

Comparative study between ultrasound-guided closed pleural biopsy and thoracoscopic pleural biopsy in undiagnosed exudative pleural effusions

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Abstract

Pleural biopsies are often required to establish a diagnosis in exudative pleural effusions, which remain undiagnosed after initial pleural fluid analysis. Medical thoracoscopy offers a high diagnostic yield but has limited availability in resource-constrained settings. This prospective comparative study evaluated the diagnostic yield between ultrasound-guided closed pleural biopsy and medical thoracoscopy among patients with undiagnosed exudative pleural effusions with pleural-based lesions at least 10 mm in size. Both groups achieved an equal diagnostic yield of 92% despite fewer biopsy specimens being taken in the ultrasound-guided biopsy group (4.52 ± 0.65) compared to the thoracoscopic group (7.8 ± 1) ($p < 0.0001$). In conclusion, ultrasound-guided closed pleural biopsy is a suitable alternative to medical thoracoscopy in patients with undiagnosed exudative pleural effusion having pleural thickening or nodularity of at least 10 mm in size, in terms of having a similar diagnostic yield as compared to medical thoracoscopy.

Key words: ultrasound-guided pleural biopsy, image-guided pleural biopsy, closed pleural biopsy, medical thoracoscopy, exudative pleural effusion.

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Introduction

Pleural effusions are commonly encountered in medical practice. Understanding the underlying cause is vital for appropriate management, as treatment strategies can vary and are sometimes mutually exclusive. Pleural fluid is labeled as exudative if it meets any one of Light's criteria. Initial pleural fluid analysis, which includes tests for biochemical markers, microbiological tests, and cytological examination, can pinpoint the cause in 60-80% of cases. Despite these measures, 20-40% of cases remain undiagnosed after the initial fluid analysis, often leading to a pleural biopsy to confirm the diagnosis [1-3].

A parietal pleural biopsy can be performed through invasive methods (medical or surgical thoracoscopy) or semi-invasive methods [closed pleural biopsy (CPB), which may or may not be assisted by radiological imaging]. CPB can be conducted with guidance from computed tomography (CT) and ultrasound (USG) or performed blindly [4,5].

Medical thoracoscopy (MT) allows direct visualization and biopsy of the pleura and offers a higher diagnostic yield than blind CPB and thoracocentesis. Specifically, it achieves 91-95% diagnostic accuracy rates for malignant diseases and can reach up to 100% for diagnosing pleural tuberculosis [6]. Nevertheless, the availability of MT can be limited, especially in resource-constrained settings, and not all patients may be suitable for the procedure due to under-

lying medical conditions [1]. When MT is not feasible, USG-guided CPB is a viable alternative, offering a substantial diagnostic yield with fewer complications. The present study aims to compare the diagnostic yield of USG-guided CPB and MT pleural biopsy in patients with undiagnosed exudative pleural effusion.

Materials and Methods

This prospective comparative study received approval from the institute's ethical committee, and all enrolled patients signed a written informed consent. This study investigated the diagnostic efficacy of USG-guided CPