

Closed Ultrasound Guided Pleural Biopsy - Cross-Sectional Analysis

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Abstract

Introduction: Pleural effusion represents a frequent and diagnostically complex clinical challenge with more than 60 recognized etiologies. Establishing a definitive diagnosis remains a significant problem, as standard pleural fluid analysis and initial clinical evaluation frequently leave up to 25% of cases indeterminate.

Aim: Evaluation of the diagnostic yield of ultrasound guided closed pleural biopsy in patients with pleural effusion.

Methods: This retrospective study, analyses data from 50 patients hospitalized at the University Clinic for Pulmonology and Allergology, Skopje, with indeterminate pleural effusion over a six-year period, from 2020 to 2026. The cohort consisted of patients who underwent closed pleural biopsy for the diagnostic evaluation of pleural effusions which remained indeterminate, despite of initial biochemical and cytological fluid analysis. Variables included demographics, smoking, chest ultrasound (US), chest computed tomography (CT), pleural fluid biochemistry, cytology, histopathology and final clinical outcomes including Video-Assisted Thoracic Surgery (VATS). Statistical analysis included descriptive and comparative methods using Chi-square and Fisher's exact tests, with diagnostic sensitivity calculated against the final clinical diagnosis.

Results: This study analyses 50 patients, (Mean age 67.52; range 30-81 years) predominantly male (38 patients, 76%). The majority of the patients 96% (48/50) had exudative effusion according to Light's criteria. Chest CT identified distinct mass in 40% (20/50) of cases and irregular pleural thickening in 28% (14/50). Initial ultrasound guided closed pleural biopsy yielded a conclusive diagnosis in 62% (31/50) of the total cohort. Closed biopsy successfully identified malignancy in 56% of patients (28/50), demonstrating an overall diagnostic sensitivity for malignancy of 73.7% (28/38 confirmed malignancies), which reached 90% (18/20) in the presence of a CT defined mass, compared to 57,1% (8/14) for pleural thickening. The diagnostic yield for tuberculous pleuritis was 100% (3/3). Initial nonspecific inflammatory findings occurred in 36% (18/50) of biopsies, which upon diagnostic escalation revealed secondary malignancies in 7 cases and infectious etiologies in 11 cases. Secondary VATS was performed in 7 patients, providing a definitive diagnosis in 6 of the cases.

Conclusion: Ultrasound - guided closed pleural biopsy remains an essential, highly effective first line modality for undiagnosed exudative pleural effusions. It demonstrates strong diagnostic performance for malignancy 73.7% sensitivity overall (90% for CT defined mass) and 100% yield for tuberculosis. Non-conclusive cases should undergo secondary diagnostic escalation to video assisted thoracoscopic surgery (VATS).

Keywords: *Pleural Effusions; Cytology; Pleural Punctate Biochemistry*

Introduction

Pleural effusion (PE) is a common clinical manifestation of a variety of systemic and pulmonary diseases, where four etiologies - cancer, tuberculosis (TB), pneumonia and heart failure - account for roughly 75% of all cases [1]. The annual occurrence is 350-360 per 100,000 inhabitants. The primary clinical step for diagnosis begins with differentiating transudates from exudates using Light's criteria [2] (calculating the ratio of pleural to serum lactate dehydrogenase (LDH) and protein levels) and cytological analysis of the obtained pleural fluid by thoracentesis. Pleural fluid cytology is considered the initial diagnostic test for pleural effusion [3], with a diagnostic performance of approximately 60% [4], although sensitivity varies according to tumor type (e.g. 83.6% in lung adenocarcinoma vs. 24.2% in squamous cell carcinoma and 28.9% in mesothelioma) [5]. Historically, closed pleural biopsy has been the first choice for tissue acquisition, particularly in suspected TB, as its yield for TB often exceeds 75% [6]. Nowadays closed biopsy is often the initial choice for tissue sampling method in resource-limited settings. Where available, medical thoracoscopy and image guided core biopsy of the pleura are the preferred choice, and Video-Assisted Thoracic Surgery (VATS) is the gold standard with a 95-100% success [7]. Before referring patients for VATS, it is essential to rule out absolute contraindications: hemodynamic instability, prior talc pleurodesis, and severe pleural adhesions, while weighing potential complications such as persistent air leaks, hypoxemia and bleeding [8]. According to the literature, pleural fluid cytology demonstrates an overall diagnostic sensitivity of approximately 60% of malignant pleural effusion [4]. The sensitivity of cytological analysis of the pleural fluid in a study conducted at the Clinic for Pulmonology and Allergology in Skopje, is 33.24% positive results for pleural effusions associated to malignant diseases [9].

