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FREQUENCY OF TUBERCULOSIS IN EXUDATIVE LYMPHOCYTIC PLEURAL EFFUSION

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ABSTRACT

Background: Tuberculosis (TB) remains a major cause of exudative lymphocytic pleural effusion in high-burden countries, including Pakistan. Tuberculous pleuritis is diagnostically challenging and requires integration of clinical, laboratory, and microbiological findings.

Objective: To determine the prevalence of TB among patients with exudative lymphocytic pleural effusion and evaluate the diagnostic performance of adenosine deaminase (ADA) levels, lymphocyte percentage, lactate dehydrogenase (LDH) ratio, and protein/serum protein ratio.

Methodology: A cross-sectional observational study was conducted at Northwest General Hospital, Peshawar, from November 2025 to February 2026, including 167 patients with exudative lymphocytic pleural effusion. Demographic, clinical, and laboratory data were collected. Tuberculous pleural effusion was defined using a composite reference standard based on microbiological and/or histopathological confirmation. Diagnostic performance of pleural fluid parameters was assessed, and Fisher's exact test and multivariable logistic regression were used for analysis.

Results: Among 167 patients, 79 (47.3%) had tuberculous pleural effusion. ADA showed 84.8% sensitivity, 21.6% specificity, and 51.5% accuracy. Lymphocyte percentage demonstrated 100% sensitivity but 2.3% specificity. LDH/serum ratio and protein/serum ratio showed high sensitivity but limited specificity. Comorbidities were significantly associated with TB (p=0.031) and independently predicted TB (adjusted OR=2.87; p=0.034). Microbiological confirmation included culture (29.1%), GeneXpert MTB/RIF (35.4%), and Ziehl-Neelsen staining (11.4%); caseating granulomas were identified in 44.3% of biopsied patients.

Conclusion: Tuberculosis was a frequent cause of lymphocytic exudative pleural effusion in this study population. Pleural fluid parameters provide supportive information but have limited specificity and should be interpreted with microbiological and histopathological findings. Further multicenter studies are required for validation.

KEYWORDS: TB, Pleural Effusion, Adenosine Deaminase, Lymphocyte Percentage, Lactate Dehydrogenase.

INTRODUCTION

Pleural effusion is a condition in which too much fluid gets in the pleural cavity, which is the space between the lungs and the chest. A condition may develop on the basis of many underlying causes, which are grouped as two broad categories, namely transudative and exudative [1]. Transudative effusions are usually caused by systemic diseases, such as heart failure or cirrhosis, where the effusion is of low protein concentrations [2]. On the other hand, exudative effusions occur as a result of local factors that influence capillary permeability and are commonly a result of inflammation, infection, or malignancy [3]. These effusions are of a higher concentration of protein and are normally associated with Tuberculosis (TB),[4]. TB remains a significant global health concern, as well as a typical etiological agent of exudative pleural effusion, particularly in high-burden regions such as Pakistan[5],[6].

One of the most common forms of exudative pleural effusion is caused by tuberculosis pleuritis, and it is a characteristic of a great number of diseases, especially those endemic to TB. Pleural TB is a condition that occurs when Mycobacterium TB (M. TB) enters the pleura, and in most cases the pleura fluid profile is dominated by lymphocytes [7]. The main pathophysiology of this dysfunction is an immune reaction of the body to the infection and the development of inflammation into the pleural space, which causes the collection of fluid [8]. The diagnosis usually involves the examination of the pleural fluid that may include the high level of adenosine deaminase (ADA) and interferon-gamma [9]. The use of ADA in the diagnosis of TB pleuritis has been established, and the ADA levels are the potent predictor of tuberculosis involvement[10].

TB is still very common in the world, especially in third-world countries such as Pakistan. According to the World Health Organization (WHO), the number of people that contracted TB worldwide in 2023 was 10.8 million, and the majority of high-burden nations were the countries of Pakistan, Indonesia, and India[11]. Pleural TB is one of the most frequent extrapulmonary manifestations of TB, and up to 30% of the cases of the disease occur in regions with the widespread of the disease [9]. Although it is common, the examination of pleural TB is complicated because it is paucibacillary in nature; thus, M. TB cannot be easily identified in pleural fluid cultures [9].

