Research Article / Araştırma Makalesi

J Ankara Univ Fac Med 2025;78(3):227-238
DOI: 10.65092/autfm.1722836

Patterns of Organ Involvement and Mortality in Extrapulmonary Tuberculosis: A Twelve-Year Retrospective Study

Tüberkülozda Organ Tutulum ve Mortalite Modelleri: On İki Yıllık Retrospektif Çalışma

Halime Araz[1], Saliha Kazcı[2], Fatma Eser[3], Adalet Altunsoy[4]

1 Department of Infectious Disease and Clinical Microbiology, Ankara Bilkent City Hospital, Ankara, Turkey
2 Department of Clinical Microbiology, Ankara Bilkent City Hospital, Ankara, Turkey
3 Department of Infectious Disease and Clinical Microbiology, Ankara Bilkent City Hospital, Ankara Yildirim Beyazit University, Ankara, Turkey
4 Department of Infectious Disease and Clinical Microbiology, Ankara Bilkent City Hospital, University of Health Sciences, Ankara, Turkey

ABSTRACT

Background: Extrapulmonary tuberculosis (EPTB) constitutes a significant proportion of the tuberculosis (TB) burden and has diagnostically challenging manifestations. This study aimed to evaluate the demographic, clinical, diagnostic, and treatment characteristics of adult patients with EPTB in a tertiary care setting in Türkiye.

Methods: This retrospective cohort study included adult patients (≥18 years) diagnosed with EPTB between June 2010 and March 2022 at two tertiary hospitals in Ankara, Türkiye.Demographic, clinical, diagnostic, treatment, and outcome data were also collected.Comparative analyses between survivors and non-survivors were performed using the chi-square test, Fisher's exact test, and Mann–Whitney U test, with significance set at $p < 0.05$.

Results: Ninety-three patients were included (51.6% men; median age, 55 y).The most frequent sites of involvement were the vertebral bones and joints (32.3%), lymph nodes (26.9%), and central nervous system (16.1%).Histopathological confirmation was obtained in 60.2% of patients, culture positivity in 30.1% of patients, and PCR positivity in 31.2% of patients.Standard quadruple anti-TB therapy was initiated in 95.7% of the cases, with a median total treatment duration of 6 months (range, 1–13 months).Surgical intervention was required in 22.6% of the patients.During the follow-up period, 9 patients (9.7%) died.Immunosuppressive conditions were significantly more frequent among non-survivors than among survivors (44.4% vs. 11.9%, $p = 0.027$).The median duration of dual therapy (1 vs. 4 months, $p < 0.001$) and total therapy (3 vs. 6 months, $p < 0.001$) were significantly shorter in non-survivors.

Conclusions: Adult EPTB presents with diverse and often severe manifestations.Vertebral and central nervous system involvement predominated in this tertiary-care cohort.Mortality was associated with immunosuppression and shorter treatment duration.Comprehensive diagnostic strategies and tailored management of high-risk patients are essential to improve outcomes in EPTB.

Keywords: Extrapulmonary tuberculosis; spinal TB; TB meningitis; histopathology; mortality

ÖZET

Giriş: Ekstrapulmoner tüberküloz (EPTB), küresel tüberküloz yükünün artan bir kısmını oluşturmaktadır ve Türkiye dâhil birçok ülkede insidansı yükselmektedir. Bu çalışmada, üçüncü basamak bir sağlık kuruluşunda EPTB tanısı alan erişkin hastaların demografik, klinik, tanısal ve tedaviye ilişkin özelliklerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Bu retrospektif kohort çalışmaya, Haziran 2010 – Mart 2022 tarihleri arasında Ankara'daki iki üçüncü basamak hastanede EPTB tanısı alan 18 yaş ve üzeri erişkin hastalar dâhil edilmiştir. Tanımlayıcı ve karşılaştırmalı istatistiksel analizler yapılmıştır.

Bulgular: Toplam 93 hasta dâhil edilmiştir (%51,6 erkek; medyan yaş: 55 yıl). En sık tutulan bölgeler omurga/eklemler (%32,3), lenf nodları (%26,9) ve merkezi sinir sistemi (%16,1) idi. Histopatolojik doğrulama %60,2, kültür pozitifliği %30,1, PCR pozitifliği %31,2 oranında sağlandı. AFB boyası %25,8 pozitifti. İlaç duyarlılık testi %27,9 hastada yapılmış ve iki olguda direnç saptanmıştır. Hastaların %95,7'sine standart dörtlü anti-TB tedavisi uygulanmış, medyan tedavi süresi 6 ay (1–13 ay) idi. %22,6 hastada cerrahi müdahale gerekmiştir. Takipte 9 hasta (%9,7) hayatını kaybetti. Bağışıklık baskılanması ölenlerde anlamlı düzeyde daha fazlaydı (%44,4 vs. %11,9, $p = 0,027$) ve bu hastalarda tedavi süresi daha kısaydı ($p < 0,001$).

Sonuç: EPTB erişkinlerde ciddi tablolarla seyredebilir. Vertebra ve merkezi sinir sistemi tutulumu sık olup, tanıda histopatoloji belirleyicidir. Bağışıklık baskılanması ve yetersiz tedavi süresi mortaliteyle ilişkilidir. Erken tanı ve bireyselleştirilmiş tedavi yaklaşımları önem taşımaktadır.

