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**Clinical course management and outcomes of tubercular empyema.
A prospective study in a high tuberculosis area of Pakistan**

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Ethics approval and consent to participate: this study was approved by the Institutional Review Board (IRB)/Ethical Committee and Research cell of Ayub Medical Teaching Institution with approval code of RC-EA-2024-294. All procedures performed in this study involving a human participant were conducted in accordance with the ethical standards of the institutional and national research committee and in compliance with the Helsinki Declaration. Patient confidentiality was strictly maintained, and no identifying information has been disclosed.

Informed consent: written informed consent was obtained from the each patient prior to participation in local language.

Patient consent for publication: written informed consent was obtained from the patient for publication of this clinical data.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Abstract

Mycobacterium tuberculosis (MTB) rarely causes purulent empyema compared to other bacterial pathogens. This study aimed to determine the clinical course, radiological findings, pleural fluid characteristics, surgical interventions, complications, and outcomes of tubercular empyema. This cohort study was conducted in the Department of Pulmonology at Ayub Teaching Hospital, Abbottabad, Pakistan, from July 2023 to January 20, 2026. Different types of empyema were compared using normally distributed continuous variables (age, total leukocyte count, and protein levels) through one-way analysis of variance. Homogeneity of variances was assessed using Levene's test. Tukey's post hoc test was applied when variances were equal, while the Games–Howell test was used when this assumption was violated. Associations between clinical variables and empyema types were further evaluated using Binary logistic regression. Results were reported as odds ratios with 95% confidence intervals. A p-value <0.05 was considered statistically significant. A total of 38 patients were included over 2.7 years. Of these, 53% (n=20) were male and 47% (n=18) were female. Most patients (78%) were from Khyber Pakhtunkhwa, 11% were from other provinces (Islamabad and Karachi), and 11% were from Afghanistan. The mean age was 46±18 years (range: 14-75 years). Nearly all male patients were engaged in high-risk occupations such as mining, hotel labor, driving, or teaching. Tubercular empyema was observed in 58% (n=22) of patients, and bacterial empyema in 42% (n=16). The most common presenting symptoms were cough, fever, and shortness of breath (67%). Chest pain was present in 50% of patients with bacterial empyema. Thick, calcified pleura (67%) was the most common radiological feature in tubercular empyema, followed by hilar lymphadenopathy. Pleural fluid analysis showed positivity rates of 33% for acid-fast bacilli, 44% for tuberculosis culture, and 56% for GeneXpert. Additionally, 33% of tubercular empyema cases were diagnosed via Abram's pleural biopsy. Tubercular empyema demonstrates distinct clinical, radiological, and pleural fluid characteristics. Although associated with significant complications, outcomes can be improved with timely diagnosis and appropriate management. The neutrophilic effusion doesn't exclude a workup for pleural tuberculosis.

Key words: TB pleurisy, extra-pulmonary tuberculosis, X-pert MTB/XDR, bacterial empyema, pleural calcification, Abram pleural biopsy.

Introduction

Pleural tuberculosis (TB) represents a wide clinical spectrum, ranging from a simple, self-resolving lymphocytic pleural effusion responsive to anti-tubercular therapy (ATT) to severe complications such as empyema necessitans and fibro-thorax. According to 2025 global data, *Mycobacterium tuberculosis* (MTB) remains the second leading infectious cause of death worldwide, following COVID-19. MTB is responsible for approximately 10.7 million cases annually, with the highest disease burden concentrated in South-East Asia (34%), the Western Pacific region (27%), and Africa (25%) [1].

Pakistan ranks 5th among high TB-burden countries globally, with a prevalence of 348 per 100,000, an incidence of 276 per 100,000, and a mortality rate of 34 per million, as reported by the National Tuberculosis Control Program of Pakistan [2]. Globally, tuberculosis accounts for nearly 1.6 million deaths annually [1]. In TB-endemic regions such as Pakistan, tubercular pleurisy is the second most common form of extra-pulmonary tuberculosis.

