doi: 10.30934/kusbed.1803934 **e-ISSN:** 2149-8571

Journal of Health Sciences of Kocaeli University

Original Article

http://dergipark.org.tr/kusbed

CHALLENGES IN THE DIAGNOSIS OF EXTRAPULMONARY TUBERCULOSIS AND COMPARISON OF DIAGNOSTIC METHODS

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Received: 15.09.2025 **Accepted:** 23.12.2025 **Published:** 20.01.2026

Abstract

Objective: Diagnosing extrapulmonary tuberculosis (EPTB) is difficult because of its paucibacillary nature and the need for invasive sampling. This study evaluated the diagnostic performance and inter-test agreement of commonly used methods and identified demographic and clinical features that may assist diagnosis.

Methods: This retrospective cohort study was conducted at a tertiary care hospital (2018–2025). EPTB was defined as at least one positive result from acid-fast bacilli (AFB) smear microscopy, polymerase chain reaction (PCR), solid or automated liquid cultures. Demographics, comorbidities, symptoms, laboratory results, histopathological and radiological findings were obtained from medical records. The positivity proportions were calculated, and agreement was assessed using the kappa coefficient.

Results: 46 adult patients with EPTB were included. The mean age was 51.6±20.1 years, with female predominance (67.4%). The most frequent sites were the lymph nodes (32.6%), genitourinary tract (21.7%), and musculoskeletal system (21.7%). The highest positivity was observed with automated liquid culture (76.1%), followed by solid culture (71.7%) and PCR (59.5%); AFB smears had the lowest rate (19.6%). Granulomatous inflammation was detected in 63.2% of patients who underwent pathological examination and caseous necrosis in 36.8%. There was slight agreement between AFB smear microscopy, culture, and histopathology. PCR results showed poor agreement with solid and automated liquid cultures, including negative kappa values. Radiological examinations revealed pathological findings in 88.2% of patients, predominantly lymphadenopathy.

Conclusion: Clinical and laboratory diagnosis of EPTB remains challenging. These findings support a multimodal strategy that integrates microbiological, molecular, histopathological, and radiological methods to improve diagnostic accuracy.

Keywords: *Extrapulmonary tuberculosis, mycobacterium tuberculosis, polymerase chain reaction, microbiological techniques, biopsy*.

Introduction

Tuberculosis (TB) is a preventable and chronic bacterial infection caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex.[1] In 2021, TB ranked as the 10th leading cause of death globally.[2]

The global impact of the COVID-19 pandemic, which occurred between 2020 and 2021, resulted in significant disruptions in the diagnosis, treatment, and follow-up processes for TB worldwide. A global surge in TB incidence has been reported during the post-pandemic period. According to the World Health Organization's 2024 Global Tuberculosis Report, an estimated 10.8 million people worldwide developed TB in 2023, resulting in approximately 1.25 million deaths. In 2023, with the waning impact of the pandemic, it is estimated that TB has once again ascended to the top position among deaths caused by a single infectious agent.[2]

The most common form of the disease is pulmonary TB; however, involvement of organs and tissues outside the lung parenchyma is defined as extrapulmonary tuberculosis (EPTB).[3] In 2023, EPTB was identified in 16% of newly reported TB cases.[2] On a global scale, the epidemiological proportion of EPTB generally ranges between 15% and 25% of all TB cases.[4] The most common sites of EPTB are the pleura, lymph nodes, gastrointestinal system, genitourinary system, central nervous system, and musculoskeletal system.[1,3,4] EPTB can imitate other diseases and manifest with a broad spectrum of symptoms and findings. Owing to its occult nature, diagnosis is often challenging and typically necessitates invasive procedures such as biopsy. Although TB is a preventable disease, delays in diagnosis can lead to delays in treatment and the development of related complications.[5]

Although culture is generally regarded as the gold standard for TB diagnosis, it can be time-consuming. Acid-fast bacilli (AFB) smear microscopy has low sensitivity, and false-negative results may be observed, particularly in extrapulmonary samples. Molecular methods, such as polymerase chain reaction (PCR), are becoming more prevalent in the diagnostic process because of their high sensitivity and fast turnaround times. Histopathological evaluation and other diagnostic tests primarily necessitate biopsy and radiological imaging methods play a crucial role in guiding diagnosis during this process.[6]

This study aimed to describe the clinical profile of EPTB cases and analyze the diagnostic performance, turnaround time, and agreement between different diagnostic methods.