Anahtar kelimeler: Ekstrapulmoner tüberküloz, spinal TB, TB menenjiti, mortalite, histopatoloji

Corresponding author: Halime Araz
Ankara Bilkent City Hospital, Üniversiteler Mah. Bilkent Cad. No:1 Çankaya/Ankara/Turkey
E-mail: halimecavlak@gmail.com **ORCID ID:** 0000-0003-4774-5950
Received: 23.06.2025 **Accepted:** 23.09.2025 **Publication Date:** 30.09.2025
Cite this article as: Araz, H., Kazcı, S., et. al., Patterns of organ involvement and mortality in extrapulmonary tuberculosis: a twelve-year retrospective study. *J Ankara Univ Fac Med*. 2025;78(3):227-238

Copyright© 2025 The Author. Published by Ankara University Press on behalf of Ankara University Faculty of Medicine .
This is an open access article under the Creative Commons AttributionNonCommercial 4.0 International (CC BY-NC 4.0) License.

Introduction

Despite being preventable and curable, tuberculosis (TB) remains a significant global health challenge and ranks among the top causes of death worldwide. According to World Health Organization (WHO), approximately 10.6 million individuals fell ill with TB in 2021, resulting in 1.6 million deaths, including 187,000 among people with Human Immunodeficiency Virus (HIV) (1, 2). According to the 2024 WHO Global Tuberculosis Report, TB remains the second leading infectious killer worldwide, with approximately 10.8 million new cases and 1.25 million deaths in 2023(3).Although pulmonary tuberculosis (PTB) is the most common form, extrapulmonary tuberculosis (EPTB), characterized by Mycobacterium tuberculosis infection outside the lung parenchyma, accounts for a substantial disease burden and presents unique clinical, diagnostic, and therapeutic challenges (4, 5).EPTB may involve any organ system, with the lymph nodes, pleura, bones, meninges, genitourinary tract, and gastrointestinal system being the commonly affected sites (6).The disease is insidious in onset and heterogeneous in presentation, often mimicking other conditions, leading to diagnostic delays and deferred treatment (7).Unlike PTB, which relies on sputum-based diagnostics, EPTB requires invasive procedures, histopathological confirmation, and advanced imaging, particularly when microbiological evidence is limited (8).The relative proportion of EPTB among patients with TB has increased in multiple settings, including high-burden countries and industrialized regions.This shift has been attributed to improved pulmonary TB control, better access to imaging, increased awareness of EPTB manifestations, and the rising prevalence of immunosuppressive conditions such as HIV infection, malignancies, and immunomodulatory therapies (9, 10).Data from the Turkish Ministry of Health show that extrapulmonary involvement accounts for over one-third of new TB cases, with lymphadenitis and pleural and skeletal system involvement being the most common (11-13).

Given the heterogeneity of EPTB and the paucity of long-term institutional data in Türkiye, we conducted a 12-year retrospective cohort study of adult patients with extrapulmonary tuberculosis across two tertiary hospitals. The primary objective was to characterize the demographic and clinical features, diagnostic modalities, and treatment strategies, with a particular focus on organ-specific patterns and factors associated with mortality.This study is expected to contribute to the evidence base needed for improved diagnostic and therapeutic strategies in similar, high-burden healthcare settings.

Materials and Methods

Study Design and Setting

This retrospective observational study was conducted at two tertiary care centers in Turkey. Adult patients (aged ≥18 years) diagnosed with EPTB between June 2010 and March 2022 were included. The study population consisted of patients evaluated at the Infectious Diseases and Clinical Microbiology outpatient clinics and inpatient services of Ankara Numune Training and Research Hospital (June 2014 – May 2019) and Ankara Bilkent City Hospital (June 2019 – March 2022).

Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they had a clinical, histopathological, or microbiological diagnosis of EPTB, defined as a TB infection involving anatomical sites other than the lung parenchyma.Patients with isolated pulmonary TB or concomitant pulmonary and extrapulmonary involvement were excluded unless the extrapulmonary manifestations were the primary diagnostic component.Only cases with complete clinical and diagnostic records were included in the study.

Data Collection

Patient data were obtained from the institutional electronic medical record systems (FONET® and HICAMP®) and the national MEDULLA physician platform. The following parameters were collected: demographics (age, sex, nationality, and province of residence).Medical history: presence of comorbidities (diabetes mellitus, malignancy, cardiovascular disease, chronic kidney disease, and HIV), immunosuppressive conditions, and family history of TB.Diagnostic methods: Purified Protein Derivative (PPD), interferon-gamma release assay (IGRA),

acid-fast bacilli (AFB) smear, TB polymerase chain reaction (PCR), culture, and histopathology results. Site of involvement: classified by organ system involvement (lymph nodes, central nervous system, peritoneum, bone and joints, skin, and genitourinary tract).Treatment data included standard first- or second-line anti-TB regimens, treatment duration, surgical intervention, and resistance testing. All included patients were newly diagnosed with extrapulmonary tuberculosis and had no prior history of TB.Immunosuppression was defined as the presence of HIV infection, ongoing chemotherapy, long-term corticosteroid use (>20 mg/day prednisone equivalent for >4 weeks), or treatment with other immunosuppressive drugs (methotrexate, cyclosporine, and biologics).Mortality was defined as all-cause mortality during hospitalization or follow-up, regardless of the direct attribution of TB.

