft & cage with the proper shape were implanted into the

vertebral body. Rods were finally applied, & cross linkage was established between the rod applications. One milligramme of streptomycin was applied locally, layers of suture were completed, & the material or tissue was sent for histopathological analysis. Additionally, paravertebral abscesses were drained & sent for sensitivity & culture testing.

Postoperative Treatment: After a week, the patient was able to sit on the bed with the assistance of a specially designed thoracic-lumbar-sacral orthotic, based on the patient's tolerance & trunk muscle strength. After the patient experienced no more discomfort or reached radiologic fusion, the brace was removed after six to twelve months. Similar to other paraplegics, regular care was given to the skin, joints, bowel, & bladder. Walking was introduced gradually, contingent on the lower limbs' ability to regain muscle power. Following surgery, chest physiotherapy was initiated.

Clinical evaluation: The following outcome measures were assessed using the following methods at baseline, before surgery, & just after surgery: on the fifth day, right before discharge, on the fifteenth day, one month, two months, three months, & six months.

- “Visual analog scale (VAS) for pain (Score of 0–10),

- Oswestry disability index (ODI) for low back pain (Score of 0–50),
- Preoperative & postoperative X-ray; Cobb's angle for the kyphotic angle & loss of kyphotic correction; &
- American Spinal Injury Association (ASIA) & Japanese classification for to spine for estimating the neurological status.
- Besides these outcome measures, average operation time, bony fusion, implant loosening, & implant failure were also evaluated.”

Statistical analysis: A statistician assisted in tabulating the data that was gathered in an Excel sheet. For statistical analysis, the means & standard deviations of each group's measurements were employed (SPSS 22.00 for Windows; SPSS in Chicago, USA). The student t-test & chi square test were used to compare the two groups, & a significance level of $p < 0.05$ was established.

RESULTS

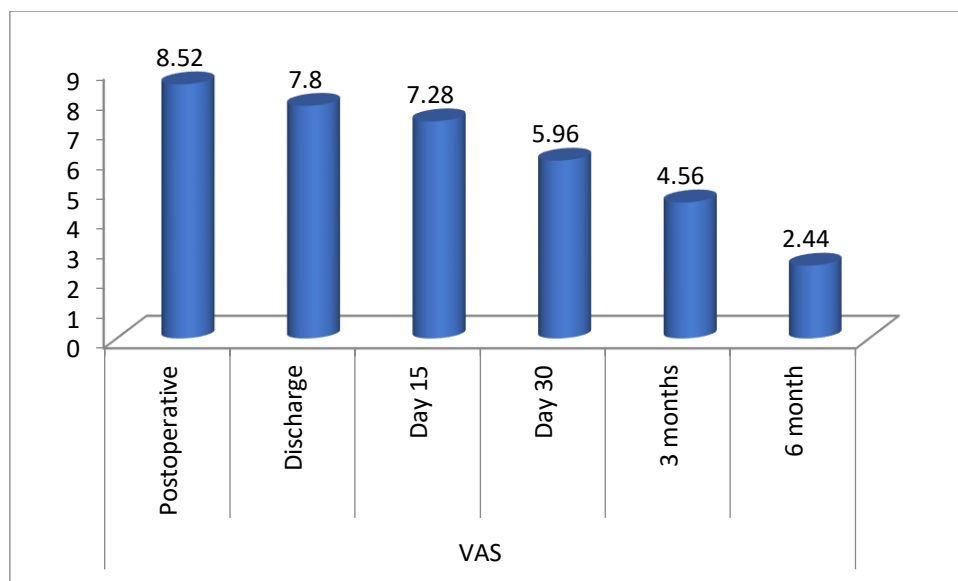
As depicted in table 1, majority of patients were in age group 18-30 years (n=9, 36%), followed by 6 (24%) subjects in age group 31-40 & 41-50 years each & 2 (8%) patients in age range 51-60 & 1 patient in age>60 years. Majority of study subjects were females (n=18, 75%) & remaining (n=6, 25%) were males as shown in table 1.

