Diagnosis of pleural tuberculosis in the era of thoracoscopic surgery

Ehab F. Salim[a], Gaser A. Ali[b]

[a]Department of Cardiothoracic Surgery, Benha University, Benha, Egypt, [b]Department of Cardiothoracic Surgery, Zagazig University, Zagazig, Egypt

Correspondence to Ehab F. Salim, MD, Department of Cardiothoracic Surgery, Benha Faculty of Medicine, Benha University, 6 Tawfiq Osman Street, Benha, Qalyubia Governorate 13511, Egypt
Tel: 00201201096361;
Fax: 0020133211152;
e-mail: ehabfawzi2002@yahoo.com

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Background
Before thoracoscopic surgery, diagnosing tuberculous (TB) pleurisy was a medical challenge. Thoracoscopy is the most accurate but expensive method for TB pleurisy diagnosis. TB is common in low-income countries, where financial limitations prevent the use of thoracoscopy, motivating the search for a cheaper alternative.
Patients and methods
A prospective study was done from January 2019 to January 2023 to evaluate diagnostic methods for patients with exudative pleural effusions (PE) of unknown etiologies. The demographic, radiological, procedural, and histological data of exudative PE patients were analyzed. All patients were examined for adenosine deaminase (ADA) and lymphocyte/neutrophil ratio in pleural fluid. Ultrasound-guided Abrams needle biopsy and video-assisted thoracoscopic surgery pleural biopsies were obtained, and histopathological results were assessed.
Results
Of 250 patients with PE, 161 (64%) had TB PE, 72 (28.8%) had malignant PE, and 17 (6.8%) had idiopathic PE. Sensitivity of ADA (≥40 U/l) was 88%, lymphocyte/neutrophil ratio (≥0.75) was 86.1%, and their overall sensitivity was 91%. They had 93.2, 86.3, and 100% specificity, respectively. For ultrasound-guided Abrams needle biopsy, the sensitivity of histopathology, culture, and combined histopathology/culture was 66, 46.5, and 78.4%, respectively. All were 100% specific. For thoracoscopic biopsy, the sensitivity of histopathology, culture, and combined histopathology/culture was 100, 86.6, and 100%, respectively. All were 100% specific. The assay sensitivity of pleural fluid and tissue Xpert *Mycobacterium tuberculosis*/rifampin resistance was 12.5 and 49.7%, respectively. Both were 100% specific. Combining ADA more than or equal to 40 U/l, lymphocyte/neutrophil ratio more than or equal to 0.75, and an ultrasound-guided Abrams needle biopsy yielded 92.4% sensitivity and 100% specificity.
Conclusion
Combining pleural fluid ADA more than or equal to 40 U/l, lymphocyte/neutrophil ratio more than or equal to 0.75, and ultrasound-guided Abrams needle biopsy can accurately detect TB PE in high-TB populations. It may be an affordable alternative to thoracoscopy in countries with limited resources.

Keywords:
pleural effusion, thoracoscopy, tuberculosis

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Introduction

In 2021, infection with *Mycobacterium tuberculosis* (MTB) was the second leading infectious disease killer, following coronavirus disease 2019. It caused 10.6 million cases of active TB disease and killed 1.6 million people globally [1].

Pleural tuberculosis (TB) is a prevalent condition with comparable epidemiological features to pulmonary TB. This condition can either self-resolve or proceed to TB empyema, which can cause severe complications, including chronic fibrothorax or empyema necessitans. The risk of developing and progressing to pulmonary TB is also significant. Diagnosing pleural TB can be difficult due to its paucibacillary nature. However, obtaining a microbiological diagnosis is crucial, especially when drug resistance is suspected. Moreover, advances in mycobacterium culture media and PCR-based procedures have improved the outcome of mycobacterial tests [2].

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Pleural TB is the second most frequent form of extrapulmonary TB after TB lymphadenitis and is responsible for 15–25% of TB cases globally and up to 50% of TB in immunocompromised populations. Pleural TB has similar epidemiological characteristics to pulmonary TB, with a higher frequency in males, immunosuppressed individuals, and socioeconomically poor groups [3,4].

Patients who have pleural TB are more likely to have coexisting pulmonary TB, with parenchymal disease being found in as much as 85% of computed tomography (CT) scans performed on these patients [5].

