

## Original Article



# Underutilization of Bacteriological Testing in Extrapulmonary Tuberculosis: A Retrospective Single-center Study from Mardin, Türkiye

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## ABSTRACT

**OBJECTIVE:** Extrapulmonary tuberculosis (EPTB) poses diagnostic challenges due to the low bacillus burden of the disease and the limited use of bacteriological tests. The aim of this study was to evaluate bacteriological confirmation rates, diagnostic methods, and sampling practices among patients diagnosed with tuberculosis (TB) in a southeastern province of Türkiye.

**MATERIAL AND METHODS:** This retrospective study included a total of 456 TB cases diagnosed between 2014 and 2019. The cases were classified as pulmonary tuberculosis (PTB), EPTB, and cases with both types of involvement. Bacteriological and histopathological confirmation rates were compared between the groups.

**RESULTS:** 41.0% of all cases were classified as EPTB. The most commonly involved site was lymph node TB (22.4%). Bacteriological confirmation rates were significantly lower in EPTB cases: acid-fast bacilli (AFB) smear positivity was 3.2% and culture positivity was 4.3%, whereas the histopathological confirmation rate was 88.8%. No bacteriological samples were taken from 63.1% of patients in the EPTB group. Among PTB cases, AFB smear positivity (71.4%) and culture positivity (66.5%) were significantly higher ( $P < 0.001$ ).

**CONCLUSION:** The findings suggest that bacteriological tests are both underused and of low diagnostic efficiency in EPTB cases. Most diagnoses are based on histopathology rather than on bacteriological confirmation. Strengthening sampling strategies and promoting the use of rapid molecular testing are critical for enhancing bacteriological validation in EPTB.

**KEYWORDS:** Tuberculosis, extrapulmonary tuberculosis, bacteriological confirmation, culture, AFB (acid-fast bacilli), histopathology

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## INTRODUCTION

Tuberculosis (TB) remains among the leading infectious diseases, with approximately 10.8 million new cases and 1.25 million deaths worldwide in 2023, according to data from the World Health Organization's Global Tuberculosis Report 2024. In line with the objectives of the "End TB Strategy", the main component of TB control programs is bacteriological confirmation of TB. This confirmation, conducted using smear microscopy, culture, and molecular methods, not only ensures a definitive diagnosis but is also critical for identifying drug resistance, selecting the appropriate treatment regimen, and guiding public health policies.<sup>1,2</sup>

However, bacteriological confirmation rates, especially in extrapulmonary tuberculosis (EPTB) cases, are well below the desired level worldwide. This deficiency reduces the reliability of clinical decision-making processes and hinders the early diagnosis of resistant strains, posing serious risks to public health.

While molecular and culture-based diagnostic methods have been integrated into routine clinical practice in developed countries, limited use of bacteriological methods for EPTB cases in many developing countries creates an important diagnostic gap.<sup>3-5</sup>

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This study was conducted to examine the use of bacteriological methods for the diagnosis of TB and to identify existing deficiencies.

## MATERIAL AND METHODS

A total of 456 patients diagnosed with TB between 2014 and 2019 were included in this retrospective, single-center study. The data were obtained from TB treatment records. Due to the extraordinary conditions affecting diagnosis and reporting during the coronavirus disease-2019 pandemic, data from 2020 onward were excluded. Therefore, the study period covered January 2014 to December 2019.

TB case classifications and terminology were based on the World Health Organization (WHO) diagnostic and classification standards.<sup>6</sup> Sites of disease involvement were classified according to WHO definitions and categorized into 11 sites: pulmonary tuberculosis (PTB) (lung parenchyma) and 10 extrapulmonary sites (pleura, lymph nodes, peritoneum, bone and joint, genitourinary system, skin, meninges, pericardium, breast, and other extrapulmonary sites such as sialoadenitis, liver, and psoas abscess).

### Based on the Site of Involvement, Patients were Classified Into Three Diagnostic Groups

1. PTB: Cases with involvement limited to lung parenchyma.
2. EPTB: Cases with involvement of one or more extrapulmonary organs without lung parenchymal involvement.
3. PTB + EPTB: Cases with both pulmonary and extrapulmonary involvement.

This classification was used to compare the diagnostic efficiency of different methods, including acid-fast bacilli (AFB) smear, culture, and histopathological examination, across groups.

Demographic and clinical variables recorded for analysis included age, sex, presence of Bacille Calmette-Guérin (BCG) scar, case definition, histopathological diagnosis, AFB smear results, type of microbiological specimen, mycobacterial culture results, drug resistance status, and treatment outcomes.