TB has been a significant social health issue in Pakistan. TB is one of the highest across the globe, and a considerable number of cases are diagnosed with pleural effusion in the country. It was mentioned in a study, that exudative lymphocytic pleural effusion is a frequent occurrence in patients with pleural TB in Pakistan[12]. Nevertheless, TB pleuritis cannot always be diagnosed. Even though clues can be obtained through a pleural fluid analysis, the diagnosis of TB may frequently need more invasive tools of diagnosis, including the pleural biopsy [10]. Higher ADA levels, especially when they are over 40 U/L, are one of the best indicators of TB pleural effusion in endemic settings[7].

Pleural fluid analysis has been documented in a number of studies to diagnose TB. Specifically, the lymphocyte predominance in pleural fluid is a crucial aspect in the diagnosis of TB pleuritis, among other causes of exudative pleural effusion [13]. Pleural fluid LDH and pleural fluid/serum protein ratio are also other markers that could help to distinguish between TB-related effusions and non-TB[8]. The existence of these diagnostic tools notwithstanding, more convenient and reliable ways of diagnosing TB in patients with exudative lymphocytic pleural effusion are still required, especially in low-resource settings.

TB pleuritis dois not occur equally in every area of the globe. TB pleuritis is common in high-endemic regions such as Pakistan, and researchers indicate that it leads to a high percentage of cases with exudative pleural effusion[12]. A study reveals that TB pleuritis is diagnosed in 30.6% of patients with exudative lymphocytic pleural effusion in Pakistan [9], and it is a substantial challenge for healthcare providers in the country. Nevertheless, since the disease is paucibacillary, diagnosis is not easy, and patients are likely to spend many years of uncertainty before obtaining a concrete diagnosis.

Besides the diagnostic issues, TB pleuritis has to be treated promptly to avoid the occurrence of such complications as lung fibrosis or respiratory failure. Any delay in the diagnosis and management of TB pleuritis may result in a high level of morbidity, especially in those patients who are not able to obtain proper healthcare in time [9]. In Pakistan, the disease burden of TB-related diseases, including pleural TB, is a serious social concern, and the prevalence of the use of it must be reduced by enhancing the rates of its early diagnosis to decrease the mortality rate and improve the outcomes of patients [13].

Considering the high incidence of TB in Pakistan and the problems related to the diagnosis of pleural TB, the study attempts to determine the prevalence of TB among patients with exudative lymphocytic pleural effusion in the Northwest General Hospital and Research Centre-Peshawar. As the study will help to understand the frequency and diagnostic features of TB in this group of patients, the study will provide valuable data that will be valuable in providing more accurate diagnoses and developing the most effective management strategies. The implications of this study will also be crucial to the policy of population health in the countries with the high prevalence of TB, where the early diagnosis and treatment may cause a significant decrease in the effects of the disease[5].

The objective of this study is to determine the frequency of tuberculosis (TB) in patients with exudative lymphocytic pleural effusion at the Department of Pulmonology, Northwest General Hospital & Research Centre, Peshawar. By evaluating the prevalence of TB in this population, the study aims to contribute to a more profound understanding of the disease's epidemiology and to improve early diagnostic approaches in regions with a high burden of TB.

MATERIALS AND METHODS

This cross-sectional observational study was conducted between November 2025 and February 2026 at the Department of Pulmonology, Northwest General Hospital and Research Centre, Peshawar, Pakistan. Ethical approval was obtained from the institutional review board of the hospital (Ref#0237, dated 29-04-2025). Written informed consent was obtained from all participants before enrollment. The study was conducted according to institutional ethical guidelines.

The study population consisted of adult patients aged 18–60 years who presented with exudative lymphocytic pleural effusion according to predefined operational criteria. The study aimed to determine the frequency of tuberculous pleural effusion and evaluate the diagnostic performance of commonly used pleural fluid parameters among patients with lymphocytic exudative pleural effusion.

