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# Determining the Diagnostic Yield and Pathological Spectrum of Thoracoscopy in Patients with Undiagnosed Exudative Pleural Effusion

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## ABSTRACT
**Background**: Roughly one in five exudative pleural effusions remains undiagnosed after initial evaluation. Medical thoracoscopy allows targeted pleural biopsy, but its yield and pathological spectrum vary with regional tuberculosis burden and patient characteristics.
**Objective**: To determine the diagnostic yield and delineate the pathological spectrum of thoracoscopy in patients with undiagnosed exudative pleural effusion.
**Materials and Methods**: This descriptive cross-sectional study was conducted at the Department of Pulmonology, Lahore General Hospital, Lahore, from September 2025 to March 2026. Sixty-two patients aged 18–60 years with exudative pleural effusion, negative GeneXpert testing, and twice-negative pleural fluid cytology were enrolled through non-probability consecutive sampling. Medical thoracoscopy with targeted pleural biopsy was performed, and specimens underwent histopathological examination. Diagnostic yield was calculated with exact 95% confidence intervals (CIs). Stratified comparisons were performed using the chi-square or Fisher exact test, with $p < 0.05$ considered statistically significant.
**Results**: The mean age was 39.6 ± 10.7 years, and 36 patients (58.1%) were male. A histopathological diagnosis was established in 55 patients (diagnostic yield 88.7%; 95% CI 78.1–95.3). Tuberculous pleurisy was the most frequent diagnosis (29 patients; 46.8%), followed by malignant pleural effusion (17; 27.4%) and inflammatory pleuritis (9; 14.5%); 7 patients (11.3%) remained undiagnosed. Diagnostic yield did not differ by age group (93.8% vs 83.3%; $p = 0.249$), sex (88.9% vs 88.5%; $p = 1.000$), or duration of symptoms (87.5% vs 89.1%; $p = 1.000$).
**Conclusion**: Thoracoscopy established a histopathological diagnosis in nearly nine of ten patients, with tuberculosis the leading cause.
**Keywords**: Pleural Effusion; Thoracoscopy; Tuberculosis, Pleural; Pleural Effusion, Malignant; Biopsy

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## 1. INTRODUCTION
Pleural effusion is a frequent presentation in respiratory practice and accompanies a wide range of pleural, pulmonary, and systemic diseases, affecting an estimated 1.5 million patients annually in the United States.[1] Congestive heart failure, malignancy, pneumonia, and pulmonary embolism are the most common causes, and treatment and prognosis depend largely on the underlying etiology.[2] Pleural fluid accumulates when its production by the pleural capillaries exceeds lymphatic drainage, a balance governed by the hydrostatic and oncotic pressures acting across the pleural membranes.[3] Distinguishing a transudative from an exudative effusion constitutes the first diagnostic step, because an exudate indicates local pleural or pulmonary pathology and requires further investigation to establish its cause.[2,4]
Tuberculosis, malignancy, and parapneumonic effusion account for most exudative effusions. Despite thorough clinical assessment and initial investigations, including pleural fluid analysis and closed pleural biopsy, the cause remains undetermined in approximately 20% of patients.[5] Medical thoracoscopy, introduced in 1910, permits direct inspection of the pleural cavity and biopsy of abnormal areas, and is regarded as the investigation of choice when less invasive tests are inconclusive.[5,6] It also allows therapeutic procedures such as talc poudrage and adhesiolysis during the same session.[5] Pooled case series summarized in the British Thoracic Society guideline reported a diagnostic sensitivity of 92.6% for malignant pleural disease.[6] In undiagnosed exudative effusion, diagnostic yields between 79.4% and 99.2% have been reported from Malaysia,[5] India,[7] Egypt,[8] and a second Indian center,[9] with the range reflecting differences in case mix, thoracoscope type, and the definition of a
diagnostic result. The predominant diagnosis also varied between series, with malignancy leading in some and tuberculosis in others.
The etiological spectrum of exudative effusion differs between regions, and the relative frequency of tuberculosis and malignancy depends on the local burden of disease, patient age, and referral patterns. Hospital-based studies from Pakistan

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have identified tuberculosis as the most common cause of pleural effusion,[10] whereas most published thoracoscopy series enrolled patients with a median or mean age above 50 years,[5,9] and the yield and pathological spectrum in adults aged 18 to 60 years in this setting remain to be defined. Locally generated estimates are therefore needed to guide diagnostic decision-making in resource-limited settings, particularly where histopathological confirmation determines whether antituberculous or oncological treatment is started. The present study was designed to determine the diagnostic yield and delineate the pathological spectrum of thoracoscopy in patients with undiagnosed exudative pleural effusion.