#### Main Points

- Low bacteriological confirmation in extrapulmonary tuberculosis (EPTB): bacteriological tests (acid-fast bacilli smear and culture) for EPTB are significantly underutilized, with positivity rates of only 3.2% and 4.3%, respectively.
- Histopathology as the primary diagnostic tool: the diagnosis of EPTB relies predominantly on histopathological findings (88.8%), indicating gaps in microbiological sampling and diagnostic algorithms.
- Need for improved sampling and molecular testing: strengthening sampling strategies and expanding rapid molecular diagnostic methods are essential to increase bacteriological confirmation rates and enhance diagnostic efficiency in EPTB.

## Ethical Approval

The study was approved by the Mardin Artuklu University Ethics Committee (approval number: 2025/10-3, date: 07.10.2025), and all procedures were conducted in accordance with the principles of the Declaration of Helsinki (1975; revised 2008). Informed consent was obtained from all participants.

## Statistical Analysis

Statistical analysis of the data was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Fisher's exact test was used for comparisons of positivity rates of diagnostic methods and sample materials between groups. Categorical variables were expressed as frequency (n) and percentage (%), and continuous variables were expressed as mean  $\pm$  standard deviation or median (minimum-maximum). The statistical significance level was set at  $P < 0.05$ .

## RESULTS

A total of 456 patients diagnosed with TB between 2014 and 2019 were included in the study. Of these patients, 229 (50.2%) were male and 227 (49.8%) were female. Most cases (n = 400, 87.7%) were newly diagnosed. A BCG scar was present in 423 patients (92.8%) (Table 1).

PTB was the most frequent form of the disease, observed in 248 patients (54.4%). EPTB was identified in 187 patients (41.0%), while combined pulmonary and extrapulmonary involvement was detected in 21 patients (4.6%). Among extrapulmonary cases, lymph node TB was the most common site of involvement, accounting for 102 patients (22.4%).

Treatment outcomes showed that 413 patients (90.6%) successfully completed treatment or were cured. Loss to follow-up occurred in 10 patients (2.2%), and treatment failure

**Table 1.** General distribution and clinical characteristics of the patient population (n = 456)

Features	Category	n	%
Sex	Female	227	49.8
	Male	229	50.2
Disease involvement site	PTB	248	54.4
	EPTB	187	41.0
	Both PTB and EPTB	21	4.6
Case definitions	New case	400	87.7
	Relapse	19	4.2
	Treatment after failure	2	0.4
	Treatment after loss to follow-up	2	0.4
	Transfer-in	33	7.2
BCG scar	Present	423	92.8
	Absent	33	7.2

Percentages (%) were calculated over the total number of cases (n = 456)

PTB: pulmonary tuberculosis, EPTB: extrapulmonary tuberculosis, BCG: Bacille Calmette-Guérin

was observed in 3 patients (0.7%). At least one major drug-resistance mutation was detected in 28 patients (6.1%).

The positivity rates of diagnostic methods differed by the site of TB involvement (Table 2). AFB smear positivity was high in patients with PTB (71.4%) but markedly lower in those with predominant extrapulmonary involvement (3.2%). Similarly, culture positivity was higher in PTB cases (66.5%) and remained relatively high in patients with combined pulmonary and extrapulmonary disease (61.9%).

In contrast, EPTB was predominantly diagnosed by histopathological examination, with a diagnostic yield of 88.8%. Microbiological confirmation in extrapulmonary cases was limited, with AFB smear and culture positivity rates remaining below 5%.

Microbiological specimen selection varied substantially according to the site of disease involvement (Table 3). In the EPTB group, microbiological sampling and culture were performed in a limited proportion of cases, with no microbiological testing conducted in 63.1% of patients, indicating a substantial underutilization of bacteriological testing in EPTB. Consequently, culture-based positivity rates could be assessed only in a restricted subset of extrapulmonary cases. Among patients with PTB, sputum was the primary diagnostic specimen, obtained from 88.3% of patients, whereas bronchoalveolar lavage was used in a minority (6.5%). Microbiological testing was not performed or was not available in only 0.8% of PTB cases.

In EPTB, microbiological testing was not performed or was not available in a large proportion (63.1%) of patients. Specimens obtained through invasive procedures, such as lymph node aspiration or tissue and bone biopsies showed very low rates of microbiological positivity, indicating that diagnosis in these cases was based mainly on histopathological findings. Among microbiological samples, pleural fluid and other sterile-site specimens were the most frequently collected.

In patients with combined pulmonary and extrapulmonary involvement, sputum specimens were commonly used (71.4%) because of pulmonary disease.

### DISCUSSION

In this study, 456 TB cases diagnosed between 2014 and 2019 were evaluated. The findings indicate that bacteriological confirmation in the diagnosis of EPTB remains limited. While AFB smear and culture positivity rates were relatively high in PTB, these methods showed a substantially lower diagnostic yield in extrapulmonary disease. In addition, the absence of microbiological sampling in a considerable proportion of EPTB cases points to important gaps in diagnostic algorithms at the regional level.

Although sputum smear microscopy and clinical or radiological findings are generally useful in PTB, biopsy and histopathological examination are often required to establish a diagnosis in EPTB. *Mycobacterium tuberculosis* culture is widely accepted as the gold standard for definitive diagnosis; however, its diagnostic yield is frequently reduced in EPTB because of the

**Table 2.** Comparison of positivity rates of diagnostic methods and 95% confidence interval in different tuberculosis involvement groups (n = 456)

Diagnostic method	Group 1: lung TB (n = 248)	Group 2: extrapulmonary TB (n = 187)	Group 3: both (pulmonary + extrapulmonary TB) (n = 21)	P value (Fisher's exact test)
AFB smear positivity	71.4% (95% CI: 65.5–76.6)	3.2% (95% CI: 1.4–6.8)	38.1% (95% CI: 19.8–60.1)	<0.001
Histopathological diagnosis positivity	2.4% (95% CI: 1.1–5.2)	88.8% (95% CI: 83.3–92.7)	71.4% (95% CI: 50.4–86.1)	<0.001
Culture positivity	66.5% (95% CI: 60.6–72.0)	4.3% (95% CI: 2.1–8.3)	61.9% (95% CI: 40.0–79.9)	<0.001

Percentages (%) were calculated based on the total number of cases in the relevant group. Ninety-five percent confidence intervals (95% CI) were calculated using the Wilson score method  
 AFB: acid-fast bacilli, TB: tuberculosis, CI: confidence interval

**Table 3.** Distribution of microbiological sample material by tuberculosis involvement groups (n = 456)

Sample material	Group 1: lung TB (n = 248)	Group 2: extrapulmonary TB (n = 187)	Group 3: both (n = 21)	P value (Fisher's exact test)
Sputum	88.3% (CI: 83.7–91.7)	20.9% (CI: 15.6–27.2)	71.4% (CI: 50.4–86.1)	<0.001
Bronchoalveolar lavage	6.5% (CI: 3.8–10.7)	0.0% (CI: 0.0–2.0)	4.8% (CI: 0.8–20.8)	<0.001
Pleural fluid	0.4% (CI: 0.1–2.4)	8.6% (CI: 5.1–13.9)	4.8% (CI: 0.8–20.8)	<0.001
Peritoneal/abdominal fluid	0.0% (CI: 0.0–1.5)	2.7% (CI: 1.1–6.4)	0.0% (CI: 0.0–16.1)	<0.001
Lymph node aspiration/biopsy	0.0% (CI: 0.0–1.5)	0.5% (CI: 0.1–3.0)	0.0% (CI: 0.0–16.1)	<0.001
Biopsy/bone tissue	0.0% (CI: 0.0–1.5)	1.1% (CI: 0.3–4.0)	0.0% (CI: 0.0–16.1)	<0.001
No test/not tested	0.8% (CI: 0.2–3.2)	63.1% (CI: 55.9–69.8)	14.3% (CI: 4.8–36.3)	<0.001
Other	4.0% (CI: 2.1–7.5)	15.0% (CI: 10.5–20.8)	9.5% (CI: 2.6–28.5)	<0.001

Percentages (%) were calculated based on the total number of cases in the relevant group. Ninety-five percent confidence intervals (95% CI) were calculated using the Wilson score method  
 TB: tuberculosis, CI: confidence interval

paucibacillary nature of the disease and limitations related to specimen acquisition and processing.<sup>7</sup>

WHO has emphasized bacteriological confirmation as a key component of TB control strategies and has recommended the widest possible use of microscopy, culture, and molecular diagnostic methods.<sup>1</sup> Despite these recommendations, bacteriological diagnosis remains challenging worldwide, particularly in EPTB. In a large multicenter meta-analysis conducted by Diriba et al.<sup>3</sup>, the pooled bacteriological confirmation rate in EPTB was reported as 43%, with substantial heterogeneity across studies, even among developing countries.