Pleural TB is believed to be a delayed hypersensitivity reaction caused by MTB bacilli in the pleura and pleural space [6]. It typically occurs 6–12 weeks after a primary infection or due to reactivation of TB in low-TB incidence areas [7]. MTB bacilli typically enter the pleural space through the rupture of a subpleural caseous focus, even without overt parenchymal illness [6].

Patients and methods

This prospective study was conducted between January 2019 and January 2023 in Benha and Zagazig University Hospitals in Egypt. A clinical workup for pleural effusion was performed on every patient. This workup included a chest radiograph, sputum smears for acid-fast bacilli (AFB), and pleural fluid analysis, including biochemistry, cytology, and microbiology. CT chest with intravenous contrast was done routinely for all patients. A diagnosis of pleural effusion (PE) of unknown etiology was made after all these investigations, and no diagnosis was established. The study included all patients with exudative PE of unknown etiology based on Light's criteria. All patients were screened for HIV. HIV-positive patients were excluded from this study. A written informed consent was acquired. The local ethics committee approved the study.

Every pleural biopsy was obtained using a standardized protocol. Local anesthesia was administered to the thoracic wall while the patient was in the sitting position. An ultrasound-guided Abrams needle collected pleural fluid, and four to six biopsy specimens were taken. Flexible bronchoscopy with broncho-alveolar lavage was done. Under general anesthesia, video-assisted thoracoscopic surgery (VATS) was done, and biopsies were taken from evident inflammatory regions. An intercostal drain was inserted for up to 72 h after VATS. No serious postoperative complications developed.

Pleural samples were kept in saline for TB culture and 4% formalin for histology and AFB staining. AFB was stained using the Ziehl–Neelsen method, and mycobacteria were cultured on solid media alongside the conventional Bactec procedure. Bronchial wash was processed for AFB staining and TB culture. The pleural fluid's pH, biochemical indicators, Gram stain, bacterial and TB culture, cytology, and differential white blood cell count were all evaluated. The adenosine deaminase (ADA) was measured. Pleural fluid and pleural tissue Xpert MTB/rifampin (RIF) assay were examined.

TB pleurisy was diagnosed when pleural fluid or bronchial wash tested positive for AFB or MTB, or pleural biopsy specimens showed granulomatous inflammation and caseous necrosis on histopathology. Malignancy was identified with pleural biopsy or bronchoscopy. Idiopathic effusions are those that cannot be diagnosed with all available information.

Patients with TB pleurisy were treated with a 6-month anti-TB regimen and followed up for 6 months after therapy.

Statistical analysis

SPSS (IBM Crop. Released 2023. IBM SPSS Statistics for Windows, Armonk, NY, USA), version 29.0.2.0 was used for the statistical analysis of the collected data. Results were given as mean±SD, median, and range or numbers of patients with the percentage in parenthesis.

A standard sample size equation was used to calculate the sample size. We used the 20% proportion of PE of unknown etiology as previously reported in the literature [8]. Using a 95% confidence interval and a 5% margin of error, the sample size was estimated to be 246 or larger.

Results

This prospective study included 250 patients with exudative PE of unknown etiology. The mean age was 49.3 ± 17.3 years. Of the 250 patients, 165 (66%) were males. Seventy-seven (30.8%) patients were current smokers, 70 (28%) patients were former smokers, and 102 (40.8%) patients had never smoked (Table 1). Twenty-five (10%) patients had diabetes, 24 (9.6%) patients had chronic obstructive pulmonary disease, and 18 (7.2%) patients had a history of close contact with TB patients. Twelve (4.8%) patients had liver cirrhosis. Furthermore, five (2%) patients were health care workers. Five (2%) patients had psychiatric problems, while another five (2%) were addicted to alcohol. Three (1.2%) patients received long-term corticosteroid therapy (Table 1).

The most prevalent symptoms were cough in 177 (70.8%) patients, fever in 175 (70%) patients, dyspnea in 127 (51%) patients, and chest pain in 107 (42.8%)

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patients. Other symptoms reported by some patients include expectoration in 92 (37%) patients, fatigue in 100 (40%) patients, weight loss in 50 (20%) patients, anorexia in 47 (18.8%) patients, and hemoptysis in seven (2.8%) patients (Table 2).