## MATERIALS AND METHODS

Study Design, Setting, and Duration

This descriptive cross-sectional study was conducted in the Department of Pulmonology, Lahore General Hospital, Lahore, Pakistan.

Sample Size

The sample size was calculated for the estimation of a single population proportion.[11]

$$n = \frac{Z_{1-\alpha/2}^{2}\, P\, (1-P)}{d^{2}}$$

In this formula, n is the required sample size, $Z(1-\alpha/2)$ is the standard normal deviate for the chosen confidence level (1.96 for 95% confidence), P is the expected proportion (anticipated diagnostic yield of thoracoscopy), and d is the absolute precision (margin of error). The proposal specified an anticipated yield of 80% (P = 0.80) and a 95% confidence level but did not state the precision. An absolute precision of 10% (d = 0.10) was therefore assumed for this manuscript and requires confirmation. Substitution of these values gave:

$$n = \frac{(1.96)^{2}\times 0.80\times(1-0.80)}{(0.10)^{2}} = \frac{3.8416\times 0.16}{0.01} = 61.47 \approx 62$$

A total of 62 patients was required.

**Sampling Technique and Participant Selection**

Patients were recruited by non-probability consecutive sampling from the outpatient department and the inpatient wards. Consecutive patients with pleural effusion were assessed for eligibility on the basis of clinical evaluation and initial pleural fluid analysis, which included simultaneous pleural fluid and serum measurements of protein and lactate dehydrogenase (LDH), GeneXpert testing for Mycobacterium tuberculosis, and pleural fluid cytology for malignant cells on two occasions. Eligible patients were enrolled after written informed consent.

**Inclusion and Exclusion Criteria**

Patients of either sex aged 18–60 years with undiagnosed exudative pleural effusion were included. An exudative effusion was identified by Light's criteria,[12] which required at least one of the following: a pleural fluid to serum protein ratio above 0.5, a pleural fluid to serum LDH ratio above 0.6, or a pleural fluid LDH exceeding two-thirds of the upper limit of normal for serum LDH. The effusion was classified as undiagnosed only when GeneXpert testing for tuberculosis was negative and pleural fluid cytology for malignancy was negative on two occasions. Patients not fit for thoracoscopy were excluded, including those with severe uncorrected hypoxemia despite continuous oxygen administration, inability to tolerate the lateral decubitus position for the duration of the procedure, unstable hemodynamic status, coagulation defects, or other contraindications to thoracoscopy. Pregnant women and patients who declined consent for thoracoscopy or study participation were also excluded.

Age, sex, body mass index (BMI, kg/m²), duration of symptoms (days), and comorbidities (including diabetes mellitus and hypertension) were recorded at enrollment on a structured proforma. The findings of the initial pleural fluid analysis, namely the pleural fluid to serum protein ratio, the pleural fluid to serum LDH ratio, and the pleural fluid LDH (IU/L), were also documented.

Medical thoracoscopy was performed as an inpatient procedure by an experienced pulmonologist under aseptic conditions. Patients were placed in the lateral decubitus position with the affected side uppermost, and transthoracic ultrasound was used to identify a safe site of entry. After skin preparation and draping, local anesthesia with 2% lignocaine was infiltrated at the marked entry point, intravenous sedation was administered, and supplementary oxygen was delivered through a nasal cannula. Vital signs and cardiac rhythm were monitored continuously. An 11 mm cannula (metallic or plastic) with a trocar was inserted after dilatation of the tract, and a semi-rigid or rigid thoracoscope was introduced into the pleural cavity. All pleural fluid was aspirated to permit a clear view, and the volume aspirated (mL) and the visual appearance of the pleural cavity (normal or abnormal) were recorded. Under direct vision, abnormal or suspicious areas of the parietal pleura were biopsied with optical forceps, and at least three to five specimens measuring at least 2 mm each were collected. The specimens were preserved in formalin and sent immediately for histopathological evaluation, including special stains and

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immunohistochemistry as required by the operational definitions. At the end of the procedure, an intercostal chest tube was inserted to drain residual fluid and air, and it was removed once lung re-expansion was confirmed and drainage was minimal.