Methods

This retrospective cohort study was conducted between 2018 and 2025 at a tertiary-care university hospital. The study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine (Approval number: 2025/302, Decision code: GOKAEK-2025/13/15). All procedures were performed in accordance with institutional ethical standards and the Declaration of Helsinki, revised in 2013. The reporting of this study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, as recommended by the EQUATOR Network.[7]

The study included adult patients with EPTB who were followed up and treated at the Infectious Diseases and Clinical Microbiology Clinic between 2018 and 2025. Owing to the rarity of the disease and the diagnostic difficulties encountered, the sample size was not calculated, and all available suitable cases were included.

Pediatric patients were excluded from the study. Furthermore, cases with positive PCR results in urine samples following intravesical Bacillus Calmette–Guérin (BCG) treatment for bladder cancer, in the absence of clinical symptoms, and without the need for antituberculosis treatment were excluded. Patient data were retrospectively obtained from the hospital's electronic record system. The diagnosis of EPTB was determined by the positivity of at least one of the following tests: AFB smear microscopy, PCR, solid culture (Lowenstein–Jensen), or automated liquid culture, BACTEC MGIT 960 System (Becton-Dickinson, Sparks, MD, USA). The presence of *Mycobacterium tuberculosis* complex DNA was detected using the *Artus M. tuberculosis* RG PCR Kit (Qiagen, Hilden, Germany), which was subsequently run on a Rotor-Gene Q real-time PCR thermocycler (Qiagen, Hilden, Germany), according to the manufacturer's instructions. The PCR assay identified *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. bovis BCG*, *M. microti*, and *M. pinnipedii*, which are members of the *Mycobacterium tuberculosis* complex. Culture methods can also detect the *M. tuberculosis* complex. The cases were grouped according to the anatomical region in which the infection occurred.

The following data were collected: age, sex, nationality, family history of TB, and patient comorbidities. The comorbidities evaluated included diabetes mellitus, insulin requirement, chronic renal failure, dialysis requirement, chronic liver disease, cirrhosis, chronic lung disease, pre-existing cardiac disease, connective tissue disease, hematopoietic or solid organ malignancy, steroid or other immunosuppressive drug use, living with HIV status, and pregnancy.

Table 1. Baseline characteristics of the extrapulmonary tuberculosis patients.

Characteristic	Total cohort (n=46)
Age (year), mean ± SD	51.57±20.08
Gender, n (%)	
Female	31 (67.4)
Male	15 (32.6)
Non-citizens, n (%)	5 (10.9)
Family history of tuberculosis	4 (8.7)
Diabetes mellitus, n (%)	5 (10.9)
Pre-existing cardiac disease, n (%)	5 (10.9)
Connective tissue disease, n (%)	4 (8.7)
Other immunosuppressive therapy, n (%)	4 (8.7)
Chronic kidney disease, n (%)	3 (6.5)
Chronic liver disease, n (%)	3 (6.5)
Steroid usage, n (%)	3 (6.5)
Chronic lung disease, n (%)	2 (4.3)
Dialysis requirement, n (%)	2 (4.3)
Solid organ malignancy, n (%)	2 (4.3)
Cirrhosis, n (%)	1 (2.2)
Hematopoietic malignancy, n (%)	1 (2.2)
PLWH, n (%)	1 (2.2)
Pregnancy, n (%)	1 (2.2)

SD: Standard deviation, PLWH: People living with HIV

The symptom questionnaire was based on the W4SS (WHO four-symptom screen) parameters recommended by the World Health Organization for TB screening.[8] Accordingly, the presence of fever, night sweats, and weight loss in the last three months was assessed. The laboratory findings included leukocyte, neutrophil, lymphocyte, hemoglobin, and platelet levels, as well as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values.