MTB causes pleural effusion through multiple mechanisms, including rupture of a sub-pleural pulmonary focus into the pleural space, reactivation of latent infection, delayed-type hypersensitivity reactions to mycobacterial antigens, and, rarely, thoracic duct compression due to enlarged crural lymph nodes. Tubercular pleural effusions are typically unilateral, small to moderate in size, and often associated with underlying lung parenchymal involvement. High-risk populations for extra-pulmonary TB include HIV-positive individuals, intravenous drug users, and immunosuppressed patients.

Tubercular empyema is defined as a chronic mycobacterial infection of the pleural space and may develop as a complication of tubercular pleuritis or pulmonary tuberculosis. It can occur through direct extension from lymph nodes, sub-diaphragmatic foci, hematogenous spread, or in association with pneumothorax. Due to the pauci bacillary nature of MTB, diagnosis remains challenging. The pleural fluid pH in tubercular empyema is typically around 7.3, correlating with culture positivity and disease burden—distinct from bacterial empyema [3,4].

Although pleural fluid is usually lymphocyte-predominant, approximately 10% of tubercular empyema cases demonstrate neutrophil predominance, which is associated with higher complication rates and greater microbiological yield on culture and sensitivity testing [5,6]. Tubercular pleural effusions may progress to pseudochyolous effusions or evolve into chronic

tubercular empyema. Radiological findings of tubercular empyema is characterized by thickened, scarred, and calcified pleura, often with associated underlying lung parenchymal destruction[7,8]. To the best of the authors' knowledge, there is limited published evidence describing the full clinical spectrum, diagnostic challenges, management strategies, and complications of tubercular empyema, making it a rarely reported but clinically significant entity in tuberculosis-related morbidity.

Materials and Methods

This prospective observational cohort study was conducted from 1 July 2023 to 20 January 2026 in the Pulmonology Division of Ayub Teaching Hospital (MTI), Abbottabad, Pakistan. The tuberculosis center is equipped with Xpert MTB/RIF Ultra, Xpert MTB/XDR, acid-fast bacilli smear microscopy, and Mycobacterium tuberculosis (MTB) culture facilities.

Patients with empyema and high clinical suspicion of pleural infection were enrolled using a non-probability convenience sampling technique. Patients were initially stratified, based on clinical history, physical examination, and primary pleural fluid analysis, into neutrophil-predominant and lymphocyte-predominant pleural effusion groups. All patients subsequently underwent systematic secondary and tertiary diagnostic evaluation, including pleural biopsy for histopathological examination and bacterial and mycobacterial cultures, together with pleural fluid bacterial and mycobacterial cultures, GeneXpert MTB/RIF, and Gram staining. Patients were classified as having tuberculous empyema cohort (TE) if Mycobacterium tuberculosis was detected by pleural fluid GeneXpert MTB/RIF or culture, or if pleural biopsy demonstrated chronic granulomatous inflammation consistent with tuberculosis. Bacterial empyema (BE) was defined by isolation of a bacterial pathogen from pleural fluid or pleural biopsy, or histopathological evidence of acute neutrophilic inflammation consistent with bacterial infection. Classification was determined using the predefined diagnostic criteria and the complete clinical, microbiological, and histopathological dataset. The CT chest and bronchoscopy was done only to deal the complications. Patients already receiving anti-tuberculous therapy or with non-tuberculous mycobacterial infection were excluded. Data were collected using a predesigned questionnaire.

Statistical analysis was performed using SPSS version 21. Continuous variables were assessed for normality using the Shapiro–Wilk test and expressed as mean $\pm$ standard deviation or median

(interquartile range) as appropriate. Between-group comparisons were made using independent t-test or one-way ANOVA for normally distributed variables and Mann–Whitney U or Kruskal–Wallis tests for non-normal data. Homogeneity of variance was evaluated with Levene's test, followed by Tukey or Games–Howell post hoc analysis where applicable.