Regarding the site of PE, it was noted that 140 (56%) patients had right-sided PE, 85 (34%) patients had left-sided PE, and 25 (10%) patients had bilateral PE. The PE size ranged from small in 53 (21.2%) patients to moderate in 50 (20%) patients to large in 147 (58.8%) patients. The color of PE was yellowish in 212 (84.8%) patients and blood-stained in 38 (15.2%) patients. No chylous effusion was detected in this study (Table 3).

The mean pleural fluid pH was 7.31 ± 1.2, with a median of 7.30 and a range of 7.21–7.45. The mean pleural fluid leukocytic count was 3899 ± 6341 cells/mm^3, with a median of 2250 cells/mm^3 and a range of 29–18 000 cells/mm^3. The mean pleural fluid lymphocyte percentage was 76.2 ± 20.1%, with a median of 81.3% and a range of 3–95%. The mean total protein concentration in pleural fluid was 49 ± 9 g/l, with a median of 50.2 g/l and a range of 21–69 g/l. The mean pleural fluid glucose was 60.3 ± 10.9 g%, with a median of 62 g% and a range of 45–150 g%. The mean pleural fluid lactate dehydrogenase was 755.3 ± 1288.7 U/l, with a median of 488 U/l and a range of 42–17 500 U/l. The mean pleural fluid ADA was 112.9 ± 49.5 U/l, with a median of 116 U/l and a range of 23–433 U/l. The mean pleural fluid cholesterol level was 95.12 ± 38.6 mg/dl, with a median of 91.6 mg/dl and a range of 10.82–167.8 mg/dl (Table 4).

Table 1 Demographic data and patients' characteristics

Variables	Mean±SD or *n* (%)
Age, years	49.3 ± 17.3
Sex, male	165 (66)
Smoking	
Current smoker	77 (30.8)
Ex-smoker	70 (28)
Never smoked	102 (40.8)
Diabetic patients	25 (10)
Long-term corticosteroid treatment	3 (1.2)
Close contact with TB patients	18 (7.2)
Alcoholism	5 (2)
Chronic obstructive pulmonary disease	24 (9.6)
Associated neoplasia	0
Psychiatric disorders	5 (2)
Liver cirrhosis	12 (4.8)
Health care workers	5 (2)

TB, tuberculosis.

Table 2 Symptoms of patients with pleural effusions of unknown etiology

Symptoms	*n* (%)
Cough	177 (70.8)
Fever	175 (70)
Dyspnea	127 (51)
Chest pain	107 (42.8)
Expectoration	92 (37)
Fatigue	100 (40)
Loss of weight	50 (20)
Anorexia	47 (18.8)
Hemoptysis	3 (3)

CT imaging revealed lung consolidations and infiltrations in 127 (50.8%) patients. One hundred five (42%) patients had lung atelectasis. Lung masses or nodules were noted in 62 (24.8%) patients. Mediastinal lymphadenopathy was detected in 112 (44.8%) patients. Pleural thickening was observed in 82 (32.8%) patients, while pleural nodularity was noted in 10 (4%) patients (Fig. 1 and Table 5).

The results of the thoracoscopy examination showed that 177 (70.8%) patients had pleural nodules, while 167 (66.8%) patients had pleural adhesions. One hundred fifty-five (62%) patients had hyperemia, 17 (6.8%) patients had plaque-like lesions, and two (6.8%) patients had ulcers. During VATS, lung masses or nodules were detected in 42 (16.8%) patients (Figs 2–4 and Table 5).

Bronchial wash was positive for TB in 15 (6%) patients with poor sensitivity (9.3%). Pleural fluid cultures showed the same results (Table 6).

ADA levels above 40 U/l were detected in 140 (56%) patients, and the sensitivity of ADA was 88% when it was above 40 U/l. The lymphocyte/neutrophil ratio of more than 0.75 was recorded in 155 (62%) patients, and the sensitivity of the lymphocyte/neutrophil ratio was 86.1% when it was above 0.75. The overall sensitivity of ADA more than or equal to 40 U/l and lymphocyte/neutrophil more than or equal to 0.75

Table 3 Side, size, and color of pleural effusions

Effusion side	*n* (%)	Size of effusion	*n* (%)	Effusion color	*n* (%)
Right	140 (56)	Small	52 (20.8)	Yellowish	212 (84.8)
Left	85 (34)	Moderate	50 (20)	Blood-stained	37 (14.8)
Bilateral	25 (10)	Large	147 (58.8)	Chylous	0

