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*Original Article*

# High diagnostic accuracy of flexible thoracoscopy for distinguishing tuberculous from malignant pleural effusions

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**Abstract:** Objective: To evaluate the diagnostic accuracy of flexible thoracoscopy in distinguishing between tuberculous pleural effusion (TPE) and malignant pleural effusion (MPE), and to provide clinicians with a reliable method for accurate diagnosis and a basis for appropriate treatment. Methods: This retrospective study was conducted at the Second People's Hospital of Gansu Province from April 2021 to June 2023. A total of 161 patients with confirmed pleural effusion were included. All patients underwent flexible thoracoscopy using the Olympus LTF-240 electronic thoracoscope. Histopathologic findings were used as the diagnostic gold standard. Results: Under flexible thoracoscopy, pleural features of TPE commonly included hyperemia, edema, fibrous adhesions, and miliary nodules. In contrast, MPE was characterized by multiple nodules, masses, leukoplakia-like changes, and pleural thickening. The areas under the curve for diagnosing TPE and MPE using flexible thoracoscopy were 0.895 and 0.883, respectively. Diagnostic performance was superior in patients with bloody pleural effusion compared to those without. There was no significant difference in the overall complication rates between the TPE and MPE groups ($P>0.05$). Additionally, in TPE patients, lactate dehydrogenase, adenosine deaminase, and tumor markers were not significantly correlated (both $P>0.05$), whereas in MPE patients, a negative correlation was observed ($P<0.05$). Conclusion: Flexible thoracoscopy demonstrated high diagnostic accuracy in differentiating TPE from MPE and was associated with good safety and patient tolerance, making it a valuable diagnostic tool in clinical practice.

**Keywords:** Flexible thoracoscopy, tuberculous pleural effusion, malignant pleural effusion, diagnostic accuracy

## Introduction

Pleural effusion (PE), the accumulation of fluid in the pleural cavity, is a common clinical condition with diverse etiologies, accounting for approximately 1.5 million new cases annually. Among its various causes, tuberculous pleural effusion (TPE) and malignant pleural effusion (MPE) are particularly challenging in terms of diagnosis and treatment [1].

TPE is an extrapulmonary manifestation of tuberculosis, typically resulting from a hypersensitivity reaction to mycobacterial antigens in the pleural space [2]. In regions with a high tuberculosis burden, TPE remains a predominant cause of PE. According to the World Health Organization, 6.3 million new tuberculosis cases were reported in 2017, with pleural involvement occurring in approximately 16% of these cases [3]. Early diagnosis and timely intervention are crucial to prevent complications such as pleural thickening, fibrous adhesions, and thoracic deformities, all of which can severely impair respiratory function and quality of life [4].

MPE, by contrast, is commonly associated with advanced-stage malignancies such as lung cancer, breast cancer, and lymphoma [5]. With the global rise in cancer incidence, the prevalence of MPE has also increased [6]. MPE is often indicative of poor prognosis and a shorter survival time. Moreover, it frequently causes severe symptoms such as dyspnea and chest pain, leading to substantial physical and psychological burden on patients, families, and healthcare systems [7].

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Traditional diagnostic approaches - including pleural fluid cytology and biochemical assays - provide limited sensitivity and are often inadequate for distinguishing between TPE and MPE in complex cases [8]. Imaging modalities such as chest CT scans also lack sufficient specificity for differential diagnosis. In this context, flexible thoracoscopy has emerged as a valuable diagnostic tool. This minimally invasive procedure allows direct visualization of pleural lesions, facilitates targeted biopsies, and substantially improves diagnostic yield [9].

Given the clinical importance of accurately differentiating TPE from MPE and the potential advantages of flexible thoracoscopy, this study aimed to assess the diagnostic performance of this technique in distinguishing between the two conditions.

## Materials and methods

### *Case selection*

We retrospectively reviewed patient records from the Second People's Hospital of Gansu Province between April 2021 and June 2023, identifying a total of 161 patients with PE.