Categorical variables were summarized as frequencies and percentages and compared using Chi-square or Fisher's exact test. Strength of association in the case–control framework was estimated using odds ratios (OR) with 95% confidence intervals. Binary logistic regression was applied to identify independent factors associated with empyema type after adjusting for confounders. Correlation between quantitative variables was assessed using Pearson or Spearman correlation coefficients. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 38 patients were enrolled over a 2.7-year period, detail shown in Figure 1. Of these, 53% (n=20) were male and 47% (n=18) were female. The majority of participants (78%) belonged to Khyber Pakhtunkhwa province, while 11% were from other regions of Pakistan (Islamabad and Karachi) and 11% were from Afghanistan. The mean age was 46 ± 18 years, with a range of 14 to 75 years. Nearly all male participants were engaged in high-risk occupations, including mining, hotel labor work, driving, or teaching. Regarding empyema classification, 58% (n=22) had tuberculous empyema and 42% (n=16) had bacterial empyema. The most common presenting symptoms were cough, fever, and shortness of breath, reported in 67% of patients. Chest pain was observed in half of the patients with bacterial empyema. Radiologically, thick calcified pleura was the most frequent finding in tuberculous empyema (67%), followed by hilar lymphadenopathy. Among patients with tuberculous empyema, acid-fast bacilli smear was positive in 33%, tuberculosis culture in 44%, and pleural fluid Gene Xpert MTB in 56%, detail shown in Figure 2. Additionally, 33% of tuberculous empyema cases were diagnosed through Abrams pleural biopsy. Fiberoptic bronchoscopy was performed in 33% (n=6) of patients; a distorted bronchial tree was the most common bronchoscopic finding (67%). *Staphylococcus aureus* was the leading organism identified in bacterial empyema (60%). In terms of complications, pneumothorax was the most frequent complication among tuberculous empyema patients (36%). The 18% patients with tubercular empyema had concomitant bacterial infections. The 54% of tubercular empyema cohort surgical intervention was done, among which 38% of

patients needed tube thoracostomy and 18% VATS were performed to drained the pus and break the loculations. The detailed comparative analysis of bacterial and tubercular empyema explained in Table 1.

The mean hospital stay for tubercular empyema cohort was 8 ± 5 while, for bacterial empyema cohort it was 10 ± 7 days with significance value of [$F_{2,31}=0.552, p>0.05$]. Since the levene's statistic was not significant the equal variance is assumed. To check for difference in hospital stay between the groups post hoc comparison were assessed by using Tukey test. The test indicates that the p value between tubercular and bacterial empyema was $p=0.609$. The detail of microbiological parameters in different types of empyema explained in Table 2.

Discussion

Tubercular empyema remains a significant health concern in tuberculosis-endemic, resource-limited countries such as Pakistan. Despite the high burden of disease, national-level data on tubercular empyema are limited. In the present study, 22 patients with microbiologically confirmed tubercular empyema were included, with diagnosis established through pleural fluid culture and GeneXpert. A subset of patients (18%) had concomitant bacterial infection.

Tubercular empyema is pathophysiologically distinct from classical tuberculous pleural effusion, which is typically a sterile, lymphocyte-predominant exudate without direct pleural invasion. In contrast, tubercular empyema represents active infection of the pleural space with viable mycobacteria, resulting in more intense inflammatory response and different biochemical characteristics.

In our study, patients with tubercular empyema were significantly older than those with bacterial empyema, with a mean difference of approximately 15 years. This finding contrasts with previous studies. Malhotra et al. reported a smaller age difference with relatively younger patients in the tubercular group, while Usman et al. reported a mean age of 42 years in empyema thoracis [9,10]. The discrepancy may be explained by differences in inclusion criteria, as previous studies included probable cases of tubercular empyema without microbiological confirmation. In contrast, our study included only definitively diagnosed cases based on culture, biopsy and GeneXpert positivity.

A notable finding in this study was that 27% of tubercular empyema cases demonstrated neutrophil predominance. This is higher than previously reported rates, such as 9.5% in

tuberculous pleural effusions described by Choi et al. Neutrophilic predominance likely reflects active pleural infection and may contribute to higher microbiological yield [5]. This is supported by our observed detection rates of 44% for culture and 33% for Abram's pleural biopsy.