The sample size was calculated using OpenEpi software based on a previously reported frequency of tuberculosis pleuritis of 30.6% among patients with exudative lymphocytic pleural effusion [12]. Considering a confidence level of 95% and an absolute margin of error of 7%, the required sample size was calculated as 167 participants.

The expected prevalence used for sample size calculation was based on previously reported literature. The sample size was estimated using the prevalence of tuberculous pleural effusion among patients with exudative lymphocytic pleural effusion reported in earlier studies. Differences between estimated and observed prevalence may occur due to variations in study populations, geographical distribution, referral patterns, and local tuberculosis epidemiology.[11] [14]

A 7% margin of error was selected considering the feasibility of recruitment within the study period and availability of eligible participants..

Patients were recruited using a non-probability consecutive sampling technique.

Patients were eligible for inclusion if they fulfilled predefined selection criteria. Adult patients aged 18–60 years presenting with pleural effusion were screened for eligibility. Patients were included when pleural fluid analysis demonstrated an exudative effusion according to Light's criteria and showed lymphocytic predominance (≥50% lymphocytes among total nucleated cells).

Patients with lymphocytic exudative pleural effusion were included irrespective of the suspected underlying cause. All enrolled patients underwent clinical evaluation and diagnostic assessment, including biochemical analysis of pleural fluid, microbiological investigations, and radiological assessment. Available pleural biopsy and histopathological findings were retrieved from patients' clinical records where these investigations had been performed for clinical indications.

Only patients with adequate pleural fluid samples, complete clinical information, and available laboratory records were included. Written informed consent was obtained from all participants before enrolment.

Patients with incomplete clinical or laboratory records, inadequate pleural fluid samples, or missing diagnostic information were excluded.

Patients with transudative pleural effusion according to Light's criteria were excluded because the study specifically focused on exudative lymphocytic pleural effusions.[15]

Patients with confirmed alternative causes of pleural effusion, including malignant pleural effusion, parapneumonic effusion, empyema, pulmonary embolism, or systemic diseases causing pleural involvement, were excluded to avoid misclassification and ensure appropriate comparison between tuberculous and non-tuberculous lymphocytic pleural effusions.

After obtaining ethical approval, eligible patients were enrolled after receiving detailed information regarding the study objectives and procedures. Data were collected using a structured data collection form designed by the researcher.

The collected variables included demographic, clinical, and laboratory information, including age, gender, residence, smoking status, socioeconomic status, presenting symptoms, duration of symptoms, comorbidities, and relevant clinical history. Clinical information was obtained through patient interviews, medical records, and available diagnostic reports.

Pleural fluid samples were obtained from all patients through diagnostic thoracentesis performed under aseptic conditions by trained medical personnel. The collected pleural fluid and tissue samples were analyzed for biochemical, microbiological, and histopathological parameters when these investigations were available.

Biochemical Analysis: Pleural fluid biochemical analysis included measurement of protein, lactate dehydrogenase (LDH), adenosine deaminase (ADA), total leukocyte count, and differential leukocyte count.

ADA was evaluated as an independent diagnostic parameter. It was not included in the tuberculosis reference definition and was analyzed separately for diagnostic performance assessment to avoid incorporation bias.

Microbiological Analysis: Microbiological evaluation included Ziehl-Neelsen staining for acid-fast bacilli, GeneXpert MTB/RIF testing for detection of *Mycobacterium tuberculosis*, and pleural fluid culture for *Mycobacterium tuberculosis*. Microbiological findings were obtained from available laboratory records. A positive pleural fluid culture, positive GeneXpert MTB/RIF result, or positive Ziehl-Neelsen staining was considered microbiological evidence of tuberculosis.

Histopathological Examination: Pleural biopsy was performed in selected patients according to clinical indication. Histopathological findings were obtained from pathology reports. The presence of granulomatous inflammation with caseous necrosis (caseating granulomas) was considered supportive evidence of tuberculous pleuritis.