The primary outcome was diagnostic yield, defined as the proportion of patients in whom thoracoscopic pleural biopsy established a histopathological diagnosis of malignancy, tuberculosis, or inflammation. The secondary outcome was the pathological spectrum, expressed as the frequency of each diagnostic category. The proposal specified no follow-up interval, and outcomes were assigned from the final histopathological report and the mycobacterial culture result. All histopathological evaluation was performed by a consultant histopathologist with a minimum of seven years of experience. Malignant pleural effusion was defined as the presence of histopathologically confirmed malignant cells in pleural tissue obtained at thoracoscopy, based on pleural infiltration by neoplastic cells, glandular structures in adenocarcinoma, or mesothelial proliferation with atypia and stromal invasion in mesothelioma. The diagnosis was confirmed by standard histopathological techniques supplemented by immunohistochemistry (TTF-1, CK7, and CK20 for adenocarcinoma; calretinin, WT-1, and D2-40 for mesothelioma). Tuberculous pleurisy was defined as chronic granulomatous inflammation, with or without caseation necrosis, in pleural biopsy specimens, confirmed by mycobacterial culture. Inflammation was defined as acute or chronic inflammatory changes in thoracoscopic biopsy specimens. Acute inflammation was characterized by neutrophilic infiltration, edema, and fibrin deposition, and chronic inflammation by lymphocytic or mononuclear infiltration, plasma cells, or fibrosis. Specific infectious causes were excluded by special stains (Gram, PAS, and GMS) and cultures of pleural tissue. An undiagnosed case was defined as failure of adequate thoracoscopic biopsy (at least three to five specimens of at least 2 mm each from visually abnormal areas) to show a specific histopathological diagnosis. This category included normal pleural tissue, non-specific pleural thickening, and minimal inflammatory change without granulomas or malignancy, after exclusion of infection, malignancy, and autoimmune disease by ancillary testing.

**Statistical Analysis**

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables, including sex, diagnostic yield, and specific pathological diagnoses, were presented as frequencies and percentages, with exact (Clopper–Pearson) 95% confidence intervals for proportions.[13] Continuous variables, including age, BMI, duration of symptoms, pleural fluid parameters, and aspirated fluid volume, were presented as mean ± standard deviation, and distribution was assessed with the Shapiro–Wilk test. Stratification by age, sex, and duration of symptoms was performed to control for potential confounding, and the effect of each stratifying variable on diagnostic yield was evaluated with the chi-square test, replaced by the Fisher exact test when more than 20% of expected frequencies were below 5. Odds ratios with 95% confidence intervals (Woolf method) were calculated for the stratified comparisons. The proposal did not define cut-offs, and strata of age ≤40 versus >40 years and duration of symptoms ≤30 versus >30 days were therefore specified for this manuscript. Characteristics across the four diagnostic categories were compared with one-way analysis of variance for approximately normally distributed continuous variables and the Fisher–Freeman–Halton exact test for categorical variables, and the age difference between tuberculous and malignant effusion was examined with Welch's t-test as an exploratory analysis. All tests were two-sided, and a p-value below 0.05 was considered statistically significant.

## RESULTS

The mean age was 39.6 ± 10.7 years (range 18–58 years), and 36 patients (58.1%) were male. Most patients were aged 31–45 years (41.9%). The mean BMI was 23.6 ± 3.2 kg/m², and the mean duration of symptoms was 49.0 ± 24.7 days. Diabetes mellitus and hypertension were present in 11 (17.7%) and 9 (14.5%) patients, respectively. Initial pleural fluid analysis showed a mean pleural fluid to serum protein ratio of 0.72 ± 0.08, a mean pleural fluid to serum LDH ratio of 1.16 ± 0.36, and a mean pleural fluid LDH of 600.6 ± 219.0 IU/L. The mean volume of pleural fluid aspirated at thoracoscopy was 912.9 ± 367.2 mL, and the pleural cavity appeared abnormal in 59 patients (95.2%) (Table 1).

**Table 1. Baseline demographic and clinical characteristics of the study participants (N = 62)**

| Characteristic | Value |
|---|---|
| Age, years, mean ± SD (range) | 39.6 ± 10.7 (18–58) |
| Age group, n (%) | |
| 18–30 years | 13 (21.0) |
| 31–45 years | 26 (41.9) |
| 46–60 years | 23 (37.1) |
| Sex, n (%) | |
| Male | 36 (58.1) |
| Female | 26 (41.9) |
| BMI, kg/m², mean ± SD | 23.6 ± 3.2 |
| Duration of symptoms, days, mean ± SD | 49.0 ± 24.7 |
| Diabetes mellitus, n (%) | 11 (17.7) |

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| Characteristic | Value |
|---|---|
| Hypertension, n (%) | 9 (14.5) |
| Pleural fluid to serum protein ratio, mean ± SD | 0.72 ± 0.08 |
| Pleural fluid to serum LDH ratio, mean ± SD | 1.16 ± 0.36 |
| Pleural fluid LDH, IU/L, mean ± SD | 600.6 ± 219.0 |
| Pleural fluid volume aspirated, mL, mean ± SD | 912.9 ± 367.2 |
| Abnormal pleural cavity at thoracoscopy, n (%) | 59 (95.2) |

Note: SD, standard deviation; BMI, body mass index; LDH, lactate dehydrogenase.