Previous studies have reported lower diagnostic yields. Ghazal et al. reported granulomatous inflammation in only 13% of cases and culture positivity in 32%, while Malhotra et al. and Usman et al. reported culture positivity rates of 33% and 21%, respectively [9-11]. The higher yields in our study may be attributed to strict inclusion of confirmed cases, differences in disease stage, or improved diagnostic techniques. Another reason for higher yield is complicated nature of empyema which is further justifiable from the results of Tousheed SZ et al [12].

The diagnostic yield of Abram's pleural biopsy in tubercular empyema appears lower than that reported for lymphocytic, sterile tuberculous effusions, where yields up to 73% have been described [13,14]. Advanced diagnostic modalities such as thoracoscopic pleural biopsy have near 100% yield, while ultrasound-guided biopsy yields up to 90% [14,15]. A meta-analysis by Kohli et al. reported a sensitivity of approximately 30% and specificity of 98% for Abram's biopsy, indicating limited sensitivity but high specificity [16].

Biochemical analysis revealed a statistically significant difference in pleural protein levels between tubercular and bacterial empyema. Tubercular empyema was associated with higher protein levels (mean 6 g/dL), with an odds ratio of 14 (95% CI: 2–7.8). These findings are consistent with Sulaimani et al., who reported that pleural protein levels greater than 5 g/dL are suggestive of tuberculosis ($p=0.009$) [17]. The elevated protein levels in tubercular empyema likely reflect increased vascular permeability and intense pleural inflammation due to direct invasion. Overall, pulmonary complications were more frequent in tubercular empyema than in bacterial empyema. Although pneumothorax and trapped lung were more commonly observed in bacterial empyema, the difference was not statistically significant ($p=0.08$). Pulmonary fibrosis and concomitant lung abscess were more frequent in tubercular empyema. Furthermore, VATS was significantly more often required in tubercular empyema than in bacterial empyema ($p=0.03$), possibly due to fibrothorax and impaired lung expansion. A recent review by Kamal YA et al. highlighted the early need of decortication in fibro-thorax improve outcomes of patients in complicated cases like empyema [18].

Conclusions

In tuberculosis-endemic settings, tubercular empyema represents an important and severe manifestation of tuberculosis. It is more frequently observed in older individuals and may be associated with high-risk populations, including those exposed to overcrowding and substance abuse. Tubercular empyema is characterized by active pleural infection, often with neutrophilic predominance and elevated pleural protein levels. Microbiological diagnostic tools, including GeneXpert, culture, demonstrate higher yields in tubercular empyema compared with sterile tuberculous effusions. The yield of Abram pleural biopsy was recorded low as compare to exudative lymphocytic sterile effusions. The neutrophilic effusion doesn't mean that pleural T.B is excluded. Pleural fluid protein and LDH may serve as useful adjuncts in differentiating tubercular empyema from other causes of empyema. However, variability in diagnostic performance necessitates further large-scale, multicenter studies to establish standardized diagnostic and management protocols.

Limitations

This study has several limitations. The sample size was relatively small, which may limit the generalizability of the findings. HIV status was not assessed, despite evidence suggesting that approximately 11% of tubercular empyema cases may occur in HIV-positive individuals, potentially introducing confounding bias.

Additionally, adenosine deaminase (ADA) levels were not measured due to cost constraints, limiting comparison with established diagnostic biomarkers for tuberculous pleural disease. The single-center design and lack of long-term follow-up further limit the external validity of the results

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Table 1. Comprehensive comparison of demographic, clinical, radiological, microbiological features and treatment outcomes in different types of empyema.