Operational Definitions

Exudative Lymphocytic Pleural Effusion

Pleural effusion was classified as exudative according to Light's criteria.[16]

Additionally, lymphocytic pleural effusion was defined as pleural fluid containing ≥50% lymphocytes among total nucleated cells.[17]

Definition of Tuberculous Pleural Effusion

Tuberculous pleural effusion was defined using a composite reference standard independent of pleural fluid ADA values.

Patients were classified as having tuberculous pleural effusion if one or more of the following criteria were fulfilled:

- Positive pleural fluid culture for *Mycobacterium tuberculosis*.
- Positive GeneXpert MTB/RIF result.
- Positive Ziehl-Neelsen staining demonstrating acid-fast bacilli.
- Pleural biopsy showing caseating granulomatous inflammation compatible with tuberculosis, supported by clinical and radiological findings.

Pleural fluid ADA level was not included as a diagnostic criterion for tuberculosis classification. Instead, ADA was evaluated separately as an index diagnostic parameter.[18][19]

Diagnostic Cut-off Values and Justification

The following diagnostic cut-off values were used for laboratory parameters:

ADA Levels (>40 U/L): This cut-off was selected based on extensive evidence supporting its use as a reliable marker for TB pleuritis in high-prevalence regions. A meta-analysis by Aggarwal et al. demonstrated that ADA >40 U/L has a pooled sensitivity of 92% and specificity of 90% for diagnosing tuberculous pleural effusion in

endemic settings. This cut-off has been validated in multiple South Asian populations, including Pakistan [Reference: Aggarwal AN, et al. Chest. 2019].[21]

Lymphocyte Percentage (>50%): Lymphocytic predominance (>50% lymphocytes) is a hallmark of TB pleuritis, reflecting the cell-mediated immune response to mycobacterial antigens. This criterion is widely accepted in the literature as a distinguishing feature of tuberculous pleural effusion [Reference: Antonangelo L, et al. J Bras Pneumol. 2020].[22]

Protein/Serum Protein Ratio (>0.5): This cut-off is derived from Light's criteria for differentiating exudative from transudative effusions. A ratio >0.5 indicates an exudative effusion, which is characteristic of TB pleuritis [Reference: Light RW. N Engl J Med. 2002].[17]

LDH/Serum LDH Ratio (>0.6): This is also part of Light's criteria for exudative effusions. The LDH ratio reflects local inflammation and tissue damage, which are prominent in TB pleuritis [Reference: Light RW. N Engl J Med. 2002; Porcel JM. Med Clin North Am. 2011].[17][23]

LDH Levels: Pleural fluid LDH > two-thirds of the upper normal limit of serum LDH is the third component of Light's criteria. This threshold indicates significant pleural inflammation, consistent with TB and other exudative causes [Reference: Light RW. N Engl J Med. 2002].[17]

WBC Count: No specific diagnostic cut-off was used for WBC count; this parameter was reported descriptively to characterize the study population.