Tissue acquisition is often required for definitive diagnosis of pleuritis or mesothelioma. Given the limited availability of VATS in Macedonia, image guided closed pleural biopsy has been performed routinely at our institution for over three decades and remains the preferred choice. This study evaluates the real-life performance and efficacy of closed pleural biopsy in the past 5 years.

Materials and Methods

Study population

This study analyzes the data from all of the patients who presented with pleural effusion at the Clinic for Pulmonology and Allergology in Skopje, in the period from 2020 - 2025, in whom the etiology of the effusion remained inconclusive after standard/routine investigations (visualization methods, cytology and biochemistry of the effusion) and pleural biopsy was indicated for further diagnosis.

Inclusion criteria:

- Patients aged ≥ 18 years with pleural effusion who underwent an ultrasound guided pleural biopsy using a pleural biopsy set by Ramel.

Methodology

Clinical, radiological and laboratory evaluation

In all of the patients we analyzed the following clinical parameters:

- **Demographics:** Age, gender.
- **Risk factors:** Presence of relevant comorbidities: cardiomyopathy, malignancy, autoimmune/rheumatic conditions, tuberculosis (TB).
- **Smoking status:** Patients were registered as non-smokers or active smokers. The ex-smokers who quit smoking 15 or more years ago were recorded as non-smokers.

- **Imaging methods:** Chest ultrasound (US) was performed in all of the included patients to assess effusion laterality (unilateral vs. bilateral) and echogenicity. Chest computed tomography (CT) was routinely evaluated for specific pleural abnormalities, categorized as “tumor/mass” and “pleural thickening”, in addition of the presence of effusion.
- **Pleural fluid biochemistry:** According to Light’s classification [10], pleural fluid and venous blood samples were analyzed for pH, proteinogram and lactate dehydrogenase (LDH) in order to distinguish exudative and transudative effusions [12].

Diagnostic procedures and pathological analysis

- **Tissue samplings:** For all patients, ultrasound guided closed pleural biopsy was performed under local anesthesia [13]. Multiple tissue specimens from the parietal pleura and concomitant pleural fluid aspirates were collected and submitted for histopathological and cytological evaluation.
- **Histopathology:** Tissue specimens were examined by pathologist and classified into specific malignant subtypes (e.g. small cell lung cancer [SCLC], non- small cell lung cancer [NSCLC] or subtypes), benign etiologies (e.g. granulomatous inflammation diagnosis for TB, non-specific inflammation) or non-conclusive findings.
- **Cytology:** Pleural fluid cytological aspirates were categorized into groups 1 through 5 using the Papanicolaou (Pap) classification system [14].
- **Reference standard:** Video assisted thoracoscopic surgery (VATS) was recommended for all of the patients in whom the ultrasound guided closed pleural biopsy yielded a non-conclusive or non-diagnostic result. A final definitive etiology was established using a reference standard, defined as: definitive histopathological confirmation from the index closed biopsy or VATS, microbiological identification of *Mycobacterium tuberculosis* and clinical and radiological resolution during long term follow up.
- **Statistical analysis:** Statistical analysis was performed using descriptive and comparative statistical methods. Continuous variables were presented as mean values and ranges, while categorical variables were expressed as frequencies and percentages. Comparisons between clinical, radiological and histopathological variables were analyzed using the Chi-square test or Fisher’s exact test, as appropriate. Diagnostic sensitivity of closed pleural biopsy was calculated using the final clinical diagnosis as the reference standard. A p-value <0.05 was considered statistically significant.

Results

Patient demographics, risk factors and comorbidities

This retrospective study was conducted on 50 patients (76% male [n = 38], 24% females [n = 12]) who underwent closed, US guided pleural biopsy. The median age of the cohort was 67.5 years (range 30-81), with marked male predominance (76%).

31 patients (62%) had a significant smoking history. Active smoking was notably higher within the confirmed malignant subgroup, accounting for 23 of the 38 malignant cases (60.5%; Fisher’s exact test, p = 0.772). When evaluated by histopathological subtype:

- Small cell lung carcinoma (SCLC): Demonstrated the strongest association with tobacco use: with 100% (3/3) of patients being active smokers.
- Squamous cell carcinoma: Showed an 80% (4/5) active smoking prevalence.
- Adenocarcinoma represented the most frequent malignancy in the cohort (n = 16), with 56.3% (9/16) recorded as active smokers.