Variables		Tubercular empyema (22)	Bacterial empyema (16)	Sig (<i>p</i>)	Variables		Tubercular empyema (22)	Bacterial empyema (16)	Sig (<i>p</i>)
Gender	Male	12	08	0.94	Cell type	Neutrophil	06	14	0.00
	Female	10	08			Lymphocyte	12	02	
Profession of patients	Teacher	02	06	0.11	Chest CT	lymphadenopathy	04	0	0.02
	Labor	08	02			Collapse effusion	8	10	
	At home	08	06			Collapse + loculation	06	6	
	Driver	02	02			Tree in bird	2	0	
	Hotel	02	00			Hydro-pneumo	2	0	
	IV drug use	6	0			0.00	Immune status	Immunocompromised	
T.B contact	At home	10	02	Diabetes mellitus	02	02			
	In Public	12	06	Elder citizen	06	00			
	Past T.B	04	02	0.20	End organ damaged	04		08	
Symptom	Chest pain	05	09	0.036	Biopsy and finding	Abram biopsy positive	6	0	0.006
	SOB	11	03			Caseous necrosis	01	0	0.03
	Cough	06	04			AFB	04	0	
							Granuloma	01	
Gram Staining	Cocci	-	08	0.00	Pleural culture	Staph aureus	02	6	0.002
	Rods	-	04			Pseudomonas	0	2	
	AFB	06	-			Mycobacterium TB	10	0	
Pleural fluid Gene-Xpert		12	0	0.003	Tube thoracostomy		08	14	0.036
					VATS		04	02	
Complications				0.08	Bronchoscopy Finding				0.037
Pneumothorax		08	06		Distorted bronchial tree		4	0	
Lung abscess		04	02		Secretions/Mucus		0	10	
Trapped lung		0	02		Normal		2	0	
Lung fibrosis		2	0		Not performed		16	06	

Table 2. Group statistics and post hoc analysis among different types of empyema with odds ratios and confidence interval (CI).* The 4 patient with bacterial and T.B empyema excluded from analysis.

Variables	Tubercular Empyema*	Bacterial Empyema	Bonferroni corrected P value	Test of Homogeneity of variance		ANOVA		Post Hoc Analysis		Odds ratio T.B vs. Bacterial empyema	95% CI	
				Levine's statistics	Sig.	F	Sig.	B/w T.B vs. Non T.B			lower	upper
Age	54±14	39±16	0.0095	1.23	0.30	4.4	.019	0.027	-	7.08	8.5	8.8
Cell count	2368±1093	2850±2342	0.002	14	0.001	3.4	0.04	-	0.745	2.01	1	165
Protein	6gram±.8	4gram±.6	0.000	0.04	0.83	46	0.00	0.001	-	14.5	12.5	16.5
LDH	2037±1772	10520±16484	0.025	8.5	0.006	4	0.05	-	0.135	2.1	0.8	1.8
Glucose	23±39	06±6	0.10	6.7	0.004	1.6	0.20	-	0.293	1.2	01	08
Albumin	4±0.6	1.5±0.4	0.015	4	0.030	71	0.00	-	0.001	2.17	1.8	4.8