Data were analyzed using SPSS version 22. Categorical variables including gender, residence, smoking status, socioeconomic status, comorbidities, microbiological findings, and tuberculosis status were presented as frequencies and percentages. Continuous variables including age, symptom duration, and pleural fluid parameters were assessed for normal distribution using the Shapiro-Wilk test and presented as mean ± standard deviation. Comparison of continuous variables between TB and non-TB groups was performed using independent sample t-test. Associations between categorical variables and tuberculosis status were assessed using chi-square test or Fisher's exact test where appropriate. Diagnostic performance parameters, including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy, were calculated for ADA, lymphocyte percentage, protein/serum protein ratio, and LDH/serum LDH ratio. For diagnostic accuracy analysis, tuberculosis status was determined using the composite reference standard described above. Since ADA was evaluated as an index diagnostic test, it was not incorporated into the tuberculosis definition to avoid incorporation bias. Multivariable logistic regression analysis was performed to identify independent predictors of tuberculosis after adjustment for age, gender, residence, smoking status, socioeconomic status, comorbidities, and laboratory parameters. The number of predictors included in the regression model was restricted according to the number of outcome events to minimize model overfitting. A two-sided p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 167 patients with exudative lymphocytic pleural effusion were included in the study. Tuberculosis status was determined using the predefined composite reference standard, which included microbiological confirmation and/or histopathological evidence supported by compatible clinical and radiological findings. Based on this reference standard, 79 patients (47.3%) were classified as having tuberculous pleural effusion, whereas 88 patients (52.7%) were classified as having non-tuberculous pleural effusion. The mean age of the study population was 40.3 ± 12.6 years. Patients with tuberculous pleural effusion had a mean age of 40.9 ± 12.4 years, while patients with non-tuberculous pleural effusion had a mean age of 39.7 ± 12.7 years. The study population consisted of 97 females (58.1%) and 70 males (41.9%). A higher proportion of participants were from rural areas (95; 56.9%) compared with urban areas (72; 43.1%). Regarding smoking status, 95 patients (56.9%) were non-smokers and 72 (43.1%) were smokers. The socioeconomic distribution showed that 62 patients (37.1%) belonged to the poor socioeconomic group, 53 (31.7%) belonged to the middle socioeconomic group, and 52 (31.1%) belonged to the higher socioeconomic group. Comorbidities were present in 137 patients (82.0%). The most common comorbidities were hypertension (28; 16.8%), chronic kidney disease (26; 15.6%), HIV/AIDS (24; 14.4%), chronic liver disease (23; 13.8%), diabetes mellitus (21; 12.6%), and multiple comorbidities (10; 6.0%). The most frequently reported symptoms were cough (31; 18.6%), fever (29; 17.4%), and fatigue (24; 14.4%).

The demographic and clinical characteristics stratified according to tuberculosis status are presented in Table 1.

Table 1: Demographic and Clinical Characteristics of the Study Population

Characteristic	Total, n (%)	TB (n=79)	Non-TB (n=88)
Age (years)	40.3±12.6	40.9±12.4	39.7±12.7
Female	97 (58.1%)	46 (47.4%)	51 (52.6%)
Male	70 (41.9%)	33 (47.1%)	37 (52.9%)
Rural	95 (56.9%)	44 (46.3%)	51 (53.7%)
Urban	72 (43.1%)	35 (48.6%)	37 (51.4%)
Non-Smoker	95 (56.9%)	46 (48.4%)	49 (51.6%)
Smoker	72 (43.1%)	33 (45.8%)	39 (54.2%)
Poor	62 (37.1%)	29 (46.8%)	33 (53.2%)
Middle Class	53 (31.7%)	24 (45.3%)	29 (54.7%)
Rich	52 (31.1%)	26 (50.0%)	26 (50.0%)

None	30 (18.0%)	13 (43.3%)	17 (56.7%)
Hypertension	28 (16.8%)	10 (35.7%)	18 (64.3%)
CKD	26 (15.6%)	14 (53.8%)	12 (46.2%)
HIV/AIDS	24 (14.4%)	11 (45.8%)	13 (54.2%)
CLD	23 (13.8%)	9 (39.1%)	14 (60.9%)
Diabetes Mellitus	21 (12.6%)	11 (52.4%)	10 (47.6%)
Multiple	10 (6.0%)	10 (100%)	0 (0%)

CKD: Chronic Kidney Disease; CLD: Chronic Liver Disease

Comparison of Pleural Fluid Biochemical Parameters

The comparison of biochemical parameters between tuberculous and non-tuberculous pleural effusion groups is presented in Table 2. The mean ADA level was 74.3 ± 28.1 U/L among patients with tuberculosis and 76.4 ± 28.3 U/L among patients without tuberculosis. The mean lymphocyte percentage was 64.1 ± 8.8% in the TB group and 64.7 ± 8.7% in the non-TB group. Similarly, LDH level, protein/serum protein ratio, LDH/serum LDH ratio, and WBC count showed overlapping distributions between the two groups. No statistically significant differences were observed between TB and non-TB groups for any evaluated laboratory parameter (all $p>0.05$). These findings demonstrate substantial overlap in pleural fluid biochemical characteristics between tuberculous and non-tuberculous lymphocytic exudative pleural effusions. Therefore, these parameters should be interpreted as supportive findings and not as independent diagnostic markers.