Inclusion criteria: (1) Clear evidence of PE on chest ultrasound or computed tomography (CT); (2) Age over 18 years; (3) No prior anti-tuberculosis or anti-cancer treatment; (4) A definitive diagnosis confirmed by pathology or cytology; (5) Availability of complete medical records.

Exclusion criteria: (1) History of other pleural diseases; (2) Recent pleural interventions (e.g., thoracentesis, surgery); (3) Contraindications to thoracoscopy; (4) Presence of systemic diseases mimicking TPE or MPE (e.g., systemic lupus erythematosus, rheumatoid arthritis with pleural involvement); (5) Diagnosis of another solid malignancy within the past three years with potential pleural metastasis; (6) Pregnancy or lactation.

### *Intervention methods*

The diagnoses of TPE and MPE were based on the following criteria: TPE: Diagnosis met Light's criteria for exudative pleural effusion [10], with exclusion of malignancy. Mycobacterium tuberculosis was identified in sputum or pleural fluid smears. MPE: Also met Light's criteria for exudative effusion. Diagnosis was confirmed by pleural biopsy or exfoliative cytology of pleural fluid, along with immunohistochemical analysis. For diagnoses based on exfoliative cytology, the presence of malignant cells was confirmed in multiple effusion samples, with tuberculosis definitively excluded.

Flexible thoracoscopy was performed using the Olympus LTF-240 flexible electronic thoracoscope and its matched trocar under local anesthesia with sedation or general anesthesia. Patients were placed in a lateral decubitus position with the affected side upward. After a small incision and insertion of the puncture cannula, the thoracoscope was introduced for direct visualization. Following fluid drainage, the pleural surface was inspected for abnormalities such as granulomas, nodules, and thickening, and targeted biopsies were obtained.

In TPE cases, thoracoscopic findings typically included granulomatous lesions, hyperemia, and fibrinous exudates. Histologic analysis often revealed caseating granulomas and *Mycobacterium tuberculosis*. In MPE cases, irregular pleural thickening, nodules, or masses were observed, with biopsy confirming malignancy. Final histopathologic diagnosis served as the gold standard for evaluating the diagnostic performance of flexible thoracoscopy.

### *Data collection*

Data were extracted from the hospital's electronic medical records. For 161 patients with confirmed PE, baseline demographic information, pleural effusion characteristics, serum biomarker levels, and hematologic values were collected.

Specific data included: Serum biomarkers: lactate dehydrogenase (LDH), adenosine deaminase (ADA), carcinoembryonic antigen (CEA), cytokeratin fragment 21-1 (CYFRA21-1), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Effusion characteristics: volume, appearance, and other macroscopic features.

### *Primary and secondary outcomes*

*Primary outcome:* Diagnostic accuracy of flexible thoracoscopy in distinguishing TPE from

**Table 1.** Comparison of baseline data

| | TPE (n=70) | MPE (n=85) | $\chi^2$/t | P |
|---|---|---|---|---|
| Age, years | 65.76±4.53 | 66.19±4.80 | 0.569 | 0.570 |
| Gender, male | 39 | 50 | 0.152 | 0.697 |
| LDH, U/L | 226.74±70.51 | 174.84±52.97 | 5.228 | <0.001 |
| ADA, U/L | 47.47±8.80 | 19.59±5.76 | 23.696 | <0.001 |
| Albumin, g/l | 37.52±3.79 | 36.67±3.13 | 1.529 | 0.128 |
| Smoking history | 23 | 31 | 0.221 | 0.638 |
| Location of pleural effusion, left side | 29 | 44 | 1.646 | 0.200 |
| Color of pleural effusion, bloody pleural effusion | 18 | 50 | 17.089 | <0.001 |
| Length of hospital stay, days | 15.38±2.21 | 15.94±2.27 | 1.547 | 0.124 |
| CEA, ng/ml | 1.66±0.12 | 11.22±1.23 | 64.738 | <0.001 |
| CYFRA21-1, ng/ml | 1.24±0.45 | 5.71±1.29 | 27.627 | <0.001 |
| AST, U/L | 18.07±3.74 | 20.19±4.20 | 3.284 | 0.001 |
| ALT, U/L | 16.18±4.16 | 18.72±3.63 | 4.058 | <0.001 |
| Type of TPE | | | | |
| Pulmonary tuberculosis | 35 | | | |
| Tuberculous pleural effusion | 41 | | | |
| Type of MPE | | | | |
| Non small cell lung cancer | | 73 | | |
| Small cell lung cancer | | 12 | | |

Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion; LDH, lactate dehydrogenase; ADA, adenosine deaminase; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin fragment 21-1; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

MPE, determined by comparison with histologic diagnosis.

*Secondary outcomes:* (1) Correlation between LDH, ADA, and tumor markers and the type of PE (TPE vs. MPE); (2) Diagnostic sensitivity, specificity, and area under the ROC curve (AUC).

*Statistical analysis*

Statistical analyses were conducted using R software (version 4.2.0) and SPSS version 23.0. Continuous variables expressed as mean ± SD were compared using the t-test; categorical variables were expressed as frequencies (percentages) and analyzed using the chi-square test. Venn diagrams were used to illustrate the overlap in positive diagnostic results across different methods. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic performance, and AUC values and optimal cut-offs were calculated. Pearson correlation analysis was used to assess the relationships between LDH, ADA, and tumor markers in patients with different types of PE. A two-sided *P*-value of <0.05 was considered significant.

## Results

*Comparison of baseline characteristics*

Among the 161 patients, histologic diagnosis confirmed 70 cases of TPE 85 cases of MPE, 4 cases of empyema, and 2 cases of parapneumonic effusion. The baseline characteristics of TPE and MPE patients are summarized in **Table 1**. No significant differences were observed between the groups in age, sex, total protein level, smoking history, location of effusion, or length of hospital stay (all P>0.05). However, significant differences were found in levels of LDH, ADA, effusion color, CEA, CYFRA21-1, AST, or ALT.

*Comparison of thoracoscopic findings*

Under flexible thoracoscopy, the pleura of TPE patients typically exhibited hyperemia, edema, fibrous adhesions, miliary nodules, and carbon deposition. In contrast, MPE patients frequently presented with multiple pleural nodules of varying sizes and irregular shapes, often cauliflower-like or papillary in appearance. Other features included pleural surface roughness,

**Table 2.** Comparison of thoracoscopic findings

| | Congestion and edema | Fibrous adhesion | Pleural thickening | Leukoplakia-like changes | Miliary nodules | Multiple nodules and masses |
|---|---|---|---|---|---|---|
| TPE (n=70) | 62 | 59 | 29 | 3 | 37 | 13 |
| MPE (n=85) | 46 | 21 | 64 | 28 | 3 | 48 |
| $\chi^2$ | 21.568 | 54.563 | 18.344 | 19.701 | 48.784 | 23.102 |
| P | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

