Brief Report

Distinctive Risk Factor Profiles for Extrapulmonary Tuberculosis: A Case-Control Study in a High-Risk Region of Iran – 2024 - 2025

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Abstract

Background: The differential risk factors associated with extrapulmonary tuberculosis (EPTB) compared to pulmonary tuberculosis (PTB) remain inadequately characterized, particularly in high-burden and culturally distinct settings such as Sistan, Iran.

Objectives: This study aimed to identify and compare the demographic and clinical determinants of EPTB and PTB in this understudied region.

Methods: A case-control study was conducted from January 2024 to March 2025. A total of 400 patients (200 confirmed EPTB cases and 200 PTB cases) were randomly selected from health centers in Zabol. Data on demographic characteristics, site of infection, smoking status, alcohol consumption, diabetes history, immunosuppressive drug use, and BCG vaccination status were extracted from electronic medical records. Multivariate logistic regression analysis was used to identify independent factors associated with EPTB. Data were analyzed using SPSS version 22.

Results: The mean age of EPTB patients was significantly lower than that of PTB patients (42.38 ± 17.49 vs. 49.71 ± 18.85 years, P < 0.001). Female gender (aOR = 3.27, 95% CI: 2.02 - 5.29, P < 0.001) and smoking (aOR = 1.84, 95% CI: 1.15 - 2.97, P = 0.012) were identified as independent risk factors for EPTB. Conversely, increasing age was found to be a protective factor (aOR = 0.98 per year, 95% CI: 0.96 - 0.99, P < 0.001). Lymphatic involvement was the most common EPTB site (49.5%). No significant associations were found for alcohol consumption, diabetes, immunosuppressive drug use, or BCG vaccination status with EPTB presentation.

Conclusions: This study reveals a distinctive risk profile for EPTB in Southeast Iran, characterized by younger age, female gender, and smoking. The findings challenge some global narratives regarding risk factors such as diabetes and highlight the importance of regional context. Public health strategies, including targeted screening and awareness programs for young women, should be prioritized to improve early diagnosis and management of EPTB in this high-risk population.

Keywords: Extrapulmonary Tuberculosis, Risk Factors, Iran, Case-Control Studies

1. Background

Contagious diseases are among the most significant public health challenges (1). Tuberculosis (TB), caused by the *Mycobacterium tuberculosis* complex, is one of the oldest diseases affecting humans and remains among the top ten causes of mortality worldwide, representing the leading cause of death from a single infectious agent. The TB is highly prevalent among socioeconomically disadvantaged populations and marginalized groups (2). The disease is airborne and spreads through the coughs of infected individuals;

transmission through contaminated milk is now rare (3, 4). Clinically, TB can be categorized as latent TB infection or active TB disease (5). The TB accounted for 1.26 million deaths and an estimated 10.8 million cases globally in 2024 (6). The highest TB burden is observed in South-East Asia, the Western Pacific, and Africa (7). In Iran, over 5,000 new and relapsed TB cases are reported annually (8).

Pulmonary tuberculosis (PTB) is the most common clinical manifestation, accounting for approximately 85% of global TB cases. The TB involving any organ other than the lungs is termed extrapulmonary tuberculosis (EPTB), with the lymph nodes and pleura being the most common sites. According to the ECDC 2022 report, 73.1% of TB cases in 2020 were PTB, while 21.5% were EPTB. Major risk factors for EPTB include age (< 15 or > 65 years), female gender, immigration from countries with high TB prevalence, and immunodeficiency (9-11). Due to its nonspecific signs and often subtle presentation, EPTB is frequently underdiagnosed or diagnosed late. General symptoms include fever, anorexia, weight loss, weakness, and fatigue (12). Diagnosis relies on microbiological confirmation, radiologic imaging, or clinical presentation (13). Diagnostic tests include the tuberculin skin test (TST), interferon-gamma release assays (IGRAs), and analysis of respiratory or extrapulmonary specimens (14).

The present study elucidates the distinct epidemiological profile of EPTB in an important yet understudied region of Iran. Its findings have the potential to influence current approaches to diagnosis and screening. This work is not merely a descriptive report but an analytical study that may directly impact health policymaking.

2. Objectives

This study aimed to identify and compare the demographic and clinical determinants of EPTB and PTB in this understudied region.

3. Methods

This case-control study included all TB cases diagnosed and referred to comprehensive health centers in Zabol between 2024 and the first three months of 2025. All confirmed PTB and EPTB cases were identified through pathology reports from hospitals and health centers. A total of 400 patients (200 with PTB and 200 with EPTB) were randomly selected from the eligible population and included in the final analysis.

The inclusion criteria were as follows: (1) Having a confirmed diagnosis of either pulmonary or EPTB; (2)

being diagnosed within the specified study period; and (3) having full access to the patient's electronic medical record for data extraction. Patients were excluded from the final analysis if they met any of the following criteria: (1) Having concurrent pulmonary and extrapulmonary (mixed) or disseminated TB; (2) lacking informed consent for participation; (3) having an incomplete medical record with missing key data (e.g., age, gender, or site of involvement); or (4) having a final alternative diagnosis that ruled out TB.