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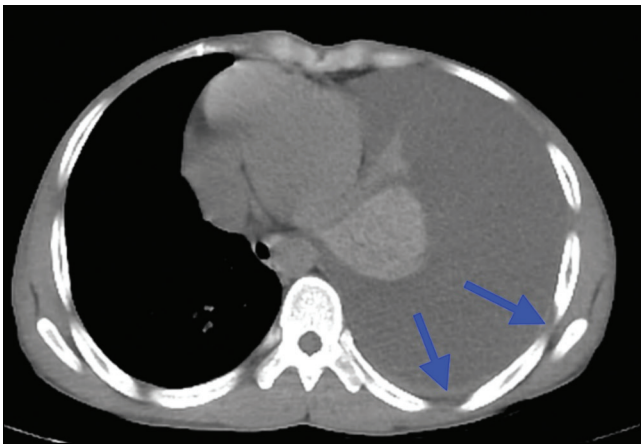
Table 4 Chemical properties of pleural effusions

Pleural fluid analysis	Mean±SD	Median	Range
pH	7.31 ± 1.2	7.30	7.21–7.45
Leukocytic count, cells/mm^3	3899 ± 6341	2250	29–18 000
Lymphocytes, %	76.2 ± 20.1	81.3	3–95
Total proteins, g/l	49 ± 9	50.2	21–69
Glucose, g%	60.3 ± 10.9	62	45–150
LDH, U/l	755.3 ± 1288.7	488	42–17 500
ADA, U/l	112.9 ± 49.5	116	23–433
Cholesterol, mg/dl	95.12 ± 38.6	91.6	10.82–167.8

ADA, adenosine deaminase; LDH, lactate dehydrogenase.

Figure 1



Severe left pleural effusion with contralateral mediastinal shift, associated with collapse of the underlying left lung lobes and mild nonuniform scattered sheets of pleural thickening (arrows).

was 91%. Their specificity was 93.2, 86.3, and 100%, respectively (Table 6).

For ultrasound-guided Abrams needle biopsy, histopathology and AFB stain were positive in 105 (42%) patients, culture was positive in 74 (29.6%) patients, and the overall positive results of combined histopathology/culture were positive in 124 (49.6%) patients. The sensitivity of histopathology, culture, and combined histopathology/culture was 66, 46.5, and 78.4%, respectively. Each method had 100% specificity (Table 6).

Combining ADA, a lymphocyte/neutrophil ratio of 0.75, and ultrasound-guided Abrams needle biopsy resulted in positive results in 147 (59%) patients with 92.4% sensitivity and 100% specificity (Table 6).

For thoracoscopic biopsy, histopathology and AFB stain were positive in 161 (64%) patients, culture was positive in 123 (49%) patients, and the overall positive results of combined histopathology/culture were positive in 161 (64%) patients. Sensitivity was 100, 86.6, and 100%, respectively. All have a 100% specificity (Fig. 5 and Table 6).

Pleural fluid Xpert was positive in 20 (8%) patients, while pleural tissue Xpert was positive in 108 (34.4%) patients. The sensitivity of pleural fluid and pleural tissue Xpert was 12.5 and 49.7%, respectively. Both were 100% specific (Table 6).

One hundred sixty-one (64%) patients were diagnosed with TB PE. Seventy-two (28.8%) patients had malignant PE. Seventeen (6.8%) patients had idiopathic PE (Table 7).

An anti-TB therapy regimen that lasted for 6 months was administered to patients who had been diagnosed with TB pleurisy. Following the completion of the treatment, the patients were assessed for a further 6 months. On follow-up, 152 patients recovered well after completion of the anti-TB therapy. Two patients died after acute myocardial infarction. Seven patients were lost to follow-up.

Malignant PE was detected in 72 (28.8%) patients. Metastatic adenocarcinoma was diagnosed in 52 patients with primary lung cancer, while mesothelioma was observed in eight patients. The remaining cases with malignant PE were seven patients with primary breast cancer and five patients with primary ovarian carcinoma. All patients with malignant PE were detected by VATS. Five patients were detected by ultrasound-guided Abrams needle biopsy.