Table 1: Age and gender distribution among the study subjects

Age Group (in years)	N	%
18-30	9	36
31-40	6	24
41-50	6	24
51-60	2	8
>60	1	4
Gender		
Male	6	25
Female	18	75
Total	24	100

The mean visual analog scale (VAS) for pain postoperatively was 8.52 ± 0.586 , at discharge was 7.80 ± 0.408 , at 15th day was 7.28 ± 0.737 , at 30th day was 5.96 ± 0.539 , at 3 months was 4.56 ± 0.583 & at 6 months was 2.44 ± 0.507 , showing a statistically

significant difference ($p < 0.01$) as shown in graph 1. When intracomparison of VAS was done, it showed a statistically significant difference in each level except for at Postoperative vs Discharge level. (Table 2)



GRAPH 1: VAS score at different intervals

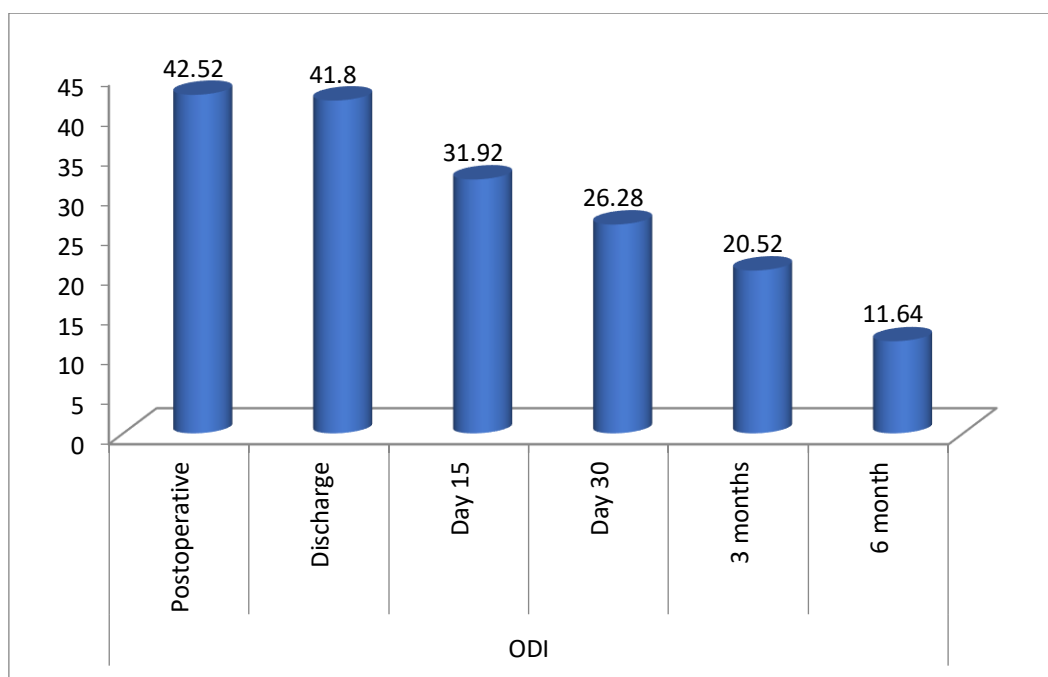
Table 2: Intracomparison of VAS at each interval

Post Hoc Analysis	p value
Postoperative vs Discharge	0.09
Postoperative vs Day 15	0.031*
Postoperative vs Day 30	0.002*
Postoperative vs 3 month	<0.01*
Postoperative vs 6 month	<0.01*

*: statistically significant

The mean ODI postoperatively was 42.52 ± 1.917 , at discharge was 41.80 ± 1.633 , at 15th day was 31.92 ± 3.353 , at 30th day was 26.28 ± 26.28 , at 3 months was 20.52 ± 2.771 & at 6 months was 11.64 ± 1.604 , showing a statistically significant

difference ($p < 0.01$). (graph 2) When intracomparison of ODI at each interval was done, it showed a statistically significant difference ($p < 0.01$) in every level except for at Postoperative vs Discharge level. (Table 3)



GRAPH 2: ODI at different intervals

Table 3: Intracomparison of ODI at each interval

Post Hoc Analysis	p value
Postoperative vs Discharge	0.10
Postoperative vs Day 15	<0.01*
Postoperative vs Day 30	<0.01*
Postoperative vs 3 month	<0.01*
Postoperative vs 6 month	<0.01*

*: statistically significant

The mean COBB angle postoperatively was 34.48 ± 3.853 , at discharge was 27.96 ± 3.668 , at 15th day was 26.28 ± 3.234 , at 30th day was 24.56 ± 3.292 , at 3 months was 23.28 ± 3.208 & at 6 months was 34.48 ± 3.853 , showing a statistically significant

difference ($p < 0.01$). When intracomparison of COBB angle was done, it showed a statistically significant difference in each level except for at Postoperative vs 6-month level. (Table 4).