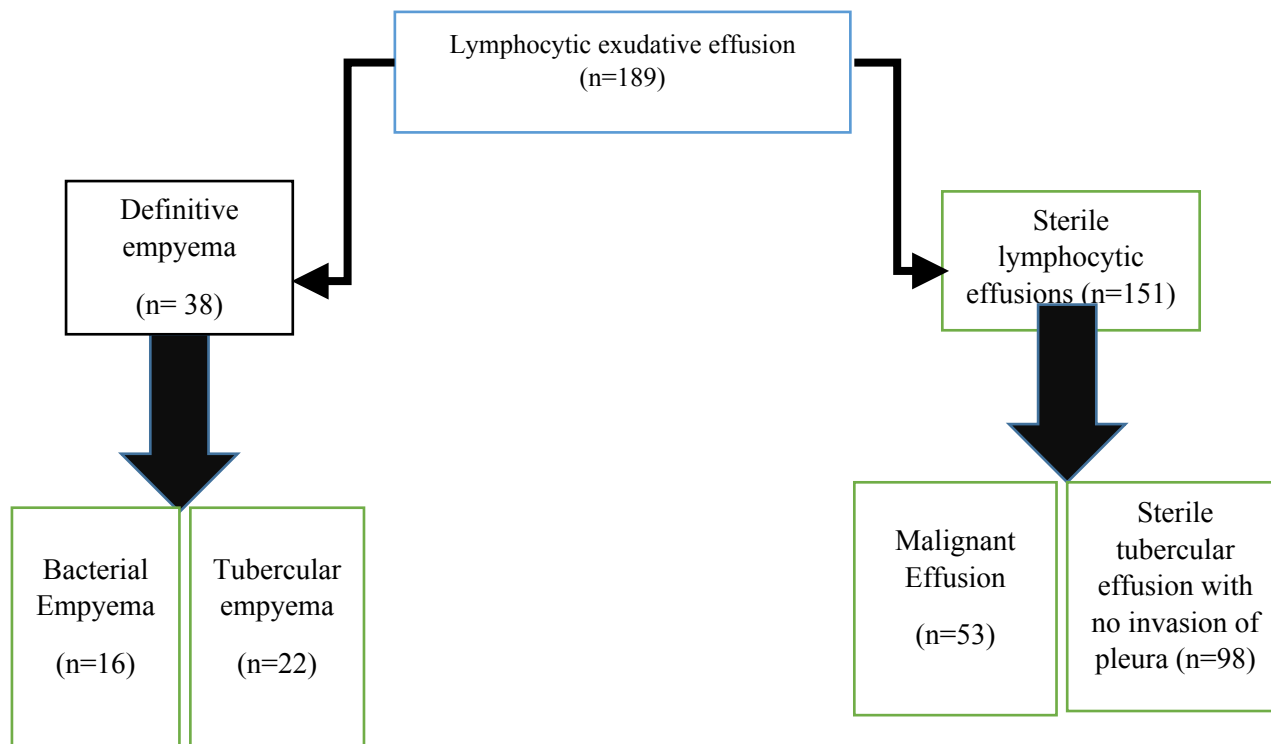


Figure 1. Flow diagram presenting the patient selection on the bases of inclusion criteria.

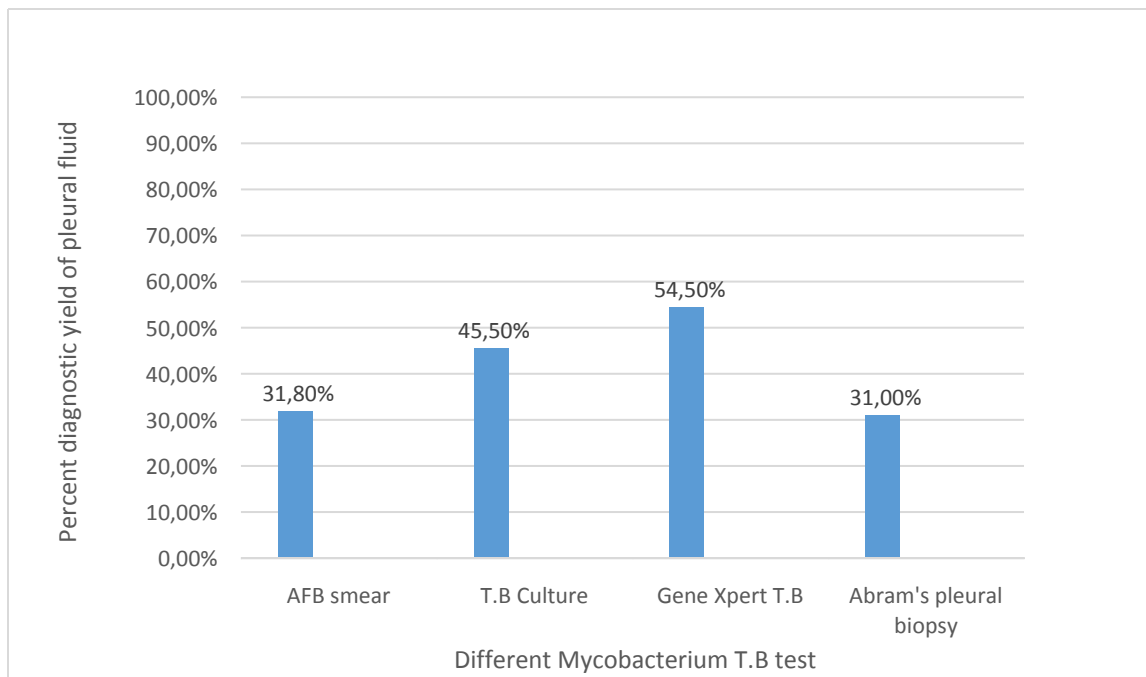


Figure 2. Diagnostic yield of different Mycobacterium tuberculosis test in pleural sample.