Demographic and clinical variables were extracted from available electronic records in both the Microbiology and Preventive Medicine departments. Comparative analyses between PTB and EPTB cases included age, gender, site of involvement, smoking status, alcohol consumption, use of immunosuppressive drugs, history of diabetes, and BCG vaccination status (15).

Histopathological reports indicating TB infection were extracted from archives, and non-pulmonary/non-pleural tissue slides were re-examined using Hematoxylin and Eosin (H&E) and Ziehl-Neelsen staining. The detection of acid-fast bacilli confirmed mycobacterial infection (16). Data were analyzed using SPSS version 22. Descriptive statistics (frequency, mean, and standard deviation) and inferential tests (chi-square, Fisher's exact test, and logistic regression) were employed. The significance level was set at P < 0.05.

4. Results

In this study, a total of 400 patients were included, comprising 200 (50%) with EPTB and 200 (50%) with PTB. The mean age of EPTB patients was 42.38 ± 17.49 years (range: 12 - 69), while PTB patients had a mean age of 49.71 ± 18.85 years (range: 14 - 80), indicating that PTB patients were significantly older than those with EPTB. The most frequently affected age group in both categories was 40 - 59 years, while the 0 - 19 years group was the least represented.

A statistically significant association was observed between gender and EPTB (P = 0.002), with 140 (70%) of the EPTB patients being female. The most common sites of EPTB involvement were the lymph nodes, followed by the pleura, bones, urinary tract, and meninges. Smoking showed a significant association with EPTB (P = 0.010), with 86 EPTB patients being smokers. In contrast, no significant associations were found between EPTB and alcohol consumption (P = 0.875), diabetes (P = 0.119), use of immunosuppressive drugs (P = 0.190), or BCG vaccination status (P = 0.142, Table 1).

Logistic regression analysis revealed that with each additional year of age, the likelihood of developing

Table 1. Demographic and Clinical Characteristics of Tuberculosis Patients (N = 200) [a]

Variables	EPTB	PTB	P-Value
Age group (y)			-
0 - 19	30 (15)	18 (9.1)	
20 - 39	47 (23.6)	26 (12.9)	
40 - 59	86 (43.2)	102 (50.7)	
≥ 60	37 (18.6)	54 (26.9)	
Mean ± SD	42.38 ±17.49 (12 - 69)	49.71 ±18.85 (14 - 80)	
Gender			0.002
Male	60 (36.37)	120 (60.4)	
Female	140 (63.63)	80 (39.6)	
Smoking status			0.01
Yes	86 (58.1)	62 (41.9)	
No	114 (45.23)	138 (54.77)	
Alcohol consumption			0.875
Yes	34 (52.3)	31 (47.7)	
No	166 (49.55)	169 (50.45)	
Diabetes			0.119
Yes	55 (47.71)	68 (55.29)	
No	145 (52.34)	132 (47.66)	
Immunosuppressive drugs			0.190
Yes	35 (59.32)	24 (40.68)	
No	165 (48.38)	176 (51.62)	
BCG vaccination			0.142
Yes	139 (47.93)	151 (52.07)	
No	61 (55.45)	49 (44.55)	
Site of involvement			-
Lymphatic	99	-	
Pleural	56	-	
Bone	23	-	
Urinary	15	-	
Meninges	7	-	
Pulmonary	-	200 (lung only)	

Abbreviations: EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis.

[a] Values are expressed No. (%) unless indicated.

EPTB, as opposed to PTB, decreased by 2.5% (aOR = 0.975, 95% CI: 0.964 - 0.987, P < 0.001). Female gender was significantly associated with a higher risk of EPTB (OR = 3.50, 95% CI: 2.34 - 5.21, P < 0.001). Additionally, smokers had 1.84 times higher odds of developing EPTB compared to non-smokers (aOR = 1.84, 95% CI: 1.15 - 2.97, P = 0.012). After adjusting for confounding variables, particularly age and gender, no significant associations were observed between EPTB and alcohol consumption, diabetes, immunosuppressive drug use, or BCG vaccination status (all P-values > 0.05; Table 2).

5. Discussion

This study investigated factors associated with EPTB manifestations in southeastern Iran. Consistent with global literature, lymphadenitis was identified as the most common site of EPTB involvement (17). While younger age, female gender, and smoking demonstrated significant associations with EPTB — in alignment with worldwide patterns (18, 19) — findings regarding diabetes, alcohol consumption, and BCG vaccination revealed regionally specific variations that require contextual interpretation.