The total number of positive samples differed among the methods. Diagnostic tests, including AFB smear microscopy, PCR, solid culture, and automated liquid culture methods, were compared in terms of positivity proportion and turnaround time. Turnaround time was calculated in days from the time the sample was collected to the time the results were reported. The agreement between the diagnostic methods was analyzed statistically. An intersection analysis was performed with intervene the web application.[9]
Additionally, granulomatous inflammation and caseous necrosis were evaluated by histopathological examinations. Regarding imaging findings, the results of computed tomography (CT) and/or magnetic resonance imaging (MRI) of the relevant anatomical region were reviewed and recorded. Furthermore, microorganism resistance patterns were recorded due to their epidemiological significance, and mortality development within 30 days after diagnosis was also evaluated within the scope of the study.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA, Licensed in Kocaeli University as spss.kocaeli.edu.tr). The distribution of continuous variables was assessed with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed data were expressed as mean ± standard deviation (SD), and non-normally distributed variables as median and interquartile range (IQR). Group comparisons were conducted using the independent-samples t-test or the Mann–Whitney U test, as appropriate. Categorical variables were summarized as frequencies and percentages and compared using the Chi-square test.
Agreement between diagnostic methods (AFB smear microscopy, PCR, solid culture [Lowenstein–Jensen], automated liquid culture, and histopathology) was evaluated using the Kappa (κ) coefficient and interpreted according to the Landis and Koch criteria.[10] The McNemar test was used to assess the discordance between paired diagnostic results. A two-tailed p value <0.05 was considered statistically significant.

Results

The study population comprised 46 patients with EPTB. The mean age of the patients was 51.6±20.1 years, and the prevalence of female sex was higher. The demographic characteristics and distribution of comorbidities are summarized in Table 1, and the clinical characteristics, laboratory findings, and treatment outcomes are presented in Table 2.
The most common site of involvement was the lymph nodes. This was followed by genitourinary involvement. In genitourinary TB cases, the *Mycobacterium tuberculosis* complex was identified in the urine of seven patients, in a tubal sample from one patient, in an endometrial sample from one patient, and in a testicular sample from one patient.

The mean symptom duration was 80 days (interquartile range [IQR]: 30–152.5 days), with fever being the most prevalent symptom. Most patients exhibited elevated CRP and ESR levels. Leukocyte counts were within the normal range in 39 patients, and neutrophil counts were within the normal range in 40 patients. Lymphopenia was observed in 12 patients, and anemia was observed in 26 patients.

Table 2. Clinical presentation, laboratory findings, and outcomes among patients with extrapulmonary tuberculosis.

Site of extrapulmonary tuberculosis, n (%)	**Total cohort (n=46)**
Lymph node	15 (32.6)
Genitourinary system	10 (21.7)
Peritoneum	6 (13)
Bone/joint	5 (10.9)
Spine (spondylodiscitis)	5 (10.9)
Central nervous system	3 (6.5)
Breast	2 (4.3)
Clinical presentation	
Duration of symptoms, days, median (IQR)	80 (30–152.5)
Fever, n(%)	8 (17.4)
Night sweats, n(%)	6 (13)
Weight loss in the last three months, n(%)	6 (13)
Laboratory findings	
Leukocyte (µL), mean ± SD	6841.36±2257.64
Neutrophil (µL), median (IQR)	4113 (3350–5355)
Lymphocyte (µL), mean ± SD	1570.73±731.77
Lymphopenia, n (%)	12 (26.7)
Platelets (µL), mean ± SD	268175.56±93950.76
Hemoglobin (g/dL), median (IQR)	12 (11–13)
Anemia, n (%)	26 (57.8)
CRP (mg/L), median (IQR)	14 (6–50.5)
CRP ≥ 5 mg/L, n (%)	36 (80)
ESR (mm/h), median (IQR)	29 (18.5–40.5)
ESR ≥ 20 mm/h, n(%)	32 (71.1)
Resistance to at least one anti-TB drug, n (%)	5 (14.3)
Mortality within 30 days, n(%)	2 (4.3)

IQR: Interquartile range, CRP: C-Reactive protein, ESR: Erythrocyte sedimentation rate, TB: Tuberculosis

In the context of drug susceptibility testing, two patients were found to be resistant to isoniazid. Furthermore, isoniazid resistance was detected in two patients, rifampicin resistance in one, ethambutol resistance in one, and combined isoniazid and rifampicin resistance in one patient. Within 30 days of diagnosis, only two patients died, and their clinical characteristics are summarized below.
The first patient was a 79-year-old man with chronic kidney disease who was receiving peritoneal dialysis. He was admitted to the hospital with a diagnosis of spondylodiscitis

Table 3. Sensitivity and turnaround time of diagnostic tests in extrapulmonary tuberculosis.