The 17 (6.8%) patients with idiopathic PE were followed up closely for 6 months. Nine patients recovered spontaneously without long-term medications (most probably, PE was a simple uncomplicated parapneumonic effusion that responded to initial antibiotic therapy). Five patients were diagnosed with rheumatoid arthritis and autoimmune pleuritis, which improved after starting corticosteroid treatment. The remaining three patients were lost to follow-up (Table 7).

Comment

There is a high degree of regional variation in the incidence of pleural TB, which depends on the general

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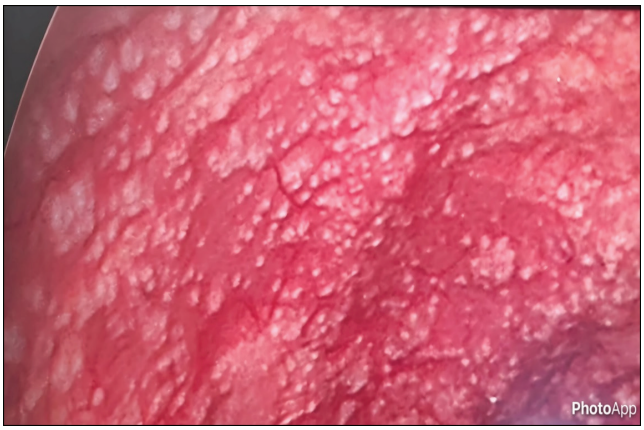
Table 5 Computed tomography and thoracoscopic findings

CT imaging	*n* (%)	Thoracoscopic finding	*n* (%)
Lung consolidations and infiltrations	127 (50.8)	Pleural nodules	177 (70.8)
Lung atelectasis	105 (42)	Pleural adhesions	167 (66.8)
Lung masses or nodules	62 (24.8)	Hyperemia	155 (62)
Mediastinal lymphadenopathy	112 (44.8)	Plaque-like lesions	17 (6.8)
Pleural thickening	82 (32.8)	Ulcers	2 (0.8)
Pleural nodularity	10 (4)	Lung masses or nodules	42 (16.8)

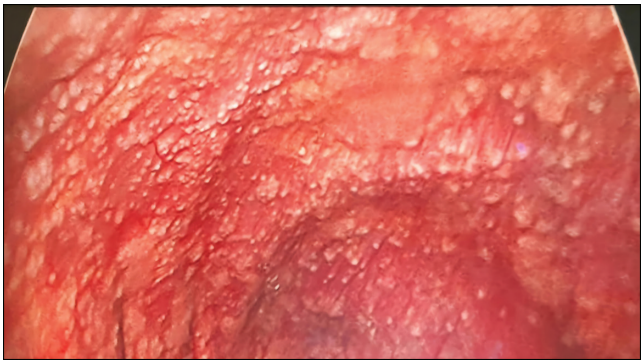
CT, computed tomography.

Figure 2



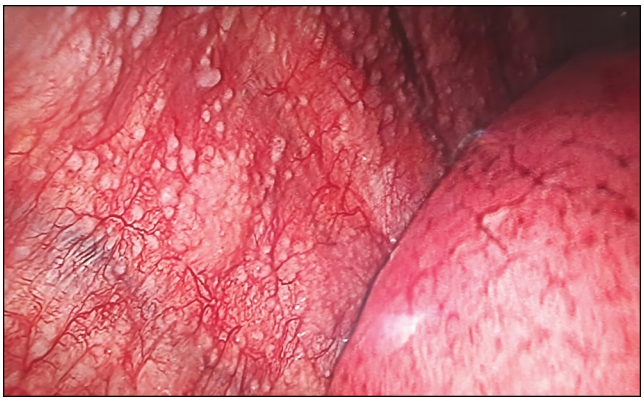
Thoracoscopic imaging showing pleural thickening and nodularities suggestive of TB pleurisy. TB, tuberculosis.