Table 2: Comparison of Laboratory Parameters between TB and Non-TB Groups

Parameter	TB (n=79) Mean ± SD	Non-TB (n=88) Mean ± SD	p-value
Age (years)	40.9 ± 12.4	39.7 ± 12.7	0.534
Symptom duration (weeks)	6.3 ± 3.5	6.4 ± 3.4	0.712
Protein/Serum ratio	0.69 ± 0.12	0.70 ± 0.11	0.994
LDH/Serum ratio	0.70 ± 0.06	0.70 ± 0.06	0.891
LDH (U/L)	441.8 ± 215.2	428.5 ± 218.1	0.740
ADA (U/L)	74.3 ± 28.1	76.4 ± 28.3	0.957
Lymphocytes (%)	64.1 ± 8.8	64.7 ± 8.7	0.660
WBC (cells/mm³)	5150 ± 2018	4892 ± 1932	0.068

The association between demographic characteristics, smoking status, socioeconomic status, and comorbidities with tuberculosis confirmation is presented in Table 3.

No significant association was observed between tuberculosis status and gender, residence, smoking status, or socioeconomic category.

A significant association was observed between comorbidity status and TB confirmation ($p=0.031$). This association was mainly influenced by patients with multiple comorbidities, among whom all patients were classified as having tuberculosis.

Table 3: Association between Categorical Variables and TB Confirmation Status

Variable	Category	TB (n=79)	Non-TB (n=88)	Test	p-value
Gender	Female	46 (47.4%)	51 (52.6%)	χ^2	0.658
	Male	33 (47.1%)	37 (52.9%)		
Residence	Rural	44 (46.3%)	51 (53.7%)	χ^2	0.443
	Urban	35 (48.6%)	37 (51.4%)		
Smoking	Non-Smoker	46 (48.4%)	49 (51.6%)	χ^2	0.845
	Smoker	33 (45.8%)	39 (54.2%)		
SES	Poor	29 (46.8%)	33 (53.2%)	χ^2	0.362
	Middle	24 (45.3%)	29 (54.7%)		
	Rich	26 (50.0%)	26 (50.0%)		
Comorbidities	None	13 (43.3%)	17 (56.7%)	Fisher's	0.031
	Hypertension	10 (35.7%)	18 (64.3%)		
	CKD	14 (53.8%)	12 (46.2%)		
	HIV/AIDS	11 (45.8%)	13 (54.2%)		
	CLD	9 (39.1%)	14 (60.9%)		
	Diabetes	11 (52.4%)	10 (47.6%)		
	Multiple	10 (100%)	0 (0%)		

Fisher's exact test used due to zero cell count. Significant association found (p=0.031). All 10 patients with multiple comorbidities had confirmed TB.

The diagnostic performance of ADA, lymphocyte percentage, protein/serum protein ratio, and LDH/serum LDH ratio was assessed using the composite reference standard for tuberculosis diagnosis. Importantly, pleural fluid

ADA was not included in the tuberculosis case definition and was evaluated independently as an index diagnostic parameter to avoid incorporation bias. At the predefined cut-off value of ADA >40 U/L, ADA demonstrated sensitivity of 84.8% and specificity of 21.6%. Other evaluated parameters showed high sensitivity but limited specificity, indicating considerable overlap between tuberculous and non-tuberculous lymphocytic exudative pleural effusions. These findings suggest that individual biochemical parameters may assist clinical decision-making but cannot reliably differentiate tuberculosis from other causes of lymphocytic exudative pleural effusion when used alone.