Test	**Sensitivity, % (n/N)**	**Turnaround time, (days)**
AFB smear microscopy	19.6 (9 / 46)	2 (1–3)†
PCR	59.5 (22 / 37)	5.7±2.6‡
Solid culture (LJ)	71.7 (33 / 46)	39 (26–46)†
Automated liquid culture	76.1 (35 / 46)	38.8±10.5‡

AFB: Acid fast bacilli, PCR: Polymerase Chain Reaction, LJ: Lowenstein–Jensen
†Data expressed as median (IQR), ‡Data expressed as mean ± SD

affecting the T9–T10 vertebrae. During the clinical course, tuberculosis was suspected; however, before the culture results became available, the patient died of respiratory and subsequent cardiac arrest secondary to aspiration pneumonia. The patient did not receive antituberculous therapy prior to death because of rapid clinical deterioration.

The second patient was a 35-year-old foreign female who was being treated for tuberculous meningitis. She was admitted to the intensive care unit due to coma and died despite intensive supportive treatment.

The positivity proportions of the diagnostic tests are presented in Figure 1 as a radar plot, and the sensitivity and turnaround times are presented in Table 3. The highest positivity rate was identified in automated liquid culture, with a percentage of 76.1%, followed by 71.7% in solid culture and 59.5% in PCR testing. AFB microscopy exhibited the lowest positivity rate (19.6%). Granulomatous inflammation was detected in 24 of 38 patients (63.2%) who underwent pathological examination, and caseous necrosis was detected in 14 (36.8%).

Table 4. Agreement between diagnostic methods for extrapulmonary tuberculosis.

Diagnostic method	Agreement status			
	Kappa (κ)	Kappa *p*-value	McNemar *p*-value	Agreement level*
AFB vs. PCR	0.024	1	0.003	Slight
AFB vs. Solid culture (LJ)	0.037	0.711	<0.001	Slight
AFB vs. Automated liquid culture	0.076	0.421	<0.001	Slight
AFB vs. Pathological finding	0.087	0.686	<0.001	Slight
PCR vs. Solid culture (LJ)	-0.448	0.011	0.690	Poor
PCR vs. Automated liquid culture	-0.522	0.002	0.557	Poor
PCR vs. Pathological finding	-0.063	1	0.791	Poor
Automated liquid culture vs. Solid culture (LJ)	0.775	<0.001	0.625	Substantial
Solid culture (LJ) vs. Pathological finding	0.038	1	0.454	Slight
Automated liquid culture vs.Pathological finding	0.131	0.434	0.180	Slight

AFB: Acid fast bacilli, PCR: Polymerase Chain Reaction, LJ: Lowenstein–Jensen.

*Agreement interpretation according to Landis and Koch (1977): κ < 0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and >0.80 = almost perfect agreement. Negative Kappa values indicated poor agreement. Pathological finding: granulomatous inflammation, caseating or non-caseating

Figure 2 presents the intersection distributions between the tests via an UpSet plot, and Table 4 provides a comprehensive summary of the agreement analysis between the tests. The agreement between AFB smear microscopy and PCR was low (κ=0.024). AFB smear microscopy showed slight agreement with both solid (κ=0.037) and automated liquid (κ=0.076) cultures. PCR demonstrated poor agreement with solid culture (κ=–0.448) and automated liquid culture (κ=–0.522). A substantial level of agreement was observed between the automated liquid and solid (Lowenstein–Jensen) cultures (κ=0.775).

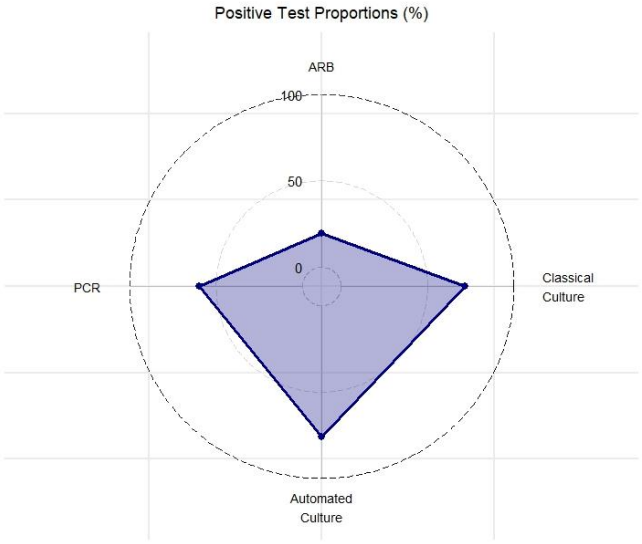

Figure 1. Positive test proportions of diagnostic methods for extrapulmonary tuberculosis.