Ethical Approval

The study protocol was approved by the Ethics Committee of Ankara Bilkent City Hospital (Decision No: E2-22-1952, Date: 08/06/2022). This study was conducted in accordance with the Declaration of Hel-

Table 1. Demographic and Clinical Characteristics of the Patients Diagnosed with Extrapulmonary Tuberculosis

Parameter	n (%)
Sex	
– Male	48 (51.61)
– Female	45 (48.39)
Age, Median (Min–Max)/Mean ± SD	55 (18–88) (52.20 ± 18.90)
Nationality	
– Turkish citizen	84 (90.32)
– Foreign national	9 (9.68)
Place of residence	
– Ankara	56 (60.22)
– Outside Ankara	37 (39.78)
Family history of tuberculosis	
– Absent	85 (91.40)
– Present	6 (6.45)
– Unknown	2 (2.15)
Comorbidity status	
– No comorbidity	52 (55.91)
– At least one comorbidity	41 (44.09)
• Diabetes mellitus	17 (18.28)
• Malignancy	12 (12.90)
• Cardiovascular disease	20 (21.51)
• Chronic kidney disease	3 (3.23)
• HIV infection	2 (2.15)
Immunosuppression	
– Absent	79 (84.95)
– Present	14 (15.05)

SD: Standard deviation. HIV: Human immunodeficiency virus. Percentages are column percentages, unless otherwise specified.

Table 2. Diagnostic Evaluation of Patients with Extrapulmonary Tuberculosis

Diagnostic Parameter	n (%)
PPD	
– Negative	35 (37.63)
– Positive	58 (62.37)
IGRA	
– Negative	14 (15.05)
– Positive	38 (40.86)
– Not performed	41 (44.09)
Acid-Fast Bacilli Smear	
– Negative	51 (54.84)
– Positive	24 (25.81)
– Not performed	18 (19.35)
TB PCR	
– Negative	22 (23.66)
– Positive	29 (31.18)
– Not performed	42 (45.16)
Histopathology	
– Compatible with TB	56 (60.22)
– Not compatible with TB	3 (3.23)
– Not available	34 (36.56)
Culture	
– Negative	40 (43.01)
– Positive	28 (30.11)
– Not performed	25 (26.88)
Diagnostic approach	
– Diagnosis prior to treatment	61 (65.59)
– Diagnosis confirmed after treatment initiation	32 (34.41)

PPD: purified protein derivative; IGRA: interferon-gamma release assay; AFB: acid-fast bacilli; PCR: polymerase chain reaction.The percentages represent the proportion of total patients (n = 93).

sinki and the institutional data protection regulations.The need for individual informed consent was waived because of the retrospective nature of the study.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 20.0 (Armonk, NY: IBM Corp).Continuous variables are expressed as mean ± standard deviation (SD) and median (minimum–maximum), depending on the distribution. Categorical variables are presented as frequencies and percentages.

Table 3. Distribution of Extrapulmonary Tuberculosis Sites of Involvement

Site of Involvement	n (%)
Vertebral bone and joint	30 (32.26)
Peripheral lymphadenitis (non-thoracic)	25 (26.88)
Meningitis	15 (16.13)
Peritoneal / gastrointestinal system	11 (11.83)
Genitourinary system	7 (7.53)
Cutaneous	3 (3.23)
Non-vertebral bone and joint	2 (2.15)

Percentages are based on the total number of patients (n = 93). A single patient may present with more than one site of involvement, although primary sites are prioritized for treatment.

Comparisons between survivors and non-survivors were performed using the chi-square or Fisher's exact test for categorical variables and independent-samples t-test or Mann–Whitney U test for continuous variables, depending on the distribution. Statistical significance was set at $p < 0.05$.

Results

A total of 93 adult patients were included, comprising 48 men (51.6%) and 45 women (48.4%), with a median age of 55 years (range, 18–88 years).Most patients were Turkish citizens (90.3%), while nine (9.7%) were foreign nationals (six Syrian, two Afghan, and one Iraqi). Comorbidities were present in 44.1% of patients, most frequently cardiovascular disease (21.5%) and diabetes mellitus (18.3%). Immunosuppression was documented in 15.1% of the cases (Table 1).

Diagnostic evaluation revealed a positive PPD result in 62.4% of patients and a positive IGRA result in 40.9% of patients.The AFB smear, TB PCR, and culture positivity rates were 25.8 %, 31.2%, and 30.1 %, respectively.Histopathological confirmation was obtained in 60.2% of the cases.The diagnosis was established before treatment initiation in 65.6% of patients (Table 2).

The most common sites of involvement were the vertebral bones and joints (32.3%), lymph nodes (26.9%), and central nervous system (16.1%).Less frequent sites included the peritoneal/gastrointestinal (11.8%), genitourinary (7.5%), cutaneous (3.2%), and non-vertebral skeletal (2.2%) localizations (Table 3).

First-line quadruple therapy was administered to 95.7% of the patients.The median duration of dual therapy was 4 months (range, 0–10 months), and the median total treatment duration was 6 months (range, 1–13 months).Surgical intervention was performed in 22.6% of the cases.Drug susceptibility testing was performed in 27.9% of patients, of whom 2.2% showed resistance (Table 4).

During the follow-up period, 9 patients (9.7%) died. No significant differences between survivors and non-survivors were observed in age, sex, nationality, place of residence, family history of TB, AFB or culture positivity, or surgical intervention. Immunosuppression was significantly more frequent among non-survivors than among survivors (44.4% vs. 11.9%, $p = 0.027$).The median duration of dual therapy (1 vs. 4 months, $p < 0.001$) and total therapy (3 vs. 6 months, $p < 0.001$) were significantly shorter in non-survivors.No association with drug resistance was identified, although the subgroup numbers were small (Table 5).