Pre-existing comorbidities were documented in 11 cases (22%). Medical history revealed prior presence of cardiovascular condition (heart failure) 1 patient (2%), oncological disease 7 patients (14%), autoimmune/rheumatologic disorders 3 patients (6%). None of the included patients had a prior history of active tuberculosis (TB).

Thoracic imaging and pleural fluid biochemistry

- **Ultrasonography:** Initial thoracic ultrasonography demonstrated that the vast majority of the cohort (n = 44; 88%) presented with unilateral pleural effusions, while bilateral involvement was observed in only six cases (12%).
- **Pleural biochemistry and Light's criteria:** Pleural fluid LDH levels demonstrated wide variability ranging from 15 to 1600 U/L across the cohort. Mean LDH levels were highest in patients with oncological malignancy (485.6 U/L), followed by tuberculous effusion (460 U/L), and 326 U/L in inflammatory effusion. Pleural pH values ranged from 7.293 to 8.0. According to Light's criteria: 48 cases (96%) were classified as exudates, confirming that closed biopsy was appropriately targeted toward local pleural pathology.
- **Chest computed tomography (CT):** Chest CT demonstrated a distinct pleural mass/tumor in 20 cases (40%), of which 18 (90%) yielded positive diagnostic biopsy for malignancy. In contrast, cases presenting with irregular pleural thickening (n = 14; 28%) yielded a positive biopsy in only 8 cases (57.14%). This difference was found to be statistically significant (Fisher's Exact Test, p = 0.038), identifying the presence of a CT-defined mass as a strong predictor for a conclusive biopsy result.

Histopathological results

Ultrasound - guided closed pleural biopsy yielded a definitive, conclusive diagnosis in 31 of 50 patients, establishing an initial diagnostic yield of 62%.

- **Confirmed malignancy:** (n = 28; 56% of total cohort) closed US guided pleural biopsy successfully identified malignancy in 28 patients. Adenocarcinoma was the predominant histopathological subtype 53.57% (n = 15/28). Other identified primary and metastatic subtypes included squamous cell carcinoma was 10.7% (n = 3/28), small cell lung cancer 10.7% (n = 3/28), and malignant pleural mesothelioma was diagnosed in 10.7% (n = 3/28) and adeno-squamous carcinoma of the lung (n = 1). Metastasis in pleura of unknown origin were identified in 3 patients (n = 3/28).
- **Non-malignant results:** (n = 22; 44% of total cohort), of which:
- **Non-specific inflammation/infection:** (n = 18; 36% of total cohort). Initial histopathological examination revealed non-specific inflammation in 18 cases. Following clinical follow-up and diagnostic escalation, these cases were categorized into:
- **Definitive infectious etiologies:** (n = 11) in this subgroup, a definitive diagnosis of TB was established in 3 patients based on histopathological evidence of granulomatous inflammation. Additionally, pneumonia was clinically confirmed in 3 cases, chronic pleuritis in 3 cases, acute pancreatitis in 1 case (confirmed by abdominal CT) and purulent exudate/empyema in 1 case.
- **Secondary identification of malignancy:** (n = 7) Reevaluation and secondary procedures revealed underlying malignancies initially missed by closed biopsy, including adenocarcinoma (n = 2, one diagnosed with transthoracic biopsy [TTB] and one diagnosed with surgical wedge excision of the lung), squamous cell carcinoma (n = 1; TTB), mesothelioma (n = 1), non-Hodgkin lymphoma (n = 1; via fine-needle aspiration [FNA] of a peripheral lymph node), metastatic gastric carcinoma (n = 1) and metastatic melanoma (n = 1).
- **Inconclusive results:** (n = 4; 8% of total cohort) Inconclusive pathologic results were obtained from 4 biopsies. Secondary diagnostic workup confirmed definitive diagnosis in three of these patients: metastatic prostatic cancer (via VATS), a gynecological malignancy (via CT and specialized OBGYN consultation) and malignant mesothelioma (based on further oncologic follow-up). One case remained diagnostically indeterminate subsequent to the patient's demise.

Performance of video assisted thoroscopic surgery (VATS):

- **Results from VATS:** 7 patients (14%) underwent VATS after an inconclusive closed biopsy, due to high clinical suspicion of malignancy. In 6/7 of these cases, VATS provided the definitive diagnosis, identifying pleural mesothelioma, adenocarcinoma, SCLC and metastatic cancers (melanoma, prostatic and gastric cancer). One patient remained diagnostically inconclusive following VATS.