Group comparisons were performed according to the positivity of the diagnostic methods, including AFB smear microscopy, PCR, solid culture, and automated liquid culture. Among the laboratory parameters, only the ESR level differed significantly between the PCR-positive and PCR-negative patients (38.7±24.3 vs. 23.9±15.0 mm/h, p=0.031). No statistically significant differences were observed among the other diagnostic subgroups. Radiological examinations included CT and MRI. Imaging results revealed pathological findings in 30 of the 34 patients (88.2%). The most prevalent radiological finding was lymphadenopathy, which was detected in 10 patients. A total of 10 patients diagnosed with bone TB exhibited a range of radiological findings, including osteomyelitis, abscess formation, and contrast retention. In three patients diagnosed with central nervous system TB, contrast retention was observed in the brain parenchyma and meninges.

In cases of genitourinary system TB, a necrotic mass was identified in the bladder of one patient, tubal calcification was observed in another, pyonephrosis was present in one patient, pyocele was detected in one patient, and endometrial-myometrial contrast retention was noted in another patient. Furthermore, findings consistent with carcinomatous peritoneum due to intra-abdominal spread were observed in one case, and abscess formation in the breast was observed in another. Figure 3 shows the MRI findings of spondylodiscitis at the L3–L4 vertebral level, with associated paravertebral abscess formation.

Discussion

This study aimed to assess the diagnostic efficacy of various microbiological and histopathological methods used to diagnose EPTB. In the present study, the automated liquid culture method yielded the highest positivity proportion, followed by solid culture and PCR. AFB microscopy demonstrated the lowest positivity proportion.

In our cohort, the mean age was 51.6±20.1 years, and there was a female predominance of 31 out of 46 patients (67.4%), which is consistent with previous reports.[11] The distribution of involved sites also aligned with prior reports: lymph nodes (15/46; 32.6%), genitourinary tract (10/46; 21.7%), and musculoskeletal system, including spondylodiscitis (10/46;

21.7%), were the most frequent sites.[1] In contrast, comorbid conditions, including HIV infection, were uncommon in our study, which is inconsistent with studies describing a higher burden of comorbidities. Mortality was also low compared with similar studies, with only two deaths.[11]

In EPTB, symptoms vary depending on the affected organs. The most common systemic symptom is fever. In our study, fever was observed in eight patients (17.4%). The median symptom duration was 80 days. Anemia, elevated C-reactive protein levels, and increased erythrocyte sedimentation rate were prevalent and consistent with previous reports.[12] The white blood cell count was normal in 39 (84.8%) patients. Lymphopenia, which may indicate a significant immunological problem seen in more severe forms of TB, was observed in 12 patients (26.1%).[13]