Table 4: Diagnostic Performance of Conventional Parameters for TB Pleural Effusion

Parameter	Cut-off	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
ADA	>40 U/L	84.8	21.6	49.3	61.3	51.5
Lymphocytes	>50%	100.0	2.3	47.9	100.0	48.5
Protein/Serum ratio	>0.5	97.5	4.5	47.8	66.7	48.5
LDH/Serum ratio	>0.6	92.4	11.4	48.3	62.5	49.7

Microbiological and histopathological findings were evaluated among patients classified as having tuberculous pleural effusion. Microbiological investigations were performed according to clinical availability, and findings were obtained from available laboratory records. Because pleural tuberculosis is frequently paucibacillary, microbiological confirmation was obtained in a proportion of patients. Pleural fluid culture for Mycobacterium tuberculosis was positive in 23 patients (29.1%). GeneXpert MTB/RIF detected M. tuberculosis in 28 patients (35.4%), whereas Ziehl-Neelsen staining demonstrated acid-fast bacilli in 9 patients (11.4%). Pleural biopsy was performed in selected patients according to clinical indication. Among the 70 patients undergoing pleural biopsy, granulomatous inflammation was identified in 38 patients (54.3%), while caseating granulomas were observed in 31 patients (44.3%). A combination of two or more diagnostic methods confirmed tuberculosis in 52 patients (65.8%).

Table 5: Diagnostic Methods for TB Confirmation (n=79)

Diagnostic Method	Positive, n (%)	95% CI
Pleural fluid culture for *M. tuberculosis*	23 (29.1%)	20.3–39.9%
GeneXpert MTB/RIF	28 (35.4%)	25.8–46.4%
Ziehl-Neelsen staining (AFB smear)	9 (11.4%)	6.1–20.3%
Confirmation by ≥2 diagnostic methods	52 (65.8%)	54.8–75.3%

Table 5B. Histopathological Findings among Patients Undergoing Pleural Biopsy (n=70)

Histopathological finding	Positive, n (%)	95% CI
Granulomatous inflammation	38 (54.3%)	42.7–65.4%
Caseating granulomas	31 (44.3%)	33.3–55.9%

Multivariable logistic regression analysis was performed to identify independent factors associated with tuberculosis confirmation after adjustment for potential confounders including age, gender, residence, smoking status, socioeconomic status, comorbidities, and laboratory parameters. The presence of comorbidities was independently associated with increased odds of tuberculosis confirmation (adjusted OR: 2.87, 95% CI: 1.08–7.62, p=0.034). However, age, gender, residence, smoking status, socioeconomic status, ADA >40 U/L, LDH >400 U/L, and lymphocyte percentage >60% were not independently associated with tuberculosis confirmation. ADA was included as an independent predictor variable and was not used as part of the tuberculosis diagnostic reference standard.

Table 6: Multivariable Logistic Regression for TB Prediction

Variable	Adjusted OR	95% CI	p-value
Age	1.01	0.98–1.04	0.574
Male gender	1.21	0.62–2.35	0.572
Rural residence	0.72	0.38–1.36	0.312
Smoking	0.94	0.49–1.82	0.863
Middle class (vs poor)	0.74	0.34–1.60	0.452
Rich (vs poor)	0.86	0.41–1.82	0.692
Presence of comorbidities	2.87	1.08–7.62	0.034
ADA >40 U/L	1.52	0.67–3.45	0.312
LDH >400 U/L	0.89	0.46–1.72	0.735
Lymphocytes >60%	1.14	0.59–2.21	0.698

DISCUSSION

This study evaluated the frequency of tuberculous pleural effusion among patients presenting with exudative lymphocytic pleural effusion and assessed the diagnostic performance of commonly used pleural fluid parameters. Tuberculous pleural effusion was identified in 79/167 patients (47.3%), confirming tuberculosis as an important cause of lymphocytic exudative pleural effusion in this population. However, although pleural fluid parameters demonstrated high sensitivity, their specificity was limited, indicating that these parameters may assist initial clinical assessment but have limited discriminatory value and cannot replace microbiological or histopathological confirmation.