Figure 3



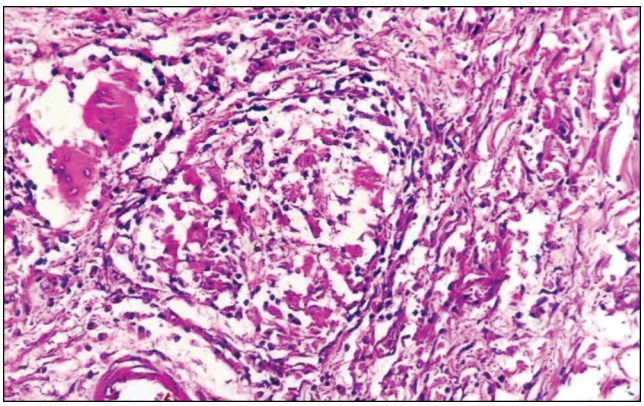
Thoracoscopic imaging showing pleural thickening and nodularities suggestive of TB. TB, tuberculosis.

Figure 4



Thoracoscopic imaging showing pleural thickening and nodularities suggestive of TB pleurisy. TB, tuberculosis.

Figure 5



Microscopic imaging of pleural tuberculosis (hematoxylin and eosin stain) showing granulomatous lesions with central caseous necrosis with the presence of epithelioid cells and Langhans giant cells.

prevalence of TB infection. The final diagnosis of pleural TB was found in 82% of the patients with exudative PE of unknown etiology in a study that was performed in South Africa. On the other hand, pleural TB was only present in 2% of the cases examined in a review of 147 thoracoscopies carried out in Denmark [2].

Diagnosing TB PE as the cause of an exudative PE can be challenging due to similarities in clinical symptoms and laboratory findings in the lack of histopathological diagnosis. TB PE occurs when a subpleural lung parenchymal caseous focus ruptures, resulting in a delayed hypersensitivity reaction to mycobacterial proteins. Mycobacterial burden is often minimal, which explains why microscopic analysis of pleural fluid is rarely positive for TB [6]. The growth of mycobacterial TB in pleural fluid requires many weeks and has a very low sensitivity that may range between 24 and 58% [9].

With this diagnostic challenge, numerous biomarkers that are present in pleural fluid have been thoroughly assessed to diagnose TB PE. These biomarkers, such as pleural fluid interferon-γ, interleukin-27, and ADA, are helpful in the diagnosis of TB PE [10].

Table 6 Comparison between different diagnostic tools for exudative pleural effusion of unknown etiology in 250 patients

	Positive (false positive) *n* (%)	Negative (false negative) *n* (%)	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Bronchial wash	15	235 (146)	9.3	100	1	0.61
Pleural fluid						
Culture	15	235 (146)	9.3	100	1	0.61
ADA ≥40 U/l	140 (8)	110 (19)	88	93.2	0.94	0.85
L/N ≥0.75	155 (15)	95 (25)	86.1	86.3	0.91	0.79
ADA ≥40 U/l and L/N ≥0.75	142	108 (14)	91	100	1	0.88
Abrams needle biopsy						
Histopathology and AFB stain	105	145 (54)	66.0	100	1	0.72
Culture	74	176 (85)	46.5	100	1	0.67
Overall	124	126 (34)	78.4	100	1	0.78
Thoracoscopic biopsy						
Histopathology and AFB stain	161	89	100	100	1	1
Culture	123	127 (19)	86.6	100	1	0.86
Overall	161	89	100	100	1	1
Xpert MTB/RIF (*Mycobacterium tuberculosis*/rifampin resistance) assay						
Pleural fluid Xpert	20	230 (140)	12.5	100	1	0.62
Pleural tissue Xpert	108	142 (109)	49.7	100	1	0.56
Combined Abrams needle biopsy, ADA ≥40 U/l and L/N ≥0.75	147	103 (12)	92.4	100	1	0.89

ADA, adenosine deaminase; AFB, acid-fast bacilli; L/N, lymphocyte/neutrophil.

Table 7 Final diagnosis of the causes of pleural effusion (*N*=250)

Final diagnosis	*n* (%)
Tuberculosis	161 (64)
Malignancy	72 (28.8)
From primary lung cancer	52 (20.8)
From primary breast cancer	7 (2.8)
From primary ovarian carcinoma	5 (2)
Mesothelioma	8 (3.2)
Idiopathic	17 (6.8)
Spontaneous recovery	9 (3.6)
Rheumatoid arthritis (autoimmune pleurisy)	5 (2)
Lost to follow-up	3 (1.2)

However, the evaluation of pleural fluid interferon-γ and interleukin-27 is prohibitively expensive and has a restricted clinical application, especially in countries with limited resources. Moreover, using these biomarkers instead of culture or biopsy does not offer a definitive diagnosis for TB PE [11].