A histopathological diagnosis was established in 55 of 62 patients, giving a diagnostic yield of 88.7% (95% CI 78.1–95.3). Tuberculous pleurisy was the most frequent diagnosis (n = 29; 46.8%), followed by malignant pleural effusion (n = 17; 27.4%) and inflammatory pleuritis (n = 9; 14.5%). Seven patients (11.3%) remained undiagnosed after adequate biopsy. Among the 55 diagnosed patients, tuberculosis accounted for 52.7%, malignancy for 30.9%, and inflammation for 16.4%. All 29 tuberculous cases showed chronic granulomatous inflammation, with caseation necrosis in 18 (62.1%), and all were confirmed by mycobacterial culture. Adenocarcinoma was the commonest malignancy (13 of 17; 76.5%), followed by malignant mesothelioma (3; 17.6%) and squamous cell carcinoma (1; 5.9%). Inflammatory pleuritis was chronic in 6 patients and acute in 3. Among the undiagnosed patients, pleural tissue was normal in 3, showed non-specific thickening in 3, and showed minimal inflammatory change in 1 (Table 2).

**Table 2. Diagnostic yield and pathological spectrum of thoracoscopy (N = 62)**

| Final diagnosis | n | % of all patients | 95% CI | % of diagnosed patients (n = 55) | 95% CI |
|---|---|---|---|---|---|
| Diagnostic yield (any histopathological diagnosis) | 55 | 88.7 | 78.1–95.3 | – | – |
| Tuberculous pleurisy | 29 | 46.8 | 34.0–59.9 | 52.7 | 38.8–66.3 |
| Malignant pleural effusion | 17 | 27.4 | 16.9–40.2 | 30.9 | 19.1–44.8 |
| Inflammatory pleuritis | 9 | 14.5 | 6.9–25.8 | 16.4 | 7.8–28.8 |
| Undiagnosed | 7 | 11.3 | 4.7–21.9 | – | – |

Clinical and thoracoscopic characteristics differed across the diagnostic categories (Table 3). Patients with tuberculosis were younger (32.9 ± 9.5 years) than those with malignancy (48.3 ± 7.7 years), with a mean difference of 15.4 years (95% CI 10.2–20.6; Welch's t-test, $p < 0.001$). The pleural fluid to serum protein ratio differed across the groups ($p < 0.001$), with lower values in inflammatory pleuritis and undiagnosed effusion, and the volume of fluid aspirated was greatest in malignant effusion (1217.6 ± 408.1 mL; $p < 0.001$). Duration of symptoms was shortest in inflammatory pleuritis (26.9 ± 14.1 days; $p = 0.005$). The pleural cavity appeared abnormal in all patients with tuberculosis, malignancy, or inflammation, but in only 4 of 7 undiagnosed patients ($p < 0.001$). Sex distribution ($p = 0.740$), the pleural fluid to serum LDH ratio ($p = 0.247$), and pleural fluid LDH ($p = 0.241$) did not differ significantly.

**Table 3. Clinical, pleural fluid, and thoracoscopic characteristics according to final diagnosis**

| Characteristic | Tuberculous pleurisy (n = 29) | Malignant effusion (n = 17) | Inflammatory pleuritis (n = 9) | Undiagnosed (n = 7) | p-value |
|---|---|---|---|---|---|
| Age, years | 32.9 ± 9.5 | 48.3 ± 7.7 | 42.6 ± 6.9 | 42.1 ± 7.8 | <0.001[a] |
| Male sex, n (%) | 18 (62.1) | 8 (47.1) | 6 (66.7) | 4 (57.1) | 0.740[b] |
| Duration of symptoms, days | 54.6 ± 24.2 | 56.4 ± 26.5 | 26.9 ± 14.1 | 36.6 ± 10.6 | 0.005[a] |
| Pleural fluid to serum protein ratio | 0.73 ± 0.06 | 0.76 ± 0.06 | 0.65 ± 0.11 | 0.67 ± 0.06 | <0.001[a] |
| Pleural fluid to serum LDH ratio | 1.16 ± 0.28 | 1.26 ± 0.51 | 1.12 ± 0.29 | 0.93 ± 0.30 | 0.247[a] |
| Pleural fluid LDH, IU/L | 617.4 ± 217.6 | 636.8 ± 243.7 | 600.3 ± 202.1 | 443.7 ± 141.4 | 0.241[a] |
| Pleural fluid volume aspirated, mL | 900.0 ± 242.8 | 1217.6 ± 408.1 | 633.3 ± 200.0 | 585.7 ± 303.7 | <0.001[a] |
| Abnormal pleural cavity, n (%) | 29 (100) | 17 (100) | 9 (100) | 4 (57.1) | <0.001[b] |

Note: Continuous variables are mean ± SD. [a]One-way analysis of variance. [b]Fisher–Freeman–Halton exact test. LDH, lactate dehydrogenase.

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Diagnostic yield was higher in patients aged ≤40 years (30 of 32; 93.8%) than in those aged >40 years (25 of 30; 83.3%), but the difference was not statistically significant (odds ratio 3.00; 95% CI 0.54–16.81; Fisher exact p = 0.249). Yield was nearly identical in men (32 of 36; 88.9%) and women (23 of 26; 88.5%; p = 1.000) and did not differ by duration of symptoms (≤30 days, 14 of 16, 87.5%; >30 days, 41 of 46, 89.1%; p = 1.000). The wide confidence intervals reflect the small number of undiagnosed patients (Table 4).

**Table 4. Diagnostic yield of thoracoscopy stratified by age, sex, and duration of symptoms**

| Stratum | Patients, n | Diagnosed, n (%) | 95% CI | Odds ratio (95% CI) | p-value[a] |
|---|---|---|---|---|---|
| Age ≤40 years | 32 | 30 (93.8) | 79.2–99.2 | 3.00 (0.54–16.81) | 0.249 |
| Age >40 years | 30 | 25 (83.3) | 65.3–94.4 | Reference | |
| Male | 36 | 32 (88.9) | 73.9–96.9 | 1.04 (0.21–5.12) | 1.000 |
| Female | 26 | 23 (88.5) | 69.8–97.6 | Reference | |
| Duration ≤30 days | 16 | 14 (87.5) | 61.7–98.4 | 0.85 (0.15–4.91) | 1.000 |
| Duration >30 days | 46 | 41 (89.1) | 76.4–96.4 | Reference | |

Note: CI, confidence interval (exact Clopper–Pearson for proportions; Woolf method for odds ratios). [a]Fisher exact test, used because more than 20% of expected frequencies were below 5. Cut-offs for age and duration were specified for this manuscript and were not defined in the proposal.

## DISCUSSION

The present study demonstrated that medical thoracoscopy provided a histopathological diagnosis in 55 of 62 patients with undiagnosed exudative pleural effusion, corresponding to an overall diagnostic yield of 88.7% (95% CI 78.1–95.3). Tuberculous pleurisy was the most frequent diagnosis, accounting for 46.8% of all patients, followed by malignant pleural effusion in 27.4% and inflammatory pleuritis in 14.5%. These findings indicated that thoracoscopic pleural biopsy was diagnostically useful when initial pleural fluid investigations, including GeneXpert testing and repeated cytology, were inconclusive. The predominance of tuberculosis was consistent with the regional burden of pleural tuberculosis, although malignancy represented a substantial proportion of previously undiagnosed effusions. Patients with tuberculous pleurisy were significantly younger than those with malignant effusion, whereas diagnostic yield did not differ significantly according to age group, sex, or duration of symptoms. The findings were broadly consistent with previous investigations demonstrating the diagnostic value of thoracoscopy, although the reported yield and distribution of pathological diagnoses varied considerably between clinical settings.[5–9]

The diagnostic yield observed in the present study was comparable to findings reported in several earlier investigations. Kho et al. (2020) conducted a retrospective study of 209 patients undergoing medical thoracoscopy for undiagnosed exudative pleural effusion in East Malaysia and reported a conclusive pathological diagnosis in 79.4% of patients. The median age was 61 years (IQR 48.5–69.5), and the final diagnostic distribution included malignant pleural effusion in 92 patients (44%), tuberculous pleural effusion in 85, and other benign effusions in 32. The reported sensitivity of thoracoscopy was 89.1% (95% CI 80.4–94.3) for malignancy and 90.5% (95% CI 81.8–95.6) for tuberculosis, with a specificity of 100% for both conditions. Although the overall diagnostic yield was lower than the 88.7% observed in the present study, the Malaysian investigation similarly demonstrated that tissue sampling contributed substantially to diagnosis after inconclusive conventional investigations.[5] In a larger Egyptian retrospective multicenter investigation, Sobh et al. (2020) evaluated 542 patients and established a definitive diagnosis in 476 (87.8%), closely corresponding to the present findings. Malignancy accounted for 329 patients (60.7%), while tuberculosis was diagnosed in 133 (24.5%). The similarity in overall diagnostic yield despite differences in pathological distribution suggested that thoracoscopy retained diagnostic utility across populations with different underlying causes of pleural disease.[8]