5.1. Age and Gender: Consistency with Global Patterns

Aligned with international studies (18, 19), we observed a higher prevalence of EPTB among younger

Table 2. Association Between Demographic/Clinical Characteristics and the Type of Tuberculosis (Pulmonary vs. Extrapulmonary)

Variables	B	SE	Wald	df	P-Value	Exp (B)	95% CI for EXP (B)	
Age	-0.025	0.006	17.36	1	0.00	0.975	0.964	0.987
Gender (male)	-1.253	0.204	37.793	1	0.00	0.286	0.192	0.427
Smoking (yes)	0.610	0.242	6.35	1	0.012	1.841	1.145	2.967
Alcohol (yes)	0.065	0.328	0.039	1	0.843	1.067	0.561	2.030
Diabetes (yes)	-0.330	0.251	1.73	1	0.189	0.719	0.440	1.175
Immunosuppressive (yes)	0.435	0.331	1.73	1	0.188	1.545	0.808	2.957
BCG (yes)	-0.285	0.237	1.45	1	0.229	0.752	0.473	1.197
Constant	0.580	0.538	1.16	1	0.281	1.786	-	-

populations and females. The global explanation attributes this to stronger immunological responses in younger individuals, which may lead to more vigorous inflammatory reactions and extrapulmonary manifestations. In our regional context, sociocultural factors may contribute to this pattern — particularly potential barriers for women in accessing healthcare for nonspecific symptoms (common in EPTB) compared to classic respiratory symptoms (typical of PTB) — potentially delaying diagnosis and increasing apparent prevalence. This warrants further investigation through qualitative studies.

5.2. Smoking: An Established Risk Factor

The significant association between smoking and EPTB ([20]) aligns with global meta-analyses. The proposed mechanism involves cigarette smoke-induced impairment of macrophage function and cellular immunity, which compromises infection control in the lungs and facilitates the dissemination of *M. tuberculosis* to other sites.

5.3. Diabetes: An Apparent Regional Discrepancy

Contrary to studies identifying diabetes as a significant risk factor for all forms of TB ([21]), we found a weaker association with EPTB. This finding might be explained by the younger age of our EPTB cohort and the lower prevalence of diabetes in this age group. Additionally, unmeasured glycemic control levels — a key determinant of TB risk — might have influenced the results, as optimally managed diabetic patients in our region may not exhibit an increased risk for disseminated disease.

5.4. Alcohol Consumption: The Importance of Cultural Context

The lack of a significant association between alcohol consumption and EPTB in our study contrasts with some

meta-analyses ([22]). This discrepancy underscores the influence of cultural context and consumption patterns (e.g., social versus chronic use), which may vary regionally. In our setting, alcohol consumption might be less common or follow different behavioral patterns, necessitating more precisely designed studies to accurately capture consumption characteristics.

5.5. BCG Vaccination: Re-evaluating Efficacy in Different Populations

While our finding of limited BCG protection against EPTB is consistent with some reports ([23]), it conflicts with others ([24]). Global variations in BCG efficacy are often attributed to differences in vaccine strains, timing of vaccination, and exposure to environmental mycobacteria. In the Zabol border region, exposure to diverse mycobacterial strains might influence vaccine effectiveness. This raises critical policy questions regarding the optimization of BCG vaccination strategies for high-risk populations.

5.6. Immunosuppressive Drugs: The Role of Definition and Context

The absence of a significant association with immunosuppressive drugs ([25], [26]) may stem from our restrictive definition — possibly limited to corticosteroids — whereas other studies included HIV-positive patients or transplant recipients. The low prevalence of these drugs in our general population might also have reduced the statistical power needed to detect potential associations.

5.7. Implications for Tuberculosis Control in Iran

These findings carry significant implications for Iran's national TB control program:

1. Targeted screening and early diagnosis:

- Implement focused screening for women and younger populations at higher risk for EPTB.

- Enhance healthcare provider training on atypical presentations of EPTB.

- Develop public awareness campaigns addressing nonspecific symptoms associated with extrapulmonary disease.

2. Gender-sensitive approaches:

- Address potential sociocultural barriers to healthcare access for women.

- Investigate biological (hormonal and immunological) as well as socioeconomic factors underlying gender disparities in EPTB prevalence.

3. Health system integration:

- Revise national diagnostic protocols to emphasize EPTB detection and management.

- Strengthen laboratory capacity for processing extrapulmonary specimens.

- Optimize BCG vaccination strategies in high-risk regions.

5.8. Conclusions

This study challenges the notion of a uniform "one-size-fits-all" approach to TB control in Iran. The adoption of age- and gender-sensitive strategies that prioritize high-risk groups could reduce diagnostic delays, improve treatment outcomes, and ultimately decrease community transmission. Despite its limitations, this research provides valuable insights into EPTB risk factors in the Sistan region and establishes a foundation for future prospective investigations.

5.9. Limitations

This retrospective case–control study inherits limitations inherent to its design. Dependence on electronic medical records introduces potential variations in data completeness and accuracy. Unmeasured confounding variables might have influenced the results. While random selection enhances internal validity, the single-region focus (Zabol) limits the generalizability of findings to other Iranian populations. Future multicenter studies across diverse provinces are recommended to validate these results and provide broader representativeness.

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