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CLINICO-HISTOPATHOLOGICAL CHARACTERISTICS OF UNDIAGNOSED PLEURAL EFFUSION PATIENTS UNDERGOING MEDICAL THORACOSCOPY IN A TERTIARY CARE CENTRE OF SOUTHERN RAJASTHAN

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ABSTRACT

Background: Pleural effusion remains a common clinical problem with diverse etiologies, including malignancy and tuberculosis. Despite routine diagnostic investigations such as pleural fluid cytology, biochemical testing, and imaging, approximately 20–25% of cases remain undiagnosed. Medical thoracoscopy provides direct visualization of pleural pathology and targeted biopsy, improving diagnostic accuracy. Limited regional data exist regarding its diagnostic utility in Southern Rajasthan.
Aim: To evaluate the clinico-histopathological characteristics and diagnostic yield of medical thoracoscopy in patients with undiagnosed pleural effusion.
Methods: This prospective observational study was conducted over four months (June–September 2025) at a tertiary care center in Southern Rajasthan. A total of 47 adult patients with exudative pleural effusion of unknown etiology after standard evaluation underwent medical thoracoscopy. Clinical presentation, radiological findings, thoracoscopic morphology, pleural fluid biochemistry, and histopathological outcomes were recorded. Statistical analysis included Chi-square and ANOVA tests, with a p-value <0.05 considered significant.
Results: A definitive histopathological diagnosis was achieved in 45 of 47 cases, yielding a diagnostic accuracy of 95.7%. Malignant pleural effusion was the most common etiology (57.4%) with adenocarcinoma metastasis being predominant, followed by mesothelioma. Tuberculosis accounted for 36.2% of cases and was the leading non-malignant cause. Malignant effusion patients were significantly older than non-malignant cases (p=0.0245). Fever (p=0.0002) and shorter illness duration significantly correlated with tuberculosis, while chest pain (p=0.0104) and massive effusion were more associated with malignancy. Thoracoscopic findings such as nodules (p=0.0001) favored malignancy, whereas sago-like nodules, adhesions, fibrinous deposits, and pleural thickening were

significantly associated with tubercular effusion. Pleural fluid analysis revealed significantly higher LDH levels in malignancy ($p<0.0001$) and elevated ADA in tuberculosis ($p<0.0001$). Lymphocyte predominance was observed in both etiologies and was not statistically significant.
Conclusion: Medical thoracoscopy proved to be a safe and highly effective diagnostic tool for undiagnosed pleural effusion, particularly in distinguishing between tuberculosis and malignancy. Its integration into diagnostic algorithms may reduce delays and improve clinical outcomes.

Keywords: Pleural effusion, Medical thoracoscopy, Histopathology, Malignant effusion, Tubercular effusion, Diagnostic yield

INTRODUCTION

Pleural effusion, also termed hydrothorax, refers to the pathological accumulation of excess fluid within the pleural cavity, a potential space located between the visceral and parietal pleura. Under physiological conditions, a small volume of pleural fluid is present, serving as a lubricant that facilitates frictionless movement of the lungs during respiration. However, when fluid accumulation exceeds normal volume, it may compromise lung expansion, impair gas exchange, and lead to varying degrees of respiratory distress depending on the underlying etiology and rate of accumulation [1].

The volume of pleural fluid is regulated by a delicate balance between production and resorption mediated primarily through the parietal pleural microvasculature and lymphatic drainage. Normally, pleural fluid is produced and absorbed at a rate of approximately 0.01–0.02 mL/kg/hour, ensuring homeostasis under physiological conditions. Disruptions in hydrostatic pressure, oncotic pressure, capillary permeability, or lymphatic obstruction may disturb this equilibrium, resulting in transudative or exudative pleural effusion. Pleural effusion is a common clinical finding associated with a wide spectrum of local and systemic disorders, including congestive heart failure, pneumonia, tuberculosis, pulmonary embolism, autoimmune diseases, and malignancies [2].

The diagnostic evaluation of suspected pleural effusion begins with clinical assessment and imaging. Chest radiography remains a widely used first-line tool; however, its sensitivity is limited, particularly in small-volume collections. In comparison, thoracic ultrasonography is more sensitive and can detect as little as 5 mL of pleural fluid while also guiding thoracentesis and identifying septations or loculations suggestive of infection or malignancy [3].

The primary step in the diagnostic workup after imaging is thoracentesis, which enables analysis of the pleural fluid's cytological, biochemical, and microbiological characteristics. Light's criteria remain the cornerstone for differentiating transudative from exudative effusions. Despite comprehensive clinical evaluation and pleural fluid analysis, including cytology and closed pleural biopsy, a substantial proportion—approximately 20–25%—of pleural effusions remain idiopathic or undiagnosed [4]. These unresolved cases pose significant clinical challenges and necessitate more advanced diagnostic modalities.

Medical thoracoscopy, also known as pleuroscopy, has emerged as a crucial minimally invasive method for diagnosing pleural diseases, particularly in cases where noninvasive methods are inconclusive. First performed in 1910 by Hans Christian Jacobaeus, often recognized as the "father of thoracoscopy," the procedure allows direct visualization of the pleural cavity with the advantage of obtaining targeted tissue biopsies under direct vision, improving diagnostic accuracy [5].

Multiple studies have demonstrated the superior diagnostic yield of medical thoracoscopy over closed pleural biopsy. For tubercular pleural effusion, diagnostic success with closed pleural biopsy ranges between 80–90%, whereas medical thoracoscopy reports yields approaching 100%. Similarly, for malignant pleural effusion, closed biopsy yields approximate sensitivity of 50–60%, compared to 91–95% achieved with thoracoscopy [3]. These findings highlight thoracoscopy as the recommended next step for undiagnosed effusions, particularly when tuberculosis or malignancy is suspected.

In addition to its diagnostic utility, medical thoracoscopy offers therapeutic benefits. It plays a vital role in the management of recurrent malignant pleural effusions through procedures such as chemical pleurodesis, usually using talc poudrage to prevent reaccumulation. It is also applied in adhesiolysis,

management of complicated pleural infections, repair of bronchopleural fistula, and drainage of loculated effusions. In select cases, advanced procedures including sympathectomy or splanchnolysis can be performed under thoracoscopic visualization [6].

While generally safe, medical thoracoscopy has contraindications. Absolute contraindications include the absence of pleural space due to extensive adhesions or prior pleurodesis and uncorrectable coagulation disorders. Relative contraindications include inability to tolerate lateral decubitus positioning, severe respiratory distress, refractory cough, unstable cardiopulmonary status, morbid obesity, central airway tumors, and recent myocardial infarction. Complications are uncommon and typically minor, most frequently including procedural pain, minor bleeding, subcutaneous emphysema, vasovagal episodes, and delayed pleural infection [7].

Technological advances have further improved thoracoscopic techniques. The sensitivity of rigid thoracoscopy ranges from 85–93%, while semirigid thoracoscopy demonstrates sensitivity and specificity of 91% and 100% respectively, with diagnostic performance now approaching that of video-assisted thoracoscopic surgery (VATS), yet with lower invasiveness and reduced resource requirements [8].

Given its superior diagnostic capacity, medical thoracoscopy has become an invaluable tool in the evaluation of pleural effusions, especially when malignancy is suspected. It allows direct macroscopic examination of the parietal and visceral pleura, diaphragmatic surface, and lung parenchyma, enabling targeted sampling from abnormal pleural areas. This visual guidance significantly enhances diagnostic accuracy over blind biopsy techniques [9].

Despite its recognized value, the availability and use of medical thoracoscopy remain limited in many regions due to factors such as lack of expertise, insufficient infrastructure, and absence of standardized utilization protocols. Existing literature from India, particularly from the western region, remains sparse. Therefore, further research is needed to evaluate clinical presentations, thoracoscopic findings, and histopathological outcomes in patients undergoing thoracoscopy for undiagnosed pleural effusion.

The present study is designed to explore the clinico-histopathological features of patients with undiagnosed pleural effusion undergoing medical thoracoscopy at a tertiary care center in Southern Rajasthan. The findings are expected to contribute meaningful insights into regional disease patterns, improve clinical understanding, and reinforce the role of thoracoscopy as a key diagnostic modality.

MATERIALS AND METHODS

Study Design: This study was designed as a prospective observational study.

Study Setting: The study was conducted in the Department of Tuberculosis and Chest Diseases at R.N.T. Medical College and associated tertiary care teaching hospital, Udaipur, Rajasthan.

Study Period: A total duration of four months, June 2025 to September 2025.

Study Population: The study population included adult patients presenting with pleural effusion in whom the etiology remained undiagnosed following routine diagnostic evaluation, including chest radiography, thoracic ultrasonography, pleural fluid cytology, microbiological testing, and biochemical analysis.

Inclusion Criteria

- Patients aged >18 years
- Patients with pleural effusion of unknown etiology after standard diagnostic evaluation
- Patients willing to undergo thoracoscopy
- Patients providing written informed consent

Exclusion Criteria

- Patients medically unfit for thoracoscopy (including severe respiratory distress, hemodynamic instability, inability to maintain lateral decubitus position, or morbid obesity)

- Patients with contraindications such as post-pleurodesis status, absence of pleural space, central airway tumors, or uncorrectable coagulopathy
- Patients with recent (≤1 month) acute coronary syndrome or severe cardiopulmonary compromise
- Patients unwilling or declining consent for participation or procedure

Sample Size: The sample size was calculated using the formula,

$$n = \frac{Z^2 \times P(1-P)}{d^2}$$

Where:

- Z = 1.96 for 95% confidence interval
- P = 1.29%
- d = 20%

The calculated sample size was 35.9, rounded to 36 participants.

Sampling Technique: A convenient purposive sampling method was used to enroll all eligible patients who met the inclusion criteria during the study period.

Study Procedure: All eligible patients underwent a systematic clinical evaluation including detailed history, physical examination, socioeconomic assessment, and documentation of respiratory symptoms such as cough, fever, chest pain, dyspnea, hemoptysis, and weight loss. Baseline laboratory investigations included complete blood count, coagulation profile, liver and renal function tests, serum LDH, viral markers, and calculation of body mass index.

Imaging evaluation included chest radiography followed by ultrasonography or CT scan where indicated. Diagnostic thoracentesis was performed under aseptic precautions, and pleural fluid samples were analyzed for cytology, CBNAAT, culture, pH, LDH level, and biochemical parameters. Light's criteria were applied to classify effusions as exudative or transudative [10].

Patients whose diagnosis remained inconclusive following evaluation were offered medical thoracoscopy. Written consent was obtained prior to the procedure.

Thoracoscopy was performed using the Olympus Medical System Model LTF-160. Patients were kept nil by mouth for at least six hours, and intravenous access was secured contralateral to the procedure site. Continuous monitoring of ECG, pulse oximetry, and blood pressure was ensured throughout the procedure. Local anesthesia using 10% lignocaine was administered, and a 1 cm incision was made over the desired intercostal space in the axillary line. The thoracoscope was introduced via a trocar, pleural fluid drained, and targeted biopsies obtained under direct visualization. Samples were sent for histopathological and microbiological evaluation. After biopsy, an intercostal drainage tube was placed, and post-procedure monitoring was continued for a minimum of two hours.

Patients were followed until final diagnosis was established based on thoracoscopic and histopathological findings. Data were entered into a prestructured proforma.

Statistical Analysis: Data were analyzed using SPSS statistical software (version 25). Descriptive statistics including mean, percentage, and standard deviation were used to summarize numerical and categorical variables. Categorical variables were compared using the Chi-square test, while continuous variables were analyzed with ANOVA to assess differences between diagnostic groups. A p-value <0.05 was considered statistically significant.

Ethical Considerations: Ethical approval for the study was obtained from the Institutional Ethics Committee of R.N.T. Medical College, Udaipur prior to initiation of data collection (IEC Approval No.: RNT/Acad./Ethical/2025/703 dated 27.05.2025). Written informed consent was obtained from all participants before inclusion. Confidentiality of patient identity and clinical records was strictly maintained throughout the study.

RESULTS

A total of 47 patients with undiagnosed pleural effusion underwent medical thoracoscopy with pleural biopsy. The diagnostic approach yielded conclusive etiological classification in 45 patients (95.7%), while 2 cases (4.3%) remained inconclusive, resulting in a diagnostic yield of 95.7%. Malignancy was the leading cause, with adenocarcinoma metastasis dominating the malignant subgroup, while tuberculosis accounted for nearly all non-malignant diagnoses. All metastatic malignancies originated from primary lung carcinoma. Table 1 shows the etiological distribution and histopathology findings.

Table 1. Etiological Distribution and Histopathology Findings (n=47)

Etiology Category	Diagnosis	Frequency (n)	% of Total
Malignant (n=27; 57.4%)	Adenocarcinoma Metastasis	17	36.2%
	Mesothelioma	6	12.8%
	Small Cell Carcinoma	3	6.4%
	Squamous Cell Carcinoma	1	2.1%
Non-Malignant (n=18; 38.3%)	Tuberculosis	17	36.2%
	Parapneumonic Effusion	1	2.1%
Inconclusive	Non-specific findings	2	4.3%

Patients with malignant effusion were significantly older (p=0.0245). No statistically significant associations were found between etiology and sex, residence, BMI, tobacco exposure, or alcohol intake. Table 2 shows demographic and habitual characteristics.

Table 2. Demographic and Habitual Characteristics

Parameter	Malignant (n=27)	Non-Malignant (n=18)	Total (n=47)	p-value
Mean Age (years)	62.4 ± 12.3	51.8 ± 15.6	58.3 ± 14.5	**0.0245***
Sex (Male %)	63%	55.6%	57.4%	0.208
Rural Residence %	77.8%	83.3%	80.9%	0.723
Normal BMI %	96.3%	100%	97.9%	0.588
Smoking History %	77.7%	72.2%	74.5%	0.156
Alcohol Use %	63%	50%	55.3%	0.387

*significant at $p<0.05$

Most malignant effusions presented late (>4 weeks), whereas tubercular effusions presented earlier and were significantly associated with fever. Chest pain was significantly more frequent in malignant effusions. Table 3 shows clinical profile and duration of illness.

Table 3. Clinical Profile and Duration of Illness

Variable	Malignant	Tubercular	Total	p-value
Symptom Duration >4 weeks (%)	88.9%	58.8%	72.3%	**0.0001***
Chest Pain (%)	85.2%	47.1%	-	**0.0104***
Fever (%)	14.8%	76.5%	-	**0.0002***
Dyspnea (%)	96.3%	88.2%	87.2%	0.55

*significant at $p<0.05$

Distinct thoracoscopic patterns emerged: nodules and hemorrhagic fluid strongly suggested malignancy, whereas adhesions, fibrin, and classic "sago-like nodules" supported a tubercular etiology. Table 4 shows thoracoscopic and radiological findings.

Table 4. Thoracoscopic and Radiological Findings

Variable	Malignant (n=27)	Tubercular (n=17)	Total	p-value
Nodules (%)	88.9%	23.5%	59.6%	**0.0001***
Sago-like Nodules (%)	0%	35.3%	12.8%	**0.003***
Pleural Adhesions (%)	11.1%	70.6%	31.9%	**0.001***
Fibrin Deposits (%)	7.4%	70.6%	29.8%	**0.001***
Massive Effusion (%)	59.3%	27.7%	44.7%	0.105
Right-sided Effusion (%)	77.8%	83.3%	80.8%	0.80
Hemorrhagic Fluid (%)	88.9%	16.7%	57.4%	**0.001***

*significant at $p<0.05$

LDH was significantly higher in malignant effusions, while ADA was markedly elevated in tubercular effusions. Table 5 shows pleural fluid analysis.

Table 5. Pleural Fluid Analysis

Parameter	Malignant	Tubercular	p-value
Protein (g/dL)	4.1 ± 0.5	4.9 ± 0.7	0.073
LDH (U/L)	855.9 ± 343.1	373.4 ± 105.9	**<0.0001***
Glucose (mg/dL)	66.4 ± 20.3	58.2 ± 25.4	0.27
ADA (U/L)	18.8 ± 9.0	84.4 ± 36.1	**<0.0001***

*significant at $p<0.05$

Lymphocytic predominance was characteristic across both malignant and tubercular effusions, with neutrophilia seen only in parapneumonic cases. Table 6 shows cellular predominance.