Discussion

National and Global Perspectives Our 12-year retrospective cohort highlights the growing burden of EPTB in Turkey and worldwide. Globally, EPTB accounts for 15–20% of all tuberculosis cases(14). According to the WHO, 16% of the 7.1 million TB cases notified in 2019 were extrapulmonary, ranging

Table 4. Anti-Tuberculosis Treatment Characteristics and Drug Resistance Status

Treatment Parameter	n (%)
Initial anti-TB regimen	
– INH, RIF, PZ, ETB (first-line quadruple)	89 (95.70)
– Moxifloxacin, Cycloserine, ETB, Streptomycin	3 (3.23)
– INH, RIF, ETB, Streptomycin	1 (1.08)
Duration of quadruple therapy, Median (Min–Max)/ Mean ± SD	2 (1–3) (2.10 ± 0.30)
Duration of dual therapy, Median (Min–Max)/ Mean ± SD	4 (0–10) (5.40 ± 2.60)
Total treatment duration, Median (Min–Max)/ Mean ± SD	6 (1–13) (7.40 ± 2.80)
Surgical intervention	
– Not performed	72 (77.42)
– Performed	21 (22.58)
Drug susceptibility testing performed	
– Not performed	67 (72.04)
– Performed	26 (27.96)
• Susceptible	24 (25.81)
• Resistant	2 (2.15)

INH: Isoniazid; RIF: Rifampicin; PZ: Pyrazinamide; ETB: Ethambutol. SD: Standard deviation. The duration values are expressed in months.

from 8% in the Western Pacific to 24% in the Eastern Mediterranean (15). In high-income, low-incidence settings, the proportion is higher; EPTB constitutes 27% of TB cases in the United States and 38% in the Netherlands(14). Turkey has one of the highest EPTB proportions; before the COVID-19 pandemic, over one-third of Turkish TB cases were extrapulmonary. National data show that the share rising from 28.6% in 2005 to 35–36% by 2018(15).Ulusoy et al. reported that immunosuppressive medication use was significantly more frequent among patients with PTB than among those with EPTB in a Turkish cohort (16).

Recent data show that this proportion increased to 41.6% in 2020, with 3,710 extrapulmonary cases among 8,925 new TB cases(17).This increase is partly due to the declining pulmonary TB notifications during the pandemic and better EPTB recognition. Improvements in pulmonary TB control have left a larger fraction of TB presenting at extrapulmonary sites(15). The rise in immunosuppressive comorbidities also contributes to the changing epidemiology. Our cohort reflects these trends: EPTB remains significant, with median patient age in the sixth decade and nearly equal sex distribution. Unlike pulmonary TB's male predominance, many EPTB series show a balanced sex ratio, as European studies noted women and older adults at higher risk for EPTB(15). The epidemiological profile of our patients aligns with national data and shows EPTB increasing where overall TB incidence is declining(15). This emphasizes the need for continued vigilance for extrapulmonary TB under national programs as we strive to meet End TB targets amid the COVID-19 pandemic.

Patterns of Organ Involvement and Clinical Comparisons

The spectrum of organ involvement in our 93 patients demonstrated both concordance with and distinctive differences from patterns reported in the literature.In

Table 5. Comparison of Demographic and Clinical Characteristics Between Survivors and Non-Survivors

	Parameter	Survivors	Non-survivors 9)	p
Sex	Male	43 (51.19)	5 (55.56)	1.000
	Female	41 (48.81)	4 (44.44)	
Age	Mean ± SD	51.40 ± 18.40	60.60 ± 22.10	0.096
	Median (Min–Max)	54 (18–88)	71 (22–82)	
Nationality	Turkish citizen	75 (89.29)	9 (100.00)	0.592
	Foreign national	9 (10.71)	0 (0.00)	
Place of residence	Ankara	52 (61.90)	4 (44.44)	0.475
	Outside Ankara	32 (38.10)	5 (55.56)	
Family history of TB (n = 91)	Absent	77 (91.67)	8 (88.89)	0.572
	Present	5 (6.00)	1 (11.11)	
Immunosuppressive condition	Absent	74 (88.10)	5 (55.56)	0.027
	Present	10 (11.90)	4 (44.44)	
AFB smear	Negative	48 (57.14)	3 (33.33)	0.201
	Positive	20 (23.81)	4 (44.44)	
Culture result	Negative	35 (41.67)	5 (55.56)	0.691
	Positive	26 (30.95)	2 (22.22)	
Site of involvement	Vertebral bone and joint	27 (32.14)	3 (33.33)	–
	Lymphadenitis	23 (27.38)	2 (22.22)	
	Meningitis	12 (14.29)	3 (33.33)	
	Peritoneal / GI system	11 (13.10)	0 (0.00)	
	Genitourinary system	7 (8.33)	0 (0.00)	
	Cutaneous	2 (2.38)	1 (11.11)	
	Non-vertebral bone and joint	2 (2.38)	0 (0.00)	
Initial anti-TB regimen	INH, RIF, PZ, ETB	80 (95.24)	9 (100.00)	–*
	Moxifloxacin, Cycloserine, ETB, SM	3 (3.57)	0 (0.00)	
	INH, RIF, ETB, SM	1 (1.19)	0 (0.00)	
Duration of quadruple therapy	Mean ± SD	2.10 ± 0.30	1.90 ± 0.60	0.108
	Median (Min–Max)	2 (2–3)	2 (1–3)	
Duration of dual therapy	Mean ± SD	5.80 ± 2.30	1.30 ± 1.70	<0.001
	Median (Min–Max)	4 (4–10)	1 (0–4)	
Total treatment duration	Mean ± SD	7.90 ± 2.40	3.20 ± 2.10	
	Median (Min–Max)	6 (6–13)	3 (1–7)	<0.001
Surgical intervention	Not performed	64 (76.19)	8 (88.89)	0.678
	Performed	20 (23.81)	1 (11.11)	
Drug resistance testing	Not performed	60 (71.43)	7 (77.78)	–*
	Performed	24 (28.57)	2 (22.22)	
	• Susceptible	22 (26.19)	2 (22.22)	
	• Resistant	2 (2.38)	0 (0.00)	