Table 4: COBB angle at different intervals

COBB Angle	Minimum	Maximum	Mean	SD	Anova test	p value
Postoperative	27	40	34.48	3.853	67.42	<0.01*
Discharge	21	33	27.96	3.668		
Day 15	20	31	26.28	3.234		
Day 30	19	29	24.56	3.292		
3 months	18	28	23.28	3.208		
6 month	27	40	34.48	3.853		

*: statistically significant

No complication was encountered in any of the subjects.

DISCUSSION

Surgical intervention in active disease is still required in certain scenarios such as incapacitating pain due to instability, neurological worsening, or progressive deformity. However radical debridement by anterior approach has been replaced by posterior approaches using pedicle screws due to familiarity amongst surgeons & more importantly lesser morbidity by avoiding complications related to anterior approach.[14] Microbiological outcomes & effectiveness of debridement by posterior approach are similar to anterior approach.[15] In addition, posterior pedicle screw instrumentation with rods offer three-column control over the spinal elements, increasing the construct rigidity & thereby achieving better deformity correction.[16]

A single-stage posterior surgery can accomplish the following surgical intervention goals: debridement of the afflicted area, decompression of neural structures, repair of deformity, & spine stabilisation.[17] According to surgeons who advocate for posterior techniques, contemporary posterior spinal equipment can offer stability & firm fixation.[18-19] When posterior instrumentation & fusion are used to correct angular deformity, particularly when transpedicular instrumentation or anterior decompression combined with posterior fixation, the procedure is safer & more efficient. Furthermore, as stiff stabilisation boosts neurological rehabilitation in individuals with traumatic spinal cord injuries, posterior pedicle screw fixation may aid in neurological recovery.[20] The current study looked at & compared the clinical, functional, & radiological results for patients with TB

in the lumbar & thoracic spine using only the posterior approach.

Our study, which comprised 24 patients, demonstrated that these surgical procedures are a safe & effective way to treat patients who present with thoracolumbar tuberculosis (TB) with neurological deficits & deformity. Of these patients, 12 were treated with single-stage posterior debridement, decompression, & transpedicular screw fixation with cage & the remaining 12 patients were treated with the same procedures but with bone grafting. The current study's findings show that every patient treated with a posterior approach, regardless of a cage or bone graft, experienced full healing & improvements in their neurological function, kyphotic deformity, & back pain. Until their most recent follow-up, there was no sign of a recurrence. There were no issues with implant failure or loosening in any of the patients. In none of these cases was there a need for revision surgery or a recurrence.

There was a significant decrease ($p < 0.01$) in mean visual analog scale (VAS) score for pain when measured postoperatively till 6 months after treatment, showing a continuous decrease in score values. This result was in accordance to findings of **Jain A et al., (2017)** [21] who found that there was reduction in mean VAS score values from preoperative to 1 year follow up. When intracomparison of VAS was done, it showed a statistically significant difference in each level except for at Postoperative vs Discharge level. This suggested that after treatment there was a significant reduction in pain of subjects. **Kalanjiyam GP et al., (2022)** [22] found that mean VAS scores showed

significant improvement. **Zeng Y et al., (2019)** [23] found that there was a significant difference between the postoperative & follow-up VAS scores ($P < 0.05$), as in present study.

The mean ODI for low back pain showed a continuous reduction in values when measured postoperatively till 6 months after surgery, showing a statistically significant difference. When intracomparison of ODI was done at each interval, it showed a significant difference in each level except for that at Postoperative vs Discharge level. This shows that there was a significant decrease in lower back pain reported by patients, after treatment. Similar were the findings of **Cui X et al., (2013)** [24] there was a significant decrease ($p < 0.05$) in mean preoperative (81s%) Oswestry's Disability Index. **Zeng Y et al., (2019)** [23] also noted a significant difference in ODI score after surgery & at final follow-up visit.