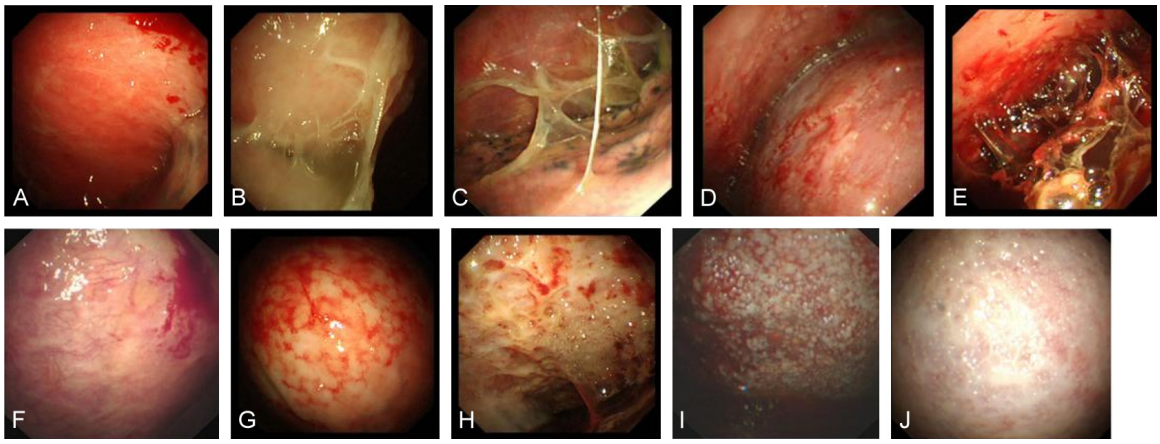


**Figure 1.** Pathologic images under thoracoscopy. A. TPE: Congestion and edema. B. TPE: Fibrous adhesion. C. TPE: Fibrous adhesion. D. TPE: Nodular lesions. E. TPE: Fibrous adhesion. F. MPE: Congestion and edema. G. MPE: Congestion and edema. H. MPE: Fibrous adhesion. I. MPE: Leukoplakia-like changes. J. MPE: Multiple nodules. Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

**Table 3.** Comparison of diagnostic results between thoracoscopy and histopathology

| | | Histopathological diagnosis | | Total |
|---|---|---|---|---|
| TPE | | Positive | Negative | |
| Thoracoscopic diagnosis | Positive | 63 | 10 | 73 |
| | Negative | 7 | 81 | 88 |
| Total | | 70 | 91 | |
| MPE | | Positive | Negative | |
| Thoracoscopic diagnosis | Positive | 74 | 8 | 82 |
| | Negative | 11 | 68 | 79 |
| Total | | 85 | 76 | |

Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

hyperplasia, thickening, and leukoplakia-like changes.

Statistical analysis revealed that hyperemia, edema, fibrous adhesion, and miliary nodules were significantly more common in TPE, whereas multiple nodules or masses, leukoplakia-like changes, and pleural thickening were more prevalent in MPE (**Table 2**). Representative pathological images are shown in **Figure 1**.

*Comparison of diagnostic results between thoracoscopy and histopathology*

Flexible thoracoscopy yielded 78 diagnoses of TPE and 83 of MPE. The comparison between thoracoscopic and histologic diagnoses is presented in **Table 3** and **Figure 2**.

*Diagnostic performance of flexible thoracoscopy*

For TPE, flexible thoracoscopy achieved a specificity of 89.01%, sensitivity of 90.00%, and overall diagnostic accuracy of 89.44%, with an AUC of 0.895. For MPE, specificity was 89.47%, sensitivity 87.06%, accuracy 88.20%, and AUC 0.883 (**Figure 3**).

*Comparison of complication rates*

Complications reported in both groups included chest pain, bleeding, fever, incision infec-

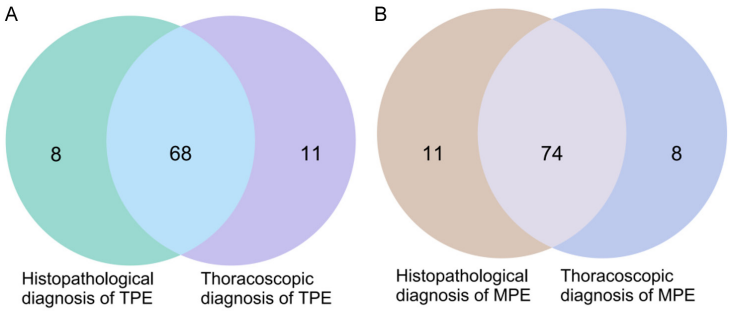


**Figure 2.** Agreement between thoracoscopic and histopathological diagnoses in patients with TPE and MPE. A. Venn diagram comparing thoracoscopic and histopathological diagnoses of TPE. B. Venn diagram comparing thoracoscopic and histopathological diagnoses of MPE. Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