Comparative data from different regions further illustrate this variability. Wilmink et al.<sup>8</sup> reported considerably higher bacteriological confirmation rates among EPTB cases at a tertiary care center in Germany with high laboratory capacity, highlighting the role of infrastructure and diagnostic resources in improving microbiological yield. In contrast, studies from developing countries report lower confirmation rates. Mbuh et al.<sup>9</sup> demonstrated that bacteriological confirmation of EPTB could be improved under field conditions if adequate laboratory infrastructure is available, although diagnostic heterogeneity persists due to insufficient sampling and the limitations of invasive procedures.

Similarly, Pang et al.<sup>10</sup> reported low culture confirmation rates among EPTB cases in a large epidemiological study from China, with marked variation according to the site of disease involvement. These findings indicate that microbiological confirmation is particularly challenging in lymph node and meningeal forms of TB, for which diagnostic sensitivity is lowest.<sup>10</sup>

Recent advances in molecular diagnostic techniques represent a significant development in the diagnosis of EPTB. Sharma et al.<sup>4</sup> reported that next-generation molecular tests, including GeneXpert and related platforms, have improved diagnostic sensitivity in extrapulmonary specimens despite the intrinsic limitations of conventional microbiological methods. Nevertheless, the effective use of these technologies remains highly dependent on appropriate specimen selection and adequate laboratory infrastructure.<sup>4</sup> In this context, comprehensive clinical evaluation and imaging modalities—such as ultrasonography, contrast-enhanced computed tomography, magnetic resonance imaging, and positron emission tomography—continue to play a critical role in guiding accurate diagnosis and sampling strategies.<sup>4</sup>

Data from Türkiye are consistent with the global literature and demonstrate persistent limitations in bacteriological confirmation of EPTB. Previous studies have reported wide variability in confirmation rates, with diagnoses frequently relying on histopathological evidence rather than on microbiological testing.<sup>11,12</sup> A multicenter study conducted between 2010 and 2014 similarly showed that histopathological methods constituted the primary diagnostic approach in EPTB, while microbiological confirmation was achieved in only a minority of cases.<sup>13</sup>

Taken together, these findings suggest that microbiological confirmation in EPTB remains suboptimal and is strongly

influenced by regional laboratory capacity, sampling practices, and access to advanced diagnostic techniques. The predominance of histopathology-based diagnosis and the limited use of bacteriological testing restrict early detection of drug-resistant strains and hinder optimization of treatment strategies. Addressing these challenges will require improved coordination between clinical and laboratory services, standardized sampling protocols, and broader implementation of rapid molecular diagnostic methods to strengthen TB control efforts.

### Study Limitations

This study has certain limitations. First, it was designed as a retrospective analysis; the data were obtained from medical records. This may have led to an incomplete assessment of some variables due to missing or non-standardized documentation. Because the study was conducted at a single center, the generalizability of the findings is limited.

### CONCLUSION

In conclusion, our study demonstrates that the insufficiency of bacteriological diagnosis in EPTB remains a significant challenge. Histopathological methods frequently substitute for microbiological confirmation, and systematic sampling practices are often inadequate. The low rate of bacteriological testing observed in EPTB cases may be partly due to patients being often first evaluated in non-pulmonary specialties. Increasing awareness of TB diagnostic methods among physicians in these disciplines may therefore contribute to improving bacteriological confirmation rates. Overall, these findings underscore the need to standardize sampling strategies and to expand access to rapid molecular diagnostics. Strengthening sampling protocols, scaling up molecular testing capacity, and enhancing laboratory infrastructure should be prioritized to improve bacteriological confirmation and support progress toward the WHO “End TB” targets.

### Ethics

**Ethics Committee Approval:** The study was approved by the Mardin Artuklu University Ethics Committee (approval number: 2025/10-3, date: 07.10.2025), and all procedures were conducted in accordance with the principles of the Declaration of Helsinki (1975; revised 2008).

**Informed Consent:** Informed consent was obtained from all participants.

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### Footnotes

### Authorship Contributions

Concept: B.Ç., M.S.B., Design: B.Ç., M.S.B., Data Collection or Processing: B.Ç., Analysis or Interpretation: B.Ç., M.S.B., M.K., Literature Search: M.S.B., Writing: B.Ç., M.K.,

**Conflict of Interest:** No conflict of interest was declared by the authors.

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