Pyrazinamide; ETB: Ethambutol; SM: Streptomycin; SD: Standard deviation. AFB: Acid-Fast Bacilli; TB: Tuberculosis; INH: Isoniazid; RIF: Rifampicin; PZ: Pyrazinamide

**Pearson's chi-square test could not be applied due to expected frequencies <5 in some cells. The duration values are expressed in months. Survivors (n = 84), Non-survivors (n = 9)*

general, TB lymphadenitis is the most common form of EPTB across many populations (13).For example, Turkish Ministry of Health data indicate that extrathoracic lymph node TB comprises approximately one-third of EPTB cases nationally (31.6%), followed by pleural TB (22–23%) as the next leading site (17). Our cohort also had a high frequency of lymph node TB (26.9% of cases), consistent with the notion that lymphatic involvement is the dominant clinical form of EPTB.However, the most frequent site in our series was skeletal TB, particularly vertebral disease, which accounted for 32.3% of cases.This is a noticeably higher share than that generally reported; typically, bone and joint TB constitutes approximately 10–15% of EPTB cases in large cohorts (13).Similarly, central nervous system (CNS) TB accounted for 16.1% of our cases, whereas population-based data often show CNS TB to be relatively rare, at approximately 3–7% of EPTB (13).The prominence of spinal and CNS TB in our study likely reflects a referral bias; being tertiary care centers, our hospitals receive complicated EPTB cases that might be managed at specialty centers, whereas more straightforward EPTB cases are often handled by general pulmonary services.Indeed, pleural TB was notably under-represented in our cohort; none of our patients had isolated pleural involvement, even though pleural TB is traditionally among the top two extrapulmonary sites in national statistics (17).This anomaly reinforces that our hospital-based series is enriched for severe, multi-system, or diagnostically challenging EPTB presentations rather than the full spectrum seen in the community setting.

Despite differences in distribution, our findings mirror the global diversity of EPTB manifestations. Consistent with published observations, virtually any organ system can be affected. In addition to lymphatic, osteoarticular, and CNS TB, we observed intra-abdominal TB in 12% of patients, genitourinary TB in 8%, and rare cutaneous TB (3%). Such heterogeneity is documented; Baykan et al. reported that the most common sites globally are peripheral lymph nodes (50% of EPTB cases), pleura (18%), and genitourinary, bone/joint, gastrointestinal, and CNS in descending order (13). A recent national survey in China found lymphatic TB most frequent but highlighted regional variations and showed no single site predominates universally (18). Our cohort's profile shows tertiary centers may see cases skewed toward severe forms, which is important when comparing clinical studies. It emphasizes the need for clinical suspicion across specialties; patients often presented to neurology, orthopedics, or gastroenterology before TB was recognized. As noted previously, EPTB can mimic other diseases and presents insidiously. The diverse organ involvement reinforces the importance of maintaining TB in the differential diagnosis for persistent lymphadenopathy, chronic back pain, unexplained meningitic syndromes, or fever of unknown origin, especially in TB-endemic regions.

Diagnostic Challenges and Advances

Our experience highlights diagnostic challenges of EPTB. Unlike pulmonary TB, where sputum microscopy and Xpert testing can rapidly confirm cases, extrapulmonary disease requires invasive sampling of inaccessible sites, with modest yields. In our cohort, 25.8% of patients had positive acid-fast bacilli smears, and 30.1% had cultures that grew M. tuberculosis. These figures align with other series; a Turkish study reported microbiological confirmation in roughly one-third of EPTB patients (15). The paucibacillary nature of EPTB means many patients are microbiologically negative despite active disease. In our study, most cases relied on clinical, radiological, and histopathological evidence. Histopathology showing caseating granulomas supported TB in 60% of patients, highlighting that tissue biopsy remains crucial when direct bacteriological proof is elusive. In 34% of patients, diagnosis was confirmed only after empiric treatment began, showing that clinicians often make therapeutic decisions based on presumptive evidence. This scenario is common; as Yıldız et al. noted, invasive procedures are required for EPTB diagnosis, and delays or misdiagnoses remain problematic (15). Critical forms like TB meningitis or miliary TB can be fatal if not recognized early, yet these forms are most difficult to diagnose definitively (15). Our findings support initiating empiric

therapy for life-threatening EPTB while awaiting results, given reasonable clinical suspicion, as recent guidelines emphasize.