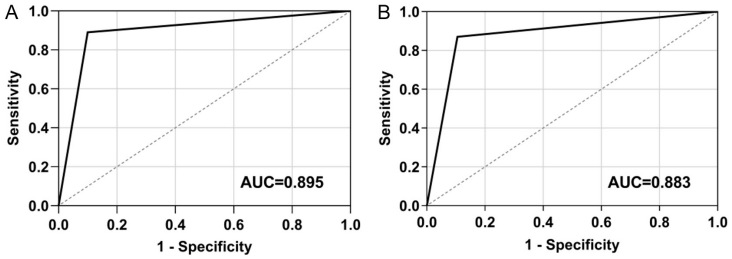


**Figure 3.** ROC curves of flexible thoracoscope for the diagnosis of TPE and MPE. A. The ROC curve of flexible thoracoscopy in the diagnosis of TPE. B. The ROC curve of flexible thoracoscopy in the diagnosis of MPE. Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

tion, and subcutaneous emphysema. The complication rate was 24.29% (17/70) in the TPE group and 25.88% (22/85) in the MPE group, with no statistically significant difference (P> 0.05) (**Table 4**).

*Biomarker correlations in TPE and MPE*

Pearson correlation analysis was used to evaluate relationships between LDH, ADA, and tumor markers (CEA, CYFRA21-1). No significant correlations were found in TPE patients (all P>0.05). However, in MPE patients, LDH and ADA levels were negatively correlated with both CEA and CYFRA21-1 (all P<0.05) (**Figure 4**).

*Diagnostic results based on pleural effusion appearance*

Among patients with hemorrhagic pleural effusion, flexible thoracoscopy diagnosed 25 cases of TPE and 48 cases of MPE. In the non-hemorrhagic group, 48 cases of TPE and 34 cases of MPE were diagnosed. Diagnostic comparisons against histopathology are shown in **Table 5** and **Figure 5**.

*Comparison of diagnostic efficacy by effusion appearance*

In hemorrhagic pleural effusion, the specificity, sensitivity, and accuracy of thoracoscopy for TPE were 82.00%, 88.89%, and 83.82%, respectively, with an AUC of 0.854. For MPE, the specificity was 80.00%, sensitivity 91.67%, accuracy 83.82%, and AUC 0.858.

In non-hemorrhagic effusions, the specificity, sensitivity, and accuracy for TPE were 83.33%, 80.39%, and 81.72%, with an AUC of 0.802; for MPE, the values were 83.61%, 75.00%, 80.65%, and AUC 0.793. Thoracoscopy demonstrated better diagnostic performance in hemorrhagic effusions compared to non-hemorrhagic ones (**Figure 6**).

## Discussion

Pleural effusion (PE) remains a diagnostic challenge in clinical practice, particularly for distinguishing between TPE and MPE. This study underscores the critical role of flexible thoracoscopy in improving diagnostic accuracy for these two common etiologies.

Our findings demonstrate that flexible thoracoscopy exhibits high diagnostic performance, with AUC values of 0.895 for TPE and 0.883 for MPE. These results confirm the reliability of this modality in differentiating pleural effusion etiologies. Compared to conventional diagnostic tools - including pleural fluid cytology, biochemical analysis, and imaging - flexible thoracoscopy offers direct visualization of pleural lesions and enables targeted biopsies, thereby significantly enhancing diagnostic yield [11, 12]. This technique is particularly valuable in complex or ambiguous cases, where traditional methods often fall short [13, 14].

The thoracoscopic features observed in TPE (e.g., pleural hyperemia, fibrous adhesions, miliary nodules) and MPE (e.g., irregular masses, leukoplakia-like changes, pleural thickening) reflect their underlying pathophysiology. In TPE, granulomatous inflammation driven by

**Table 4.** Comparison of complications

| | Chest pain | Bleeding | Fever | Incision infection | Subcutaneous emphysema | Total complications |
|---|---|---|---|---|---|---|
| TPE (n=70) | 3 | 2 | 3 | 2 | 7 | 17 |
| MPE (n=85) | 2 | 2 | 5 | 3 | 10 | 22 |
| $\chi^2$ | | | | | | 0.052 |
| P | | | | | | 0.820 |

Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

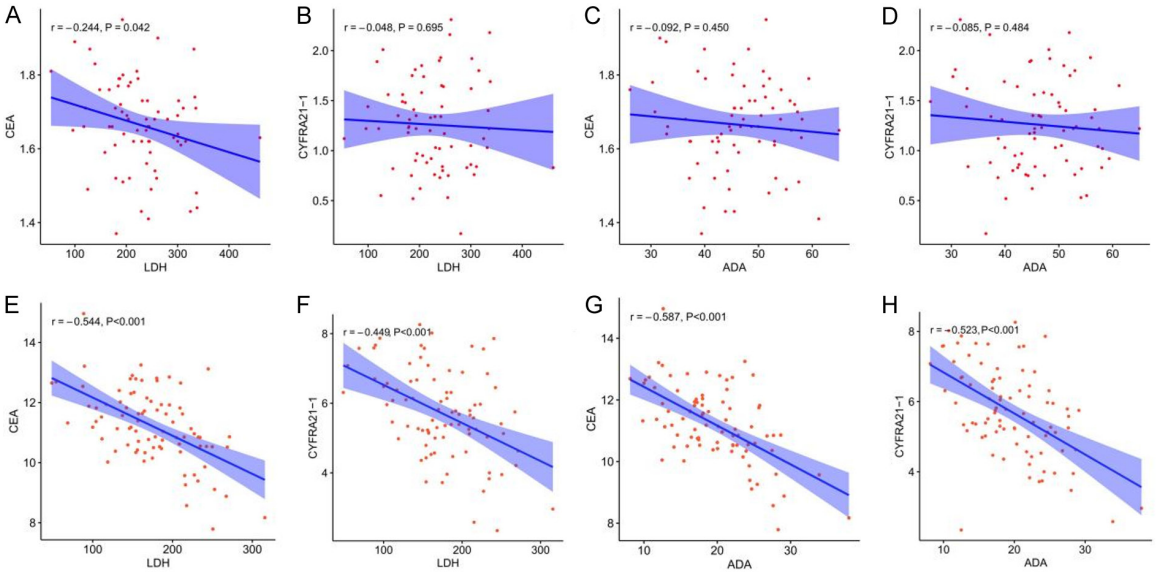


**Figure 4.** Biomarker correlations in TPE and MPE. A. There is no correlation between LDH and CEA in patients with TPE (r=-0.244, P=0.042). B. There is no correlation between LDH and CYFRA21-1 in patients with TPE (r=-0.048, P=0.695). C. There is no correlation between ADA and CEA in patients with TPE (r=-0.092, P=0.450). D. There is no correlation between ADA and CYFRA21-1 in patients with TPE (r=-0.085, P=0.484). E. There is a negative correlation between LDH and CEA in patients with MPE (r=-0.544, P<0.001). F. There is a negative correlation between LDH and CYFRA21-1 in patients with MPE (r=-0.449, P<0.001). G. There is a negative correlation between ADA and CEA in patients with MPE (r=-0.587, P<0.001). H. There is a negative correlation between ADA and CYFRA21-1 in patients with MPE (r=-0.523, P<0.001). Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion; LDH, lactate dehydrogenase; ADA, adenosine deaminase; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin fragment 21-1; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Mycobacterium tuberculosis leads to caseous necrosis and diffuse pleural inflammation [15]. In contrast, MPE is characterized by malignant cell invasion, desmoplastic responses, and vascular proliferation, accounting for its heterogenous and nodular thoracoscopic presentation [16]. The combination of visual pattern recognition and biopsy collection confers a synergistic diagnostic advantage over biomarker analysis alone.

On the biochemical front, markers such as LDH, ADA, CEA, and CYFRA21-1 differ substantially between TPE and MPE. Elevated ADA is commonly associated with TPE, while elevated CEA and CYFRA21-1 are typical in MPE. Prior studies, including that by Fei et al. [17], have reported the utility of LDH and ADA in diagnosing TPE. Our Pearson correlation analysis revealed that in TPE, there were no significant associations between LDH/ADA and tumor markers. However, in MPE, LDH and ADA levels showed a negative correlation with both CEA and CYFRA21-1. This suggests that in malignant effusions, tumor marker levels may reflect tumor metabolic activity and its effect on the pleural microenvironment.

The contrasting patterns likely reflect distinct pathophysiologic mechanisms. In TPE, elevated LDH and ADA are byproducts of immune-mediated tissue destruction, not directly influ-

**Table 5.** Diagnostic results based on pleural effusion appearance

| | | | Histopathological diagnosis | | Total |
|---|---|---|---|---|---|
| Hemorrhagic pleural effusion | TPE | | Positive | Negative | |
| | Thoracoscopic diagnosis | Positive | 16 | 9 | 25 |
| | | Negative | 2 | 41 | 43 |
| | Total | | 18 | 50 | 68 |
| | MPE | | Positive | Negative | |
| | Thoracoscopic diagnosis | Positive | 44 | 4 | 48 |
| | | Negative | 4 | 16 | 20 |
| | Total | | 48 | 20 | 68 |
| Non-hemorrhagic pleural effusion | TPE | | Positive | Negative | |
| | Thoracoscopic diagnosis | Positive | 41 | 7 | 48 |
| | | Negative | 10 | 35 | 45 |
| | Total | | 51 | 42 | 93 |
| | MPE | | Positive | Negative | |
| | Thoracoscopic diagnosis | Positive | 24 | 10 | 34 |
| | | Negative | 8 | 51 | 59 |
| | Total | | 32 | 61 | 93 |

Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

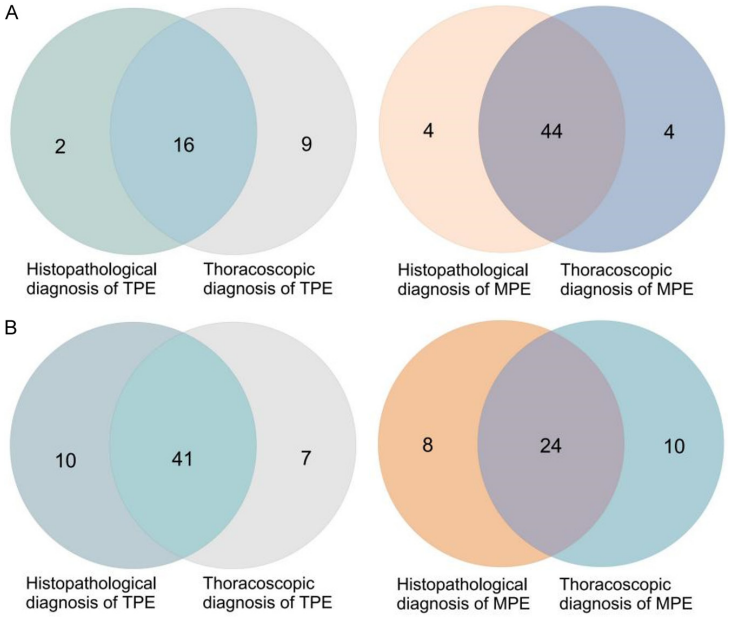


**Figure 5.** Thoracoscopic and histopathological diagnoses stratified by pleural effusion appearance. A. Venn diagrams for hemorrhagic pleural effusion: TPE (left), MPE (right). B. Venn diagrams for non-hemorrhagic pleural effusion: TPE (left), MPE (right). Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

Our data also show that the diagnostic performance of flexible thoracoscopy varies by effusion appearance. In patients with hemorrhagic pleural effusion, AUC values for diagnosing both TPE and MPE were higher (0.854 each) than in non-hemorrhagic effusions (0.802 and 0.793, respectively). This may be due to the higher prevalence of malignancy in bloody effusions, as tumor invasion of pleural vasculature can lead to hemorrhage [21]. The presence of blood may enhance visual contrast and lesion detectability, facilitating accurate sampling [22]. Conversely, non-hemorrhagic effusions often have more diverse etiologies and confounding factors, reducing diagnostic precision [23]. These findings underscore the importance of integrating effusion characteristics into the diagnostic framework for thoracoscopy.

enced by tumor markers [18]. In MPE, tumor cells may alter local metabolism - through rapid proliferation, angiogenesis, and high oxygen consumption - leading to reduced extracellular enzyme release and an inverse relationship with ADA/LDH levels [19, 20].

Importantly, the procedure demonstrated good safety. The overall complication rates were similar between the TPE (24.29%) and MPE (25.88%) groups, and primarily involved minor, self-limited events such as chest pain and mild fever. No severe complications (e.g., empyema,

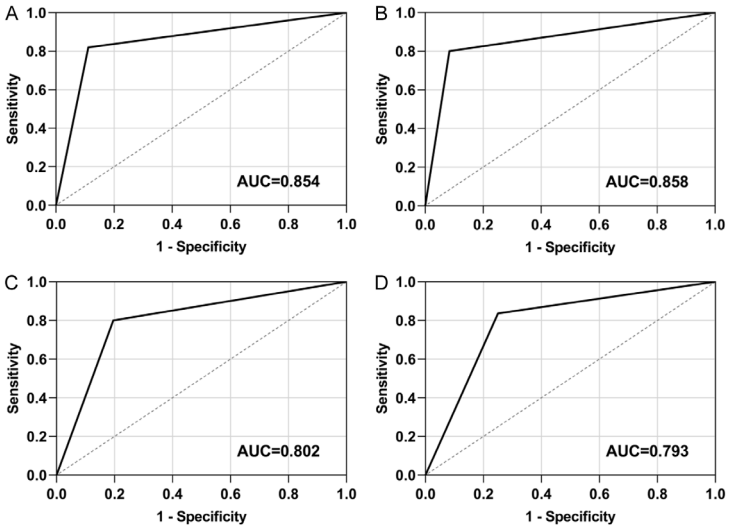


**Figure 6.** Diagnostic efficacy of the flexible thoracoscope for patients with different colors of pleural effusion. A. ROC curve of flexible thoracoscopy in the diagnosis of TPE in hemorrhagic pleural effusion. B. ROC curve of flexible thoracoscopy in the diagnosis of MPE in hemorrhagic pleural effusion. C. ROC curve of flexible thoracoscopy in the diagnosis of TPE in non-hemorrhagic pleural effusion. D. ROC curve of flexible thoracoscopy in the diagnosis of MPE in non-hemorrhagic pleural effusion. Note: TPE, tuberculous pleural effusion; MPE, malignant pleural effusion.

bronchopleural fistula) were observed [24], supporting the feasibility of performing flexible thoracoscopy even in resource-limited settings. With proper training, it may be safely implemented as an outpatient or day-case procedure to expedite diagnosis and reduce hospital burden.

This study had several limitations. First, it was a single-center retrospective analysis, which may have introduced selection bias and limit the generalizability of the findings. Future research should include multicenter, large-sample prospective studies to validate the clinical utility of flexible thoracoscopy in distinguishing TPE from MPE. Additionally, integration of molecular diagnostics or novel biomarkers with thoracoscopic findings may further improve diagnostic precision. Lastly, the promotion of standardized training for thoracoscopy operators is essential to enhance procedural consistency, minimize complications, and facilitate broader clinical adoption.

## Conclusion

Flexible thoracoscopy provides excellent diagnostic accuracy in differentiating TPE from MPE, with favorable safety and patient tolerance profiles. It should be considered a frontline tool for the evaluation of undiagnosed pleural effusions.

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## Disclosure of conflict of interest

None.

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