Higher diagnostic yields were reported in several Indian investigations. Kumar et al. (2023) conducted a single-center observational study of 160 patients with undiagnosed exudative pleural effusion who had negative GeneXpert results and twice-negative pleural fluid cytology, closely resembling the eligibility criteria of the present study. Thoracoscopy established a diagnosis in 158 patients (98.8%), compared with 55 of 62 (88.7%) in the present investigation. Malignancy was identified in 120 patients (75%), tuberculosis in 27 (17%), nonspecific inflammation in 10, and pyogenic effusion in one, while two patients remained undiagnosed. Their higher diagnostic yield may have reflected differences in the age distribution, prevalence of malignant disease, thoracoscopic technique, and the criteria used to classify a diagnostic biopsy.[7] Similarly, Tousheed et al. (2022) retrospectively evaluated 373 patients who underwent medical thoracoscopy and reported a diagnostic yield of 99.2% (370/373). The diagnostic yields were 99.5% with semirigid thoracoscopy and 100% with rigid thoracoscopy. The mean age was 51.9 ± 13.2 years, and malignancy and tuberculosis were the predominant findings. Differences between these studies and the present investigation should not be interpreted as evidence of superior procedural effectiveness because the populations, indications, and definitions of diagnostic success were not identical.[9]

More recent investigations have also demonstrated high diagnostic yields. Abdelaziz et al. (2024) studied 61 patients with undiagnosed exudative pleural effusion at Minia University Hospital, Egypt, and established a definitive diagnosis in 58 (95%). Malignancy was confirmed in 47 patients (77%), tuberculosis in 9 (14.8%), empyema in one (1.6%), and inflammatory or autoimmune pleuritis in one (1.6%), while three patients (5%) remained undiagnosed. Their study

population was older than the present population, with a mean age of 58.34 ± 16.5 years, and malignancy was substantially more frequent.[14] Kallarakal and Venugopal (2026), in a five-year retrospective investigation involving 305 patients in South India, reported a diagnostic yield of 99.4% (303/305). Malignancy accounted for 64.6% of cases and tuberculosis for 14.4%, with a mean age of 57 ± 15.5 years. These findings contrasted with the predominance of tuberculosis in the present study.[15] Thomas et al. (2017) investigated 407 patients in Qatar, a setting characterized by a relatively young study population, and reported tuberculosis in 84.5% and malignancy in 5.2%. The mean age was 33 ± 12.1 years, while the diagnostic yield for tuberculous pleural effusion was 91.4%.[16] In a prospective Singaporean investigation, Goh et al. (2024) evaluated 141 patients with a mean age of 67 ± 12 years and reported an overall thoracoscopic diagnostic accuracy of 95.7%. Malignancy was diagnosed in 116 patients (82.3%), compared with tuberculous pleuritis in 14 (9.9%). These findings further demonstrated the marked variation in pathological distribution between younger, tuberculosis-predominant populations and older populations with a greater burden of pleural malignancy.[17]

The predominance of tuberculosis in the present investigation was also consistent with previous evidence from Pakistan. Ibrahim et al. (2010), in a hospital-based investigation of pleural effusion, reported tuberculosis in 70 of 120 patients (58.2%) with exudative effusion, followed by malignancy in 28 (23.2%) and pneumonia in 12 (10%). The present study similarly identified tuberculosis as the leading diagnosis, although its frequency was lower at 46.8%, while malignant effusion accounted for 27.4%.[10] The higher prevalence of tuberculosis reported by Thomas et al. (2017) in Qatar, where 84.5% of patients had tuberculous effusion, also supported the influence of geographical and demographic characteristics on the etiological spectrum.[16] However, direct comparison of disease frequencies between these investigations requires caution because the present study included only patients aged 18–60 years with negative initial tuberculosis testing and repeated negative malignant cytology. Consequently, the observed proportions represented a selected population undergoing thoracoscopy rather than the overall distribution of exudative pleural effusion in the community.

Malignant pleural effusion was the second most frequent pathological diagnosis in the present study, identified in 17 patients (27.4%). Adenocarcinoma accounted for 13 of the 17 malignancies (76.5%), followed by malignant mesothelioma in 3 (17.6%) and squamous cell carcinoma in one (5.9%). A similar predominance of adenocarcinoma among malignant diagnoses was reported by Kumar et al. (2023), who identified metastatic adenocarcinoma in 110 of 120 malignant effusions, followed by squamous cell carcinoma in four and mesothelioma in three.[7] The identification of malignancy despite twice-negative pleural fluid cytology was clinically important because a negative cytological examination does not reliably exclude pleural cancer. Kassirian et al. (2023), in a systematic review and meta-analysis of 36 studies involving 6,057 patients with malignant pleural effusion, reported an overall cytological sensitivity of 58.2% (95% CI 52.5–63.9%). Sensitivity varied substantially by tumor type, reaching 83.6% (95% CI 77.7–89.6%) for lung adenocarcinoma but only 28.9% (95% CI 16.2–41.5%) for mesothelioma and 24.2% (95% CI 17.0–31.5%) for lung squamous cell carcinoma. These findings provided a plausible explanation for persistent diagnostic uncertainty after negative fluid cytology and supported the importance of obtaining pleural tissue when malignant disease remained clinically suspected.[18]

Tuberculous pleurisy was diagnosed in 29 patients, all of whom demonstrated chronic granulomatous inflammation on pleural biopsy, with caseation necrosis present in 18 (62.1%). Mycobacterial culture confirmed all 29 diagnoses despite negative initial GeneXpert testing. This finding emphasized the limitations of relying exclusively on molecular testing of pleural fluid in suspected tuberculous pleurisy. Pleural tuberculosis is frequently paucibacillary, and the inflammatory response within the pleural cavity may be more readily demonstrated by tissue histopathology than by detection of mycobacterial organisms in pleural fluid. Christopher et al. (2013) investigated the performance of Xpert MTB/RIF in 96 patients and identified 33 patients with tuberculosis according to their broader diagnostic criteria. Pleural fluid Xpert testing was positive in only four of these 33 patients, illustrating its limited sensitivity in this setting. Their investigation also demonstrated that histopathological examination contributed substantially to the diagnosis of pleural tuberculosis.[19] The present findings were consistent with the clinical importance of obtaining tissue after negative pleural fluid molecular testing. Nevertheless, the diagnostic performance of GeneXpert could not be estimated from the present study because all enrolled patients had negative results at baseline.

The present study also identified significant differences in clinical and thoracoscopic characteristics according to pathological diagnosis. Patients with tuberculous pleurisy were younger than those with malignancy (32.9 ± 9.5 versus 48.3 ± 7.7 years), with a mean difference of 15.4 years (95% CI 10.2–20.6; $p < 0.001$). A similar age-related pattern was reported by Thomas et al. (2017), who observed a mean age of 30.8 ± 9.5 years among patients with tuberculous pleural effusion compared with 46.8 ± 15.8 years among patients with other diagnoses ($p < 0.0001$).[16] In the present study, the pleural fluid to serum protein ratio differed significantly across diagnostic categories ($p < 0.001$), with the highest mean ratio in malignant effusion (0.76 ± 0.06) and lower values in inflammatory pleuritis (0.65 ± 0.11). The mean aspirated pleural fluid volume was also greatest in malignant effusion (1217.6 ± 408.1 mL), compared with tuberculous pleurisy (900.0 ± 242.8 mL), inflammatory pleuritis (633.3 ± 200.0 mL), and undiagnosed effusion (585.7 ± 303.7 mL), with a significant overall difference ($p < 0.001$). Goh et al. (2024) reported a mean pleural fluid removal volume of 1,489 ± 616 mL in their thoracoscopy population, in which malignancy was the predominant final diagnosis.[17] Although these observations suggested that fluid characteristics and disease extent differed according to underlying pathology, the present study did not establish diagnostic thresholds for distinguishing tuberculosis from malignancy. Therefore, these variables should be regarded as supportive clinical observations rather than substitutes for pathological confirmation.

Direct visualization of pleural abnormalities was another important finding. The pleural cavity appeared abnormal in 59

patients (95.2%), including all patients with tuberculosis, malignancy, or inflammatory pleuritis, but only four of the seven undiagnosed patients ($p < 0.001$). This association was consistent with the principal advantage of thoracoscopy, which allows biopsy specimens to be obtained directly from suspicious pleural areas. Nevertheless, abnormal macroscopic appearance cannot independently establish the underlying diagnosis, particularly because inflammatory and malignant changes may overlap. Metintas et al. (2010), in a randomized controlled trial involving 124 patients with cytology-negative exudative pleural effusion, compared medical thoracoscopy with computed tomography-guided Abrams pleural needle biopsy. Diagnostic sensitivity was 94.1% with thoracoscopy and 87.5% with CT-guided biopsy, without a statistically significant between-group difference ($p = 0.252$).[20] Similarly, Wang et al. (2015), in a nine-year investigation involving 833 patients with undiagnosed pleural effusion, reported a thoracoscopic diagnostic efficiency of 92.6% (771/833), while 62 patients (7.4%) remained without a definitive diagnosis. These findings supported the value of thoracoscopic tissue sampling but also demonstrated that no diagnostic procedure consistently establishes an etiology in every patient.[21]

Inflammatory pleuritis accounted for nine patients (14.5%) in the present study, including six with chronic and three with acute inflammatory changes. A further seven patients (11.3%) remained undiagnosed, with normal pleural tissue, nonspecific thickening, or minimal inflammatory changes. These observations require particular consideration because histopathological identification of inflammation does not necessarily establish its underlying etiology. Sundaralingam et al. (2023), using data from the International Collaborative Effusion database, analyzed 175 patients with nonspecific pleuritis from 12 centers across nine countries. An idiopathic cause was recorded in 80 patients, while pleural infection, benign asbestos-related disease, and malignancy were identified in subsequent clinical evaluation. Eleven patients (approximately 6%) developed a malignant diagnosis during follow-up, predominantly mesothelioma or lung adenocarcinoma. The median interval to malignant diagnosis was 12.2 months, with a range of 0.8–32 months. These findings indicated that a nonspecific pleural biopsy result does not always exclude underlying malignancy.[22] In the present investigation, the absence of a specified longitudinal follow-up interval prevented assessment of whether patients with inflammatory or undiagnosed histopathological findings subsequently received a more specific diagnosis. This limitation was particularly relevant when interpreting the reported diagnostic yield, which included inflammatory pleuritis as a diagnostic category.

The stratified analysis demonstrated that diagnostic yield was numerically higher among patients aged 40 years or younger than among those older than 40 years (93.8% versus 83.3%), but the difference was not statistically significant (OR 3.00; 95% CI 0.54–16.81; $p = 0.249$). Diagnostic yield was nearly identical between male and female patients (88.9% versus 88.5%; $p = 1.000$) and between patients with symptom duration of 30 days or less and those with longer symptom duration (87.5% versus 89.1%; $p = 1.000$). These findings did not establish meaningful differences in diagnostic yield across the evaluated strata. However, the wide confidence intervals indicated substantial statistical uncertainty, particularly because only seven patients remained undiagnosed. Furthermore, the observed age difference between tuberculous and malignant effusions concerned the distribution of pathological diagnoses and should not be interpreted as evidence that age independently influenced thoracoscopic diagnostic success. The small sample size and limited number of diagnostic failures restricted the ability to detect modest subgroup differences.

The findings had potential implications for the investigation of persistent undiagnosed exudative pleural effusion. The British Thoracic Society Guideline for Pleural Disease (2023) recommends pleural fluid cytology as an initial investigation when malignancy is suspected, while acknowledging that negative cytology may require further diagnostic assessment. The guideline also supports thoracoscopic or image-guided pleural biopsy according to clinical indications and local procedural availability, with tissue sampling for culture preferred in suspected pleural tuberculosis.[23] Similarly, the 2024 National College of Chest Physicians–Indian Chest Society consensus guidelines recommend medical thoracoscopy or image-guided pleural biopsy after nondiagnostic initial thoracentesis, while discouraging unguided closed pleural biopsy.[24]

The principal strengths of the present study included the clearly specified eligibility criteria, evaluation of patients following negative initial microbiological and cytological investigations, standardized thoracoscopic tissue sampling, and histopathological classification using predefined operational definitions. Non-probability consecutive sampling and referral-based selection could have influenced the observed pathological distribution. Future multicenter investigations with larger samples, standardized pathological definitions, detailed procedural assessment, and longitudinal follow-up would help determine the diagnostic performance and clinical outcomes of thoracoscopy in different populations.

## CONCLUSION

Medical thoracoscopy established a histopathological diagnosis in 88.7% of patients with previously undiagnosed exudative pleural effusion, demonstrating substantial diagnostic utility after inconclusive initial investigations. Tuberculous pleurisy was the predominant diagnosis, followed by malignant pleural effusion and inflammatory pleuritis. Patients with tuberculous pleurisy were significantly younger than those with malignancy, whereas diagnostic yield did not differ significantly according to age group, sex, or symptom duration

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