Advances in diagnostics have improved our ability to confirm EPTB. The WHO now recommends rapid molecular tests as the initial diagnostic for suspected EPTB, showing higher sensitivity than smear microscopy in extrapulmonary specimens (15). During our study, Xpert became widely available with a positive yield in 31% of patients, contributing to the high rate of microbiological confirmation. Studies show good sensitivity of Xpert in tissue and pus samples, though lower in paucicellular fluids like pleural fluid or CSF (19, 20). Molecular diagnostics has narrowed this gap. Tools like adenosine deaminase (ADA) assays for pleural or peritoneal fluid and IGRA support diagnoses (21). In our cohort, IGRA tests were positive in 41% of those tested, though many patients did not undergo IGRA. While positive IGRA or tuberculin skin tests support EPTB diagnosis, they lack specificity and often show negative in immunosuppressed patients. Our experience confirms that diagnosing EPTB requires a multimodal approach, combining clinical judgment with imaging, biopsy/histology, and microbiologic tests. The high rate of empiric treatment reflects the need to treat presumptively when diagnostic certainty is difficult. This must balance with obtaining specimens for culture and drug susceptibility testing (DST) when possible, as WHO emphasizes for managing drug-resistant TB. We performed DST in 28% of patients, finding two cases of drug-resistant TB. This low resistance rate matches the national data on multidrug-resistant TB in Turkey but suggests possible undetected resistance in culture-negative EPTB (15). New tools like next-generation sequencing and improved imaging may enhance EPTB diagnosis. Our findings highlight the need for better diagnostics and early sample collection, as delays link to worse outcomes.

Treatment Outcomes and Clinical Outcomes in Context

Despite the challenges in diagnosis, once EPTB is recognized and treated, the outcomes are generally favorable, varying by disease form and patient factors. All patients received standard combination anti-TB therapy under the National TB Program. Treatment aligned with international and local guidelines: 96% started the conventional four-drug first-line regimen(3, 22). Exceptions were patients requiring second-line drugs or those unable to use pyrazinamide. The median therapy duration was 6 months, reflecting the recommended 2-month intensive phase + 4-month continuation phase for drug-susceptible TB. However, many patients, especially those with severe disease, were treated longer at their physicians' discretion. Mean treatment length was 7.4 ± 2.8 months, with longest courses reaching 12–13 months in some cases. Extended treatments were for TB meningitis and skeletal TB patients, where clinicians often prolong therapy. WHO and Turkish guidelines recommend 6-month regimens for most extrapulmonary TB forms, similar to pulmonary TB, but acknowledge CNS or bones/joints TB may need 9–12 months (23). Tuberculous meningitis typically requires 12 months with adjunctive corticosteroids initially due to risks of inadequate treatment. In our series, all CNS TB cases received adjuvant high-dose steroids and were treated for ≥12 months. Our management aligns with WHO's latest TB guidelines (2022–2023), which emphasize individualized treatment duration for extrapulmonary disease severity, while recommending at least 6 months of rifamycin-based therapy for drug-susceptible cases (24). Ongoing trials have explored shorter regimens for limited EPTB, but such strategies remain unadopted in adults.

Treatment outcomes in our cohort were positive with important caveats. Among the 93 patients, most achieved cure or treatment completion, as documented by the national TB registry. We observed no treatment failures in drug-susceptible patients, and few defaulted or were lost to follow-up, due to robust follow-up through TB dispensaries. This reflects Turkey's TB control program strength, which employs directly observed therapy and systematic monitoring (15). Comparable success rates have been reported elsewhere; a recent study from India noted treatment success of 91% among EPTB patients, ex-

ceeding the WHO target of 90% (14). Our real-world cohort of complex cases suggests high success when patients adhere to therapy. However, mortality emerged as significant, with a 9.7% overall rate. This aligns with the 8–10% early mortality in other Turkish hospital-based EPTB series (15)and shows that some EPTB patients, especially those with disseminated or CNS disease, succumb despite treatment. This in-hospital mortality rate exceeds the average TB mortality in national program data. The TB-related death rate among notified EPTB cases in many countries is approximately 3–5% (14), indicating many extrapulmonary cases have excellent prognosis. The higher mortality in our series reflects case severity and referral patterns; our hospitals treated high-risk EPTB cases. This is supported by profiles of deceased patients: their median age was higher than survivors, and most had CNS TB, miliary TB, or advanced malignancy comorbidities. Similarly, in the Acta Medica study from Gazi University, the most frequent EPTB types among deceased patients were CNS and miliary TB, with median age of 65 years versus 49 years in survivors (15). Our findings confirm that advanced age and severe disease drive mortality risk.

Mortality Risk Factors and Comparative Clinical Features

Comparing survivors and non-survivors in our cohort revealed clinical risk factors that mirror those reported elsewhere. Immunosuppressive conditions were significantly associated with mortality: 44% of patients who died had an immunosuppressive comorbidity versus 12% of survivors. This aligns with global observations that patients with TB and impaired immunity fare worse. Although only 2.1% of patients were HIV-positive, one had disseminated TB with poor outcomes. Worldwide, HIV coinfection drives extrapulmonary and disseminated TB; in 2021, 187,000 of the 1.6 million TB deaths were in people with HIV. These patients often present with atypical or multiple-site disease and high mortality if not promptly treated. Chronic kidney disease, diabetes, and malignancy were present in several patients, potentially contributing to worse outcomes (24). Diabetes was a common comorbidity, reflecting its high prevalence in TB cohorts and association with delayed sputum conversion and treatment complications. While diabetes wasn't an independent predictor of death in our small sample, its frequency reinforces the importance of managing comorbidities during TB therapy. In the Gazi University study's multivariate analysis, independent risk factors for early mortality were older age, high ESR (>50 mm/h), miliary TB, and CNS involvement (15). Our data, though underpowered for a multivariate model, agree; all fatal cases were elderly and/or had CNS or disseminated disease. Several non-survivors experienced diagnostic delays, highlighting the importance of timely detection of severe EPTB. Our cohort's median age of 55 years exceeds that in high-burden countries but matches Turkish and European case series (15), reflecting TB demographics in a middle-income country with an aging population. The near-equal sex distribution contrasts with male-predominant pulmonary TB, while some studies note slight female EPTB predominance. European surveys show females have higher EPTB odds, possibly due to biological or healthcare access factors. While our data cannot confirm sex differences, they show EPTB affects both sexes and all ages, and clinicians should consider TB in older adults or females without classic risk factors (24, 26).