In the present study, although ADA, lymphocyte percentage, protein/serum protein ratio, and LDH/serum LDH ratio demonstrated variable diagnostic performance, no statistically significant differences were observed between the tuberculous and non-tuberculous groups for the evaluated laboratory parameters (all $p > 0.05$). These findings indicate that routine pleural fluid biochemical and cellular parameters alone have limited ability to discriminate tuberculous pleural effusion from other causes of exudative lymphocytic pleural effusion. Therefore, these parameters should be considered supportive findings rather than definitive diagnostic markers, and their interpretation should be integrated with microbiological, molecular, histopathological, and clinical information whenever available.

Although no statistically significant differences were observed between the TB and non-TB groups for individual laboratory parameters, diagnostic performance measures were reported because they evaluate a different aspect of test performance. Statistical significance testing assesses whether parameter distributions differ between groups, whereas sensitivity and specificity assess the ability of a test threshold to correctly identify patients with and without tuberculosis. Therefore, a parameter may demonstrate measurable sensitivity or specificity at a particular cut-off value even when the overall difference between groups is not statistically significant. In this study, these findings indicate that pleural fluid parameters may have supportive screening value but insufficient discriminatory ability to establish a definitive diagnosis of tuberculous pleural effusion.[14][24]

A significant association was observed between comorbidity status and tuberculosis confirmation ($p=0.031$). Patients with multiple comorbidities demonstrated a higher proportion of tuberculosis, and multivariable analysis identified comorbidities as an independent predictor of TB confirmation (adjusted OR=2.87; $p=0.034$). This finding emphasizes the importance of considering underlying clinical conditions during evaluation of patients with suspected tuberculous pleural effusion.

The diagnostic performance observed in this study is comparable with previous reports. Yang et al. reported high sensitivity of ADA in tuberculous pleuritis [19], supporting its role as a useful screening marker. Similarly, Guo et al. demonstrated improved diagnostic specificity when ADA was combined with additional biomarkers and immune-based tests [25]. Previous meta-analyses have also suggested that combined diagnostic approaches may provide better discrimination than individual pleural fluid parameters alone [7].

Previous studies from Pakistan have mainly focused on clinical characteristics and individual diagnostic modalities. Hussain et al. highlighted challenges associated with ADA interpretation in pleural tuberculosis [9], while Mohsin et al. evaluated molecular and histopathological approaches for diagnosis [26]. The present study adds to existing evidence by evaluating conventional pleural fluid parameters together with microbiological and histopathological findings in a local clinical setting.

In resource-limited settings, pleural fluid biochemical parameters remain useful as initial supportive investigations because they are inexpensive and widely available. However, confirmation using GeneXpert MTB/RIF, culture, and/or pleural biopsy should be pursued whenever feasible to improve diagnostic certainty.

Study Limitations

This study has several limitations. The single-center design and non-probability sampling may limit the generalizability of the findings. The cross-sectional design also restricts assessment of temporal relationships. As data collection relied partly on clinical records, the availability of molecular testing, pleural biopsy, and histopathological evaluation depended on routine clinical practice and was not uniform among all patients, which may have affected diagnostic confirmation. Patients receiving anti-tuberculosis therapy before pleural fluid evaluation were excluded because prior treatment could reduce microbiological yield and alter pleural fluid characteristics. The sample size was calculated before study initiation based on previously reported prevalence, and the observed prevalence did not influence the original estimation.

Future Recommendations

Future multicenter prospective studies across different regions of Pakistan are required to validate these findings and establish locally optimized diagnostic algorithms. Further research should evaluate combined diagnostic models incorporating clinical features, ADA, molecular tests, and novel biomarkers to improve specificity and diagnostic accuracy for tuberculous pleural effusion.

CONCLUSION

Tuberculosis accounted for 47.3% of exudative lymphocytic pleural effusions in this study population. Pleural fluid parameters, including ADA, lymphocyte percentage, protein ratio, and LDH ratio, demonstrated high sensitivity but limited specificity and should therefore be considered supportive rather than definitive diagnostic tools. A combined approach incorporating clinical assessment with microbiological and histopathological confirmation remains essential for accurate diagnosis of tuberculous pleural effusion.

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