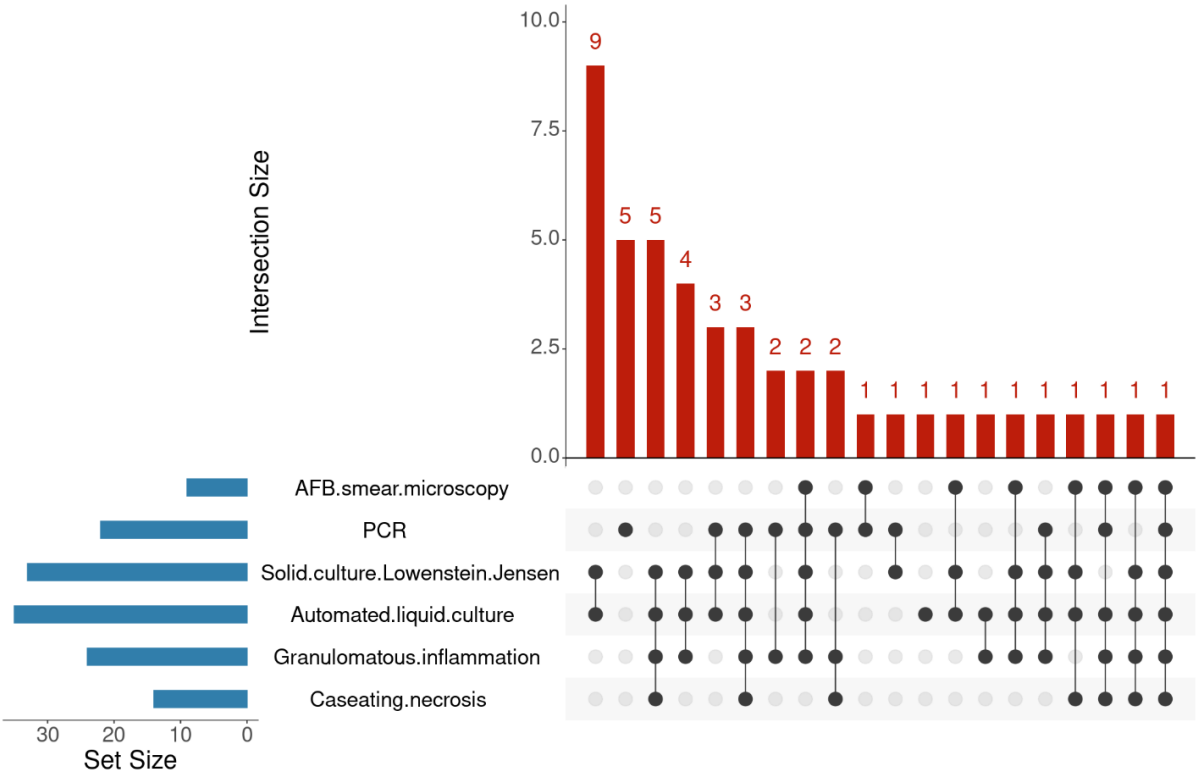

Figure 2. UpSet plot of the intersections between the diagnostic tests for extrapulmonary tuberculosis.

Our findings are consistent with those of previous reports, indicating that AFB microscopy has limited sensitivity in EPTB because of its paucibacillary nature. In our cohort, the positivity rate was 19.6%, which is within the range reported in the literature, varying from 10% to 35.2% across different studies; the detection rate in bone tissue samples may decrease to as low as 4.8%.[14,15]

Nucleic acid amplification tests, such as PCR, can overcome the diagnostic challenges posed by the paucibacillary nature of EPTB by detecting as few as 10 mycobacteria in a given sample. Although PCR offers high specificity, its sensitivity varies depending on the sample type and method used.[16]

The sensitivity of real-time PCR for EPTB is reported to be approximately 70%.[17] However, in our study, this rate was lower at 59.5%. When evaluated by sample type, next-generation real-time PCR methods, such as Xpert MTB/RIF Ultra, were reported to have a sensitivity of 94.1% for lymph node samples, 64.7% for abscess aspirates, and 60.5% for sterile body fluids.[18] Our lower sensitivity may be explained by the relatively small sample size and higher proportion of challenging specimens in our study, including bone abscesses, peritoneal fluid, and cerebrospinal fluid. The sampling technique and the anatomical tissue from which the sample was obtained also affected the positivity due to the paucibacillary nature of EPTB. These findings further support the need for a multimodal diagnostic approach that integrates molecular assays with histopathological evaluation, microbiological culture, and clinical assessment for diagnosing EPTB.

Wang et al. reported recovery rates of 75.73% with the MGIT 960 system and 43.72% with Lowenstein–Jensen (LJ), whereas Mishra et al. from northern India found 94.2% positivity with MGIT-320 and 89.8% with LJ.[19,20] The positivity rate varies according to the specimen type.[21] In our cohort, LJ culture yielded 71.7% (33/46) positivity, whereas automated liquid culture yielded 76.1% (35/46). As indicated in the relevant literature, automated liquid culture yielded a higher result than solid culture.

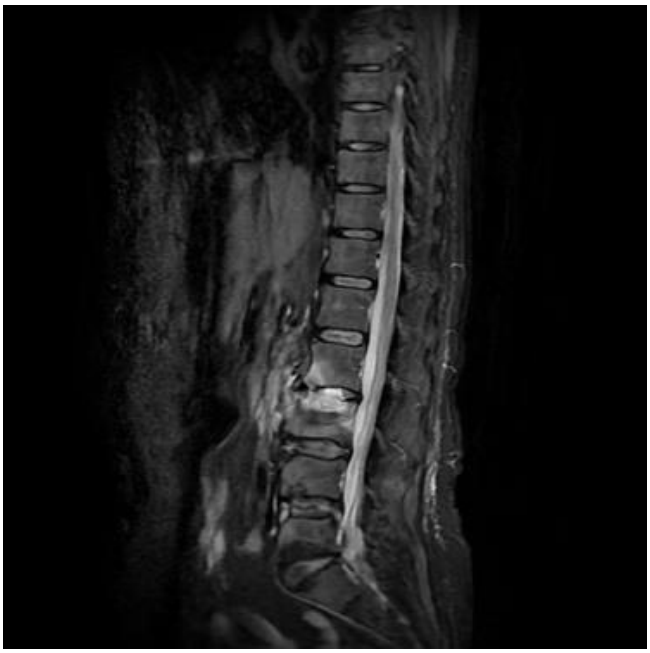

Figure 3. MRI image showing spondylodiscitis at the L3–L4 level with adjacent abscess formation.