When comparing outcomes, our results show most patients with EPTB can be cured with appropriate therapy. High treatment success is achievable for extrapulmonary disease when patients are diagnosed and supported through treatment (14). However, experience shows certain subgroups, such as the elderly, immunosuppressed, and those with CNS or disseminated TB, remain at high risk of poor outcomes. These findings call for targeted interventions, including closer monitoring of high-risk patients, managing comorbidities, and possibly novel therapies. Our findings align with national and international data, showing EPTB as an evolving challenge. It accounts for a growing proportion of TB cases in Turkey, presents with diverse manifestations, and requires a high degree of suspicion for

timely diagnosis.The distribution of organ involvement in our cohort, weighted towards severe forms such as skeletal and CNS TB, underscores the need for robust diagnostic strategies and specialist input. Our patients' outcomes were comparable to global figures, with high treatment completion but significant mortality in severe cases. These comparisons with studies and WHO reports highlight key areas for improvement: enhancing early detection, ensuring microbiological testing for EPTB patients, and sustaining TB care amid challenges such as pandemics. By integrating local insights with global evidence, we can better address the challenges of extrapulmonary TB and improve outcomes.

Study Strengths and Study Limitations

This study represents one of the few long-term institutional analyses in Türkiye that focused on adult EPTB.Its strengths include a large cohort spanning 12 years, systematic data collection across two tertiary care centers, and documentation of diagnostic modalities, organ-specific distribution, and mortality-associated factors.Multiple diagnostic test outcomes, treatment durations, and mortality comparisons provide comprehensive clinical and epidemiological insights relevant to national TB control efforts.However, as a retrospective, single-country, hospital-based study, the findings may be influenced by referral and selection bias, particularly for complex EPTB presentations such as CNS or vertebral involvement.The lack of universal microbiological confirmation limited molecular testing in the early years, and the absence of post-treatment follow-up data restricted generalizability.Small subgroup sizes also limited the power of the multivariate risk analysis of mortality predictors.

Conclusion

This 12-year retrospective cohort study demonstrated that extrapulmonary tuberculosis (EPTB) in Türkiye remains an important clinical and epidemiological challenge. Vertebral bone, lymph nodes, and central nervous system were the predominant sites of involvement, reflecting the referral profile of tertiary centers. Although most patients achieved successful outcomes with standard anti-tuberculosis therapy, mortality reached 9.7% and was strongly associated with immunosuppressive conditions and shortened treatment durations. These findings emphasize the necessity of early recognition, comprehensive diagnostic evaluation, and individualized therapeutic strategies, particularly for high-risk subgroups such as immunosuppressed patients and those with CNS disease. Sustained investment in rapid diagnostics, systematic drug susceptibility testing, and multidisciplinary management should remain priorities of national TB programs to reduce mortality and improve EPTB outcomes.

Acknowledgements: We would like to express our sincere gratitude to Dr. Filiz Duyar Ağca, one of the physicians at Ankara Tuberculosis Dispensary No. 3, for her valuable support and contributions.

Author Contributions: Surgical and Medical Practices: H.A., S.K., F.E., A.A., Concept: H.A., A.A., Design: H.A., S.K., A.A., Data Collection or Processing: H.A., S.K., F.A., Analysis or Interpretation: S.K., Literature Search: H.A., F.A., Writing: H.A., S.K., F.E., A.A.

Ethical Statement: The study protocol was approved by the Ethics Committee of Ankara Bilkent City Hospital (Decision No: E2-22-1952, Date: 08/06/2022). This study was conducted in accordance with the Declaration of Helsinki and the institutional data protection regulations.

References

1. Bagcchi S. WHO's global tuberculosis report 2022. Lancet Microbe. 2023;4(1):e20.
2. Lee H, Kim J, Kim J, Park Y-J. Review of the global burden of tuberculosis in 2023: insights from the WHO Global Tuberculosis Report 2024. Public Health Weekly Report 2025; 18(Suppl 11): S55-S69.
3. Estaji F, Kamali A, Keikha M. Strengthening the global Response to Tuberculosis: Insights from the 2024 WHO global TB report. J Clin Tuberc Other Mycobact Dis. 2025;39:100522.
4. Priyadharshini A. The spectrum of Extra Pulmonary Tuberculosis: emphasizing the importance of Microbiological diagnosis - A Case Series. Indian Journal of Tuberculosis. online June 2025.
5. Gopalaswamy R, Dusthackeer VA, Kannayan S, Subbian S. Extrapulmonary tuberculosis—an update on the diagnosis, treatment and drug resistance. J Resp. 2021;1(2):141-64.
6. Naranjo MZ, Torres JDA, Poveda ATS, García V, Paternina MA. Tuberculosis Beyond the Lungs: A Pictorial Review of Key Diagnostic Imaging Insights. Cureus. 2025;17(3).
7. Azad KAK, Chowdhury T. Extrapulmonary Tuberculosis (Eptb): An Over-

view. Bangladesh Journal of Medicine. 2022;33(2):130-7.