Table 6. Cytology—Cellular Predominance

Variable	Malignant	Tubercular	Total	p-value
Lymphocyte Predominant (%)	92.6%	100%	93.5 %	0.515
Neutrophil Predominant (%)	7.4%	0%	6.5%	-

Medical thoracoscopy demonstrated a high diagnostic yield in previously undiagnosed pleural effusions. Malignancy emerged as the most common etiology, with adenocarcinoma metastasis being predominant. Tuberculosis was the main non-malignant cause. Certain clinical, thoracoscopic, and biochemical markers—including fever, duration of symptoms, hemorrhagic fluid appearance, nodularity, ADA elevation, and LDH levels—showed statistically significant correlation with specific etiological groups, supporting their diagnostic value.

DISCUSSION

This prospective observational study evaluated the diagnostic role of medical thoracoscopy in patients with persistent undiagnosed pleural effusion despite repeated cytological, biochemical, and microbiological analysis. Thoracoscopy allows direct visualization of pleural abnormalities and guided biopsy, overcoming the limitations of blind pleural biopsy and conventional pleural fluid analysis. All 47 patients enrolled underwent thoracoscopic examination, and histopathological diagnosis was achieved in 45 cases (95.7%), demonstrating a high diagnostic yield. These findings align with previously published results, where the diagnostic accuracy of thoracoscopy has ranged between 74.3% and 95.7% across diverse clinical settings [9,11-15]. The consistency in achieving high diagnostic yield supports thoracoscopy as the preferred modality in evaluating exudative effusions when initial diagnostic measures fail.

In the present study, malignancy accounted for 57.4% of diagnosed cases and was the most common cause of pleural effusion. Tuberculosis was the predominant non-malignant etiology, contributing 36.2% of cases. A similar etiological distribution has been seen in prior studies from India and the Middle East, where malignancy slightly outweighs tuberculosis in thoracoscopy-based diagnostic cohorts [13-15]. In contrast, studies from regions with high tuberculosis burden, such as China and Southeast Asia, reported tuberculosis as the leading cause [9,12]. These differences reflect the interplay between regional cancer epidemiology, tuberculosis prevalence, and healthcare access patterns.

Among malignant pleural effusions, adenocarcinoma metastasis was the most common subtype, consistent with earlier reports from Kiani et al. [13] and Kho et al. [9]. All metastatic lesions were traced to a primary lung malignancy, reaffirming that lung cancer remains the leading cause of malignant pleural effusion. Mesothelioma was the second most frequent malignancy, consistent with its recognition as a pleural-based neoplasm with high diagnostic yield using thoracoscopy due to its characteristic diffuse pleural involvement.

A statistically significant age association ($p=0.0245$) was observed, with malignant effusions presenting at a higher mean age compared to benign effusions (62.4 vs. 51.8 years). This trend has been consistently reported globally, reflecting increasing cancer risk with advancing age [12-14]. The majority of patients (80.9%) belonged to rural backgrounds. Although residence did not correlate significantly with etiology, it reflects the referral pattern of tertiary centers serving rural populations more than etiological causation.

Smoking was common across both malignant and non-malignant groups without significant difference ($p=0.156$). Similar findings were observed by Shimoda et al. [16], suggesting that smoking predisposes to various respiratory and pleural pathologies rather than distinguishing malignant from infectious etiologies.

Certain symptoms demonstrated diagnostic value. Fever was strongly associated with tubercular effusion ($p<0.001$) and represents an important clinical indicator, consistent with established literature [18-20]. Conversely, chest pain was significantly higher in malignant pleural effusion ($p=0.0104$), likely reflecting pleural surface infiltration or nerve involvement. Dyspnea was nearly universal in both groups due to moderate-to-massive effusion volume required for thoracoscopy, consistent with the pathophysiology of mechanical lung compression [17].

A novel result in this study was the statistically significant association between duration of symptoms and etiology ($p<0.001$), where malignant effusions demonstrated a more chronic course (>4 weeks), while parapneumonic and many tubercular effusions presented earlier. No published thoracoscopic studies have previously highlighted symptom duration as a discriminatory factor, making this a meaningful contribution to diagnostic profiling.

Right-sided effusions were more frequent but did not correlate with etiology ($p=0.80$). Earlier studies have shown similar variability, asserting that pleural effusion laterality holds limited diagnostic value [20,21].

Thoracoscopic visualization, however, provided highly valuable diagnostic patterns. Pleural nodules were significantly associated with malignancy (88.9%, $p<0.001$), supporting previous evidence that nodularity strongly predicts malignant pathology [15]. In contrast, sago-like nodules, pleural adhesions, fibrinous strands, and pleural thickening were strongly linked to tuberculosis, all demonstrating significant p-values (<0.05). These patterns align with observations in studies by Kho et al. [9] and Arif et al. [15], confirming that thoracoscopic morphology can reliably distinguish malignant from tubercular effusions.

Fluid appearance also demonstrated significant diagnostic value. Haemorrhagic pleural fluid was strongly associated with malignancy (88.9%; $p=0.001$). Straw-colored effusion was strongly associated with tuberculosis, consistent with the findings of Arif et al. [15] and Lokesh et al. [20]. However, occasional hemorrhagic presentations in tuberculosis and straw-colored appearance in malignancy—as seen in prior studies including Koppu [22]—highlight the need for cautious interpretation.

Biochemical analysis also provided important diagnostic clues. Pleural fluid LDH was significantly elevated in malignant effusions ($p<0.0001$), reflecting high tumor cell turnover and necrosis, supporting observations from Devi et al. [23]. Meanwhile, ADA was markedly elevated in tubercular effusions ($p<0.0001$), consistent with prior evidence establishing ADA as a reliable discriminator between tuberculosis and malignancy [19,24]. Pleural fluid glucose and protein did not demonstrate diagnostic significance, in agreement with Kumar et al. [21], indicating limited standalone utility.

Cytological features revealed lymphocyte predominance in both malignant and tubercular effusions, with no statistically significant difference ($p=0.515$). These findings are consistent across multiple studies [16,19,20], confirming that cytology alone cannot differentiate etiologies, especially in lymphocyte-rich exudates.

Thoracoscopy was well tolerated, with no major complications reported. Minor post-procedure pain occurred in 17.3% of patients, managed conservatively. Comparable safety profiles have been reported in large cohorts [12,14,15], reaffirming the procedure's favorable risk-benefit profile.

The strong diagnostic ability of thoracoscopy demonstrated in this study emphasizes its role in early consideration for undiagnosed pleural effusions. Given the clear diagnostic distinction provided by thoracoscopic morphology, ADA and LDH levels, symptom duration, and pleural fluid appearance, a structured diagnostic pathway integrating these predictors may reduce diagnostic delays and unnecessary investigations

CONCLUSION

This study demonstrates that medical thoracoscopy is a highly effective diagnostic tool for evaluating undiagnosed pleural effusion, achieving a diagnostic yield of 95.7%. Malignancy emerged as the most common etiology, with adenocarcinoma metastasis being the predominant malignant subtype, while tuberculosis accounted for nearly all non-malignant effusions. Several clinical and investigative features showed significant diagnostic relevance: fever, shorter duration of symptoms, sago-like nodules, fibrinous adhesions, elevated ADA, and straw-colored pleural fluid were strongly associated with tubercular effusions, whereas chest pain, nodularity on thoracoscopy, hemorrhagic pleural fluid, and elevated LDH favored malignant etiology. Cytology alone could not reliably differentiate causes due to predominant lymphocytic patterns across groups. Thoracoscopy was safe and well-tolerated, with only minor, self-limiting complications observed. Overall, the findings reinforce medical thoracoscopy as a valuable diagnostic and decision-guiding modality, particularly in regions where tuberculosis and malignancy are leading causes of exudative pleural effusion.

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