As granulomatous inflammation is also present in sarcoidosis and fungal infections, histopathological findings used for diagnosing TB should be interpreted in conjunction with microbiological and molecular analyses. The prevalence of granulomatous inflammation varies among studies. For example, Wilmink et al. reported a rate of 86.8%, whereas Cuong et al. reported rates of 47.7% for granulomatous inflammation and 75.5% for caseous necrosis.[6,21] In our study, granulomatous inflammation was detected in 24 of 38 patients (63.2%) who underwent pathological examination, and caseous necrosis was detected in 14 patients (36.8%). Furthermore, the diagnostic performance of histopathological examination depends on the sampling technique and the anatomical region. One reason for the relatively low rate of histopathological confirmation in clinical patients may be the inability to determine the exact location of the lesion during the procedure.[22]

A negative kappa coefficient was observed between PCR and culture, indicating poor agreement and marked discordance between the methods. Our findings suggest that molecular testing is more effective for diagnosing certain tissue types, whereas culture yields are higher for others. These results reinforce the idea that no single test is sufficient for EPTB and support the need for an integrated multimodal diagnostic approach to improve diagnostic accuracy.

In our cohort, radiological assessments included CT and MRI scans. Imaging revealed pathological findings in 30 of 34 patients (88.2%), with lymphadenopathy being the most common finding (n=10). These findings are consistent with contemporary reviews of EPTB, which identified lymph nodes as the most frequently affected sites. The literature also notes that vertebral disease often coexists with adjacent abscesses.[23] Our study observed the same pattern in our cohort.

The limitations of our study include its retrospective design, data loss due to the study period coinciding with the COVID-19 pandemic, and the inability to access interferon-gamma release assay (IGRA) and tuberculin skin test results, as these were mostly performed at external centers. Additionally, the limited sample size prevented subgroup analyses based on the sample type. Therefore, the results should be interpreted with caution, and the generalizability of our findings to the broader population of patients with EPTB may be limited.

The strengths of this study include the coverage of the 2018–2025 period, which allows for broader assessment. A high case detection rate is thought to have been achieved in a tertiary referral center in a densely populated province. Tissue or sterile body fluid was obtained through invasive procedures, and histopathological examination was performed in all patients except those with urine samples. Notably, despite the challenges introduced by the pandemic, laboratory testing operations remained uninterrupted with no significant alterations to the established testing methodologies.

In this single-center EPTB cohort, molecular tests and other diagnostic methods revealed negative kappa values, indicating clear discordance. Histopathological examination revealed common granulomatous inflammation but less frequent caseous necrosis, which is a stronger indicator of TB. The imaging findings were consistent with those of recent studies. These results support a multimodal diagnostic strategy that combines microbiology, molecular testing, histopathology, and imaging to maximize diagnostic yield.

Acknowledgements

The abrupt passing of our colleague and friend Emel Azak continues to affect us. We respectfully remember and acknowledge her memory. We also acknowledge Associate Professor Dr. Sibel Balcı from Kocaeli University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Kocaeli, Turkey for the statistical analysis of the data.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Compliance of Ethical Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and appropriate ethical review committee approval has been received. This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association, revised in 2013, for experiments involving humans and with the protocols of the Ethics Committee of the Kocaeli University Faculty of Medicine. The project was assigned the number 2025/302 and received approval under the code GOKAEK-2025/13/15.

Consent to participate: The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers. All data were anonymized.

Financial Support

The authors declare that this research did not receive any financial support from any funding agency in public, commercial, or not-for-profit organizations.

Data Availability

The authors will share the data and materials via e-mail upon request.

Author Contributions

Ö.G.: Hypothesis; Ö.G.: Design; Z.A., S.H.Ö., M.T.D.: Data collection; Ö.G.: Literature review; M.S., S.A.: Analysis and interpretation of results; Ö.G.: Writing; M.S., S.A.: Critical review; Ö.G.: Publishing process.

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