A definitive diagnosis of TB PE requires the presence of mycobacterial TB bacilli in sputum or pleural specimens or the presence of epithelioid cell granulomas and/or caseating granulomas in pleural biopsy samples. Differential diagnosis of TB PE may necessitate more invasive maneuvers, such as ultrasound-guided Abrams needle biopsy and VATS, especially if multiple thoracenteses did not yield a precise diagnosis.

Ultrasound-guided Abrams needle biopsies are effective in investigating PEs [12,13]. Image-guided pleural needle biopsy may be the primary method of diagnosis for patients with CT-identified pleural thickening that can be targeted [13]. For patients with only PE on CT and no evident pleural pathology, VATS should be considered as the primary approach to diagnosis [14].

During VATS, we observed various abnormalities on the parietal and/or visceral pleura surface in all patients. These abnormalities included pleural nodules, pleural adhesion, hyperemia, pleural plaques, and ulceration. Our current study proved that all patients with TB PE (100%) could be accurately diagnosed with the implementation of pleural biopsy under VATS. Our data suggests that VATS is a highly effective and safe diagnostic method for managing TB PE.

In TB-endemic areas, combining pleural fluid ADA, differential cell count, and ultrasound-guided Abrams needle biopsy can all be used to reliably detect TB PE with a sensitivity of 92.7%, which is extremely close to results obtained by VATS biopsies that have a 100% sensitivity. This approach may be a less expensive option for thoracoscopy in countries with limited resources.

A large number of patients with exudative PE were included in the study, which was one of the strengths of the current study. The study population was explored and included 250 individuals altogether. Moreover, being a prospective study gives another strength to this study. Nevertheless, our research was not without restrictions. In the first place, HIV-positive patients

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were excluded from this study. Including HIV-positive participants requires classification based on CD4 count and clinical stage of the disease. We found it unfeasible to conduct this study with a significantly larger population if HIV-positive patients were included in this study. Moreover the literature indicates that HIV-positive and HIV-negative individuals with TB pleurisy have identical pleural fluid properties [15,16] and that HIV status does not affect ADA [17]. HIV-positive patients with TB pleurisy have a greater rate of positive pleural fluid smears [18]. So, it was suggested that a combined alternative approach may provide even better results in HIV-positive patients than with thoracoscopy.

The unsatisfactory results of the pleural fluid Xpert MTB/RIF assay, which had a sensitivity of only 16%, precluded its frequent usage for diagnosing TB PE [19]. However, a thoracoscopic pleural biopsy increased the accuracy of the Xpert MTB/RIF assay in diagnosing TB PE. Its sensitivity increased to 44.9% compared to the pleural fluid [20,21]. Testing pleural tissue for Xpert MTB/RIF assay is beneficial in high TB prevalence settings as it increases confidence in diagnosis and aids in early detection of multidrug-resistant TB.

Xpert data can be obtained within hours of a thoracoscopy procedure, unlike histopathology, which might take 3–5 days. The early appearance of these results makes the importance of Xpert MTB/RIF assay go beyond its role in diagnosising and detecting drug resistance. If the Xpert test is positive, this could be achieved by starting antitubercular therapy on the same day and removing the intercostal tube. Therefore, clinicians can discharge patients earlier and decrease the cost of hospital stays. Moreover, if the Xpert test is negative, malignancy is more likely. The clinician can leave the intercostal tube in place until the histopathology report is ready to perform pleurodesis through the intercostal tube if the biopsy confirms malignancy [21].

In conclusion, this study confirms that VATS pleural biopsy is the gold standard for diagnosing TB pleurisy. However, this study recommends managing exudative PEs of unknown etiology in a high-incidence area for TB. When diagnosing TB pleurisy, the first necessary step is determining the level of ADA in the pleural fluid combined with the lymphocyte/neutrophil ratio. If thoracoscopy is available and there is suspicion of TB pleurisy, thoracoscopy will be the diagnostic method of choice. If thoracoscopy is unavailable, an ultrasound-guided Abrams needle biopsy, along with pleural fluid analysis for ADA and lymphocyte/neutrophil ratio, will be an excellent alternative to thoracoscopy. This strategy offers a cost-effective and minimally-invasive diagnostic method for managing TB PE, especially in countries with limited resources.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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