8. Davidson G, Davidson DU, Okoye OK, Mensah LS, Ukaegbu EC, Agbor DBA, et al. Overview of tuberculosis: causes, symptoms and risk factors. Asian J Res Infect Dis. 2024;15(9):8-19.
9. Ammari L, Berriche A, Kooli I, Marrakchi W, Chakroun M. Epidemiology of tuberculosis. Imaging of Tuberculosis: Springer; 2022. p. 1-13.
10. Maheswary D, Ravi SSS, Leela KV, Lathakumari RH, Gireesan M. Epidemiological Trends in Pulmonary and Extra pulmonary Tuberculosis: A 5 year Retrospective Analysis of Acid Fast Bacilli. The International Journal of Mycobacteriology. 2025;14(1):56-65.
11. Dara M, Kuchukhidze G, Yedilbayev A, Perehinets I, Schmidt T, Van Grinsven WL, et al. Early COVID-19 pandemic's toll on tuberculosis services, WHO European Region, January to June 2020. Eurosurveillance. 2021;26(24):2100231.
12. Merdan YE, Etiz P. A scopus-based bibliometric analysis of global tuberculosis publications: 1849-2020. Turk Thorac J. 2022;23(3):246.
13. Baykan AH, Sayiner HS, Aydin E, Koc M, Inan I, Erturk SM. Extrapulmonary tuberculosıs: an old but resurgent problem. Insights Imaging. 2022;13(1):39.
14. VidyaRaj CK, Vadakunnel MJ, Mani BR, Anbazhagi M, Pradhabane G, Venkateswari R, et al. Prevalence of extrapulmonary tuberculosis and factors influencing successful treatment outcomes among notified cases in South India. Sci Rep. 2025;15(1):8290.
15. Yıldız PA, Karamanlıoğlu D, Özger HS, Katı H, Tunçcan ÖG, Dizbay M. Extrapulmonary tuberculosis: clinical and diagnostic features and risk factors for early mortality. Acta Medica. 2022;53(4):367-74.
16. Ulusoy TU, Agca FD, Demirköse H, Parlayan HNK, Altın N, Bulut D, et al. Comparative analysis of pulmonary and extrapulmonary tuberculosis: A seven-year experience from a refugee host country, Turkiye. Asian Pacific Journal of Tropical Medicine. 2024;17(11):508-15.
17. Topçu E, Elmaslar-Mert HT, Bal E, Kuloğlu HF. Ekstrapulmoner Tüberküloz Olgularının Retrospektif Değerlendirilmesi. Klimik Journal/Klimik Dergisi. 2024;37(3).
18. Li L, Lv Y, Su L, Liu Q, Lan K, Wei D, et al. Epidemiology of extrapulmonary tuberculosis in central Guangxi from 2016 to 2021. Eur J Clin Microbiol Infect Dis. 2023;42(2):129-40.
19. Kohli M, Schiller I, Dendukuri N, Dheda K, Denkinger CM, Schumacher SG, et al. Xpert(®) MTB/RIF assay for extrapulmonary tuberculosis and rifampicin resistance. Cochrane Database Syst Rev. 2018;8(8):Cd012768.
20. Rindi L. Rapid molecular diagnosis of extra-pulmonary tuberculosis by Xpert/RIF Ultra. Front Microbiol. 2022;13:817661.
21. Mahajan M, Prasad ML, Kumar P, Kumar A, Chatterjee N, Singh S, et al. An updated systematic review and meta-analysis for the diagnostic test accuracy of ascitic fluid adenosine deaminase in tuberculous peritonitis. Infect Chemother. 2023;55(2):264.
22. Hamdar H, Nahle AA, Ataya J, Jawad A, Salame H, Jaber R, et al. Comparative analysis of pediatric pulmonary and extrapulmonary tuberculosis: A single-center retrospective cohort study in Syria. Heliyon. 2024;10(17):e36779.
23. Miiro E, Olum R, Baluku JB. Clinical features, resistance patterns and treatment outcomes of drug-resistant extra-pulmonary tuberculosis: A scoping review. J Clin Tuberc Other Mycobact Dis. 2023;33:100390.
24. Klingmüller A, Feldmann M, Rohr S, Helmhold L, Junker L, Scherer M, et al. Clinical heterogeneity and treatment outcomes of extrapulmonary tuberculosis in a low-incidence setting: insights from a prospective cohort study. Infection. 2025:1-10.
25. Sama LF, Sadjeu S, Tchouangueu TF, Dabou S, Kuh GF, Ngouateu OB, et al. Diabetes Mellitus and HIV Infection among Newly Diagnosed Pulmonary Tuberculosis Patients in the North West Region of Cameroon: A Cross□Sectional Study. Int J Clinical Pract. 2023;2023(1):5998727.
26. Rachwal N, Idris R, Dreyer V, Richter E, Wichelhaus TA, Niemann S, et al. Pathogen and host determinants of extrapulmonary tuberculosis among 1035 patients in Frankfurt am Main, Germany, 2008–2023. Clin Microbiol Infect. 2025;31(3):425-32.