The mean COBB's angle showed a significant difference in values measured at each interval after treatment, except that for at postoperatively & at 6 months recall visit, showing that there was no significant loss of kyphosis correction at 6 months follow up. These findings were similar to results of **Jain A et al., (2017)** [21]. **Kalanjiyam GP et al., (2022)** [22] observed that there was no significant loss of correction, as in present study. **Sahoo MM et al., (2012)** [25] in a series of 18 patients treated by posterior decompression & stabilization alone observed a deformity correction from $17.7^{\circ} \pm 5.8^{\circ}$ to $9.4^{\circ} \pm 4.6^{\circ}$, as in this study. According to **Guzey et al.** [17], posterior debridement, graft implantation, & instrumentation were performed on 19 patients with single segmental tuberculous spondylitis. After three months, one patient suffered a single fractured pedicle screw, & another patient passed away from a myocardial infarction. Before surgery, the mean angulation of the 13 kyphotic deformity patients was 18.2° (range $5-42^{\circ}$); following surgery, this angle decreased to 17.3° (range $0^{\circ}-42^{\circ}$). Accordingly, the authors said that in patients with lumbar & thoracic tuberculous spondylitis, the posterior technique was adequate for infection debridement & spinal stabilisation. Similar to the current investigation, **Zhang H et al. (2013)** [26] discovered that kyphotic angles were greatly reduced postoperatively & maintained at the final follow-up.

No complication was encountered in any of the subjects. Thus, our study showed a satisfactory outcome in regard to the neurological dysfunction suffered by patients with thoracolumbar junction TB who were treated by a single-stage posterior debridement, decompression & transpedicular screw fixation approach. We are also aware of the potential risk of TB spreading to the healthy posterior regions, as posterior debridement can result in diffusion of infection & fistulas. The stability of the spine would theoretically be affected because the normal posterior column of the spine can be destroyed due to

debridement & decompression in this procedure. Fortunately, these complications were not found in our study. Long-term follow-up is needed to closely monitor the development of these potential complications. These findings were in accordance to results of **Jain A et al., (2017)** [21] who observed no complications in their study. **Campbell et al.** [20] have shown that, in contrast to isolated posterior fusion, there are greater rates of problems with combined anterior & posterior spinal fusion & isolated anterior fixation. There were no instances of non-union of the bone, pseudoarthrosis, internal fixation loosening, or recurrence at the final follow-up, i.e., no perioperative problems arose, in the study conducted by **Zeng Y et al., (2019)** [23].

CONCLUSION

Spinal Tuberculosis is usually associated with neurological deficits, kyphotic deformity, vertebral loss, back pain and can be surgically treated more effectively with single-stage posterior debridement, decompression & transpedicular screw fixation with Cage or Bone Graft. From present findings it was inferred that both Cage & Bone Graft showed good results with good neurologic recovery, Kyphotic deformity correction & significant improvement in back pain with complete healing & no complications & high success rate, & prevents kyphosis from progressing further. To date, the functional, clinical & radiological outcomes have been positive. Of course, more research with a large increase in sample size & a longer follow-up period will be necessary.

REFERENCE

1. Tuli SM. Historical aspects of Pott's disease (spinal tuberculosis) management. *European Spine Journal*. 2013; 22: 529-38.
2. Kiran NA, Vaishya S, Kale SS, et al. Surgical results in patients with tuberculosis of the spine and severe lower-extremity motor deficits: a retrospective study of 48 patients. *Journal of Neurosurgery: Spine*. 2007; 6(4): 320-6.
3. Turgut M. Spinal tuberculosis (Pott's disease): its clinical presentation, surgical management, and outcome. A survey study on 694 patients. *Neurosurgical review*. 2001; 24: 8-13.
4. Barnes PF, Bloch AB, Davidson PT, et al. Tuberculosis in patients with human immunodeficiency virus infection. *New England Journal of Medicine*. 1991 Jun 6; 324(23): 1644-50.
5. Rajasankar V. Emory Morningside Global Health Case Competition (Doctoral dissertation, School of Theology Aditi Satyavrath, Rollins School of Public Health). 2024
6. Cavus G, Gezercan Y, Ökten AI, et al. Surgical approaches to upper thoracic pott's disease with spinal instability during childhood: two cases. *Child's Nervous System*. 2018; 34: 1221-7.
7. Fam AG, Rubenstein J. Another look at spinal tuberculosis. *The Journal of rheumatology*. 1993; 20(10): 1731-40.