Diagnosis performance statistics:

- **Closed biopsy sensitivity:** When evaluated against the reference standard, ultrasound guided closed pleural biopsy demonstrated a diagnostic sensitivity for malignancy of 73.68% (28 confirmed cases out of 38 final malignancies). Closed pleural biopsy achieved a diagnostic yield of 100% (3/3) of tuberculous pleuritis.

Complications associated with closed pleural biopsy

Small post-interventional pneumothorax was detected in 4 out of 50 (8%) patients. In 2 cases (4%) hemorrhagic pleural effusion following the procedure was detected, with self-limited course. Chest tube was not necessary in any of the cases.

Discussion**Diagnostic efficacy and comparison with literature**

The diagnostic evaluation of indeterminate pleural effusions remains a significant clinical challenge, as standard pleural fluid analysis (cytology and biochemistry) frequently fails to establish a definitive etiology in up to 25% of the cases [15]. In our study, image-guided closed pleural biopsy achieved an initial diagnostic yield for malignancy of 56% across the unselected cohort (28/50) and a diagnostic sensitivity for malignancy of 73.7% (28/38) of the confirmed malignancy cases. A figure slightly higher than the 50% sensitivity typically reported in medical literature for this procedure [16]. Unlike infectious processes that may involve the pleura more diffusely, malignant cells often aggregate in specific areas, making the procedure susceptible to sampling error [17]. To minimize this risk, clinical consensus suggests that obtaining 4 to 6 tissue specimens from a single-entry site is necessary to maximize the diagnostic yield when using an Abrams' or Ramel needle [18]. The ultrasound guidance further enhances safety and diagnostic yield by real-time identification of pleural thickening and fluid pockets. In our study ultrasound guidance enabled the location of the optimal biopsy site and therefore enhanced the yield of the procedure.

Radiological correlation

Our findings underscore the critical role of radiological correlation in planning and biopsy technique selection. Chest CT identified a "tumor/mass" in 20 patients (40%), where closed biopsy yielded a diagnostic rate of 90% (18/20). Conversely, in patients presenting with irregular pleural thickening without distinct mass (n = 14) the positive diagnosis dropped significantly to 57.1 (8/14) (p = 0.038, Fisher's exact test). This observation aligns directly with the findings of Park, *et al.* who evaluated percutaneous pleural needle biopsy and reported a 96.4% diagnostic yield for lesions with nodular CT morphology, compared to only 55.6% for diffuse pleural thickening under 4.5 mm [19].

High diagnostic yield in tuberculous pleuritis

A notable finding in this study was the 100% diagnostic success rate (3/3) for tuberculosis, confirmed via histopathological identification of caseating granulomatous inflammation and microbiological confirmation of mycobacterium tuberculosis. This exceeds the yield of 75% reported in general literature for percutaneous biopsy in suspected pleural tuberculosis [20]. In regions with resource limited healthcare care or endemic tuberculosis, closed pleural biopsy remains highly effective, cost efficient, and definitive diagnostic tool for granulomatous pleuritis [21].

Role of secondary diagnostic escalation

In our path secondary diagnostic was required in 12 patients with initial non-conclusive or non-specific inflammatory closed biopsies. VATS was utilized as the secondary intervention in 7 patients (14% of the cohort), successfully establishing a diagnosis in 6 of 7 patients, including adenocarcinoma, primary pleural mesothelioma, SCLC and metastatic carcinomas (melanoma, prostate and gastric origin). In the remaining cases secondary diagnoses were established via CT guided transthoracic needle biopsy (TTB), fine need aspiration of

peripheral lymph nodes or surgical wedge resection. VATS remains a gold standard for diagnosis of pleural pathology. Nevertheless, it is an invasive procedure, associated with possible complications, therefore requiring optimal patient performance status [22].

Conclusion

Ultrasound guided closed pleural biopsy remains a highly effective, cost efficient and safe first line procedure for diagnosis of exudative pleural effusion. In our experience, ultrasound guidance achieves excellent diagnostic yield, demonstrating high sensitivity for malignancy (73.7% overall, 90% when a CT defined mass is present) and 100% diagnostic rate for tuberculous pleuritis. While closed biopsy provides a definitive and rapid diagnosis in the majority of the patients, non-conclusive or inflammatory findings should prompt secondary diagnostic escalation to video assisted thoracoscopic surgery (VATS). Overall, image guided closed pleural biopsy continues to be an essential, high yield tool in routine pulmonology practice, with an acceptably low rate of complications.

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