8. Moorthy S, Prabhu NK. Spectrum of MR imaging findings in spinal tuberculosis. *American Journal of Roentgenology*. 2002; 179(4): 979-83.
9. Halsey JP, Reeback JS, Barnes CG. A decade of skeletal tuberculosis. *Annals of the Rheumatic Diseases*. 1982; 41(1): 7-10.
10. Soares do Brito J, Batista N, Tirado A, et al. Surgical treatment of spinal tuberculosis: an orthopedic service experience. *Acta Medica Portuguesa*. 2013; 26(4): 349-56.
11. Rasouli MR, Mirkoohi M, Vaccaro AR, et al. Spinal tuberculosis: diagnosis and management. *Asian spine journal*. 2012; 6(4): 294.
12. Garg B, Kandwal P, Nagaraja UB, et al. Anterior versus posterior procedure for surgical treatment of thoracolumbar tuberculosis: a retrospective analysis. *Indian journal of orthopaedics*. 2012; 46: 165-70.
13. Moon MS, Moon YW, Moon JL, et al. Conservative treatment of tuberculosis of the lumbar and lumbosacral spine. *Clinical Orthopaedics and Related Research (1976-2007)*. 2002; 398: 40-9.
14. World Health Organization, Centers for Disease Control and Prevention. Tuberculosis prevention and care among refugees and other populations in humanitarian settings an interagency field guide.
15. Rajasekaran S, Vijay K, Shetty AP. Single-stage closing-opening wedge osteotomy of spine to correct severe post-tubercular kyphotic deformities of the spine: a 3- year follow-up of 17 patients. *European Spine Journal*. 2010; 19: 583-92.
16. Tang Y, Wu WJ, Yang S, et al. Surgical treatment of thoracolumbar spinal tuberculosis—a multicentre, retrospective, case-control study. *Journal of orthopaedic surgery and research*. 2019; 14: 1-7.
17. Güzey FK, Emel E, Bas NS, et al. Thoracic and lumbar tuberculous spondylitis treated by posterior debridement, graft placement, and instrumentation: a retrospective analysis in 19 cases. *Journal of Neurosurgery: Spine*. 2005; 3(6): 450-8.
18. Lee JS, Moon KP, Kim SJ, et al. Posterior lumbar interbody fusion and posterior instrumentation in the surgical management of lumbar tuberculous spondylitis. *The Journal of Bone & Joint Surgery British Volume*. 2007; 89(2): 210-4.
19. Zhang HQ, Guo CF, Xiao XG, et al. One-stage surgical management for multilevel tuberculous spondylitis of the upper thoracic region by anterior decompression, strut autografting, posterior instrumentation, and fusion. *Clinical Spine Surgery*. 2007; 20(4): 263-7.
20. Campbell PG, Malone J, Yadla S, et al. Early complications related to approach in thoracic and lumbar spine surgery: a single center prospective study. *World neurosurgery*. 2010; 73(4): 395-401.
21. Jain A, Jain RK, Kiyawat V. Evaluation of outcome of transpedicular decompression and instrumented fusion in thoracic and thoracolumbar tuberculosis. *Asian Spine Journal*. 2017; 11(1): 31.
22. Kalanjiyam GP, Raja SD, Rajasekaran S, et al. A prospective study comparing three different all-posterior surgical techniques in the management of thoracolumbar spinal tuberculosis. *Journal of Clinical Orthopaedics and Trauma*. 2022; 34: 102026.
23. Zeng Y, Wu W, Lyu J, et al. Single-stage posterior debridement, decompression and transpedicular screw fixation for the treatment of thoracolumbar junction (T12-L1) tuberculosis with associated neurological deficit: a multicentre retrospective study. *BMC Musculoskeletal Disorders*. 2019; 20: 1-6.
24. Cui X, Ma YZ, Chen X, et al. Outcomes of different surgical procedures in the treatment of spinal tuberculosis in adults. *Medical Principles and Practice*. 2013; 22(4): 346-50.
25. Sahoo MM, Mahapatra SK, Sethi GC, et al. Posterior-only approach surgery for fixation and decompression of thoracolumbar spinal tuberculosis: a retrospective study. *Clinical Spine Surgery*. 2012; 25(7): E217-23.
26. Zhang H, Sheng B, Tang M, et al. One-stage surgical treatment for upper thoracic spinal tuberculosis by internal fixation, debridement, and combined interbody and posterior fusion via posterior-only approach. *European Spine Journal*. 2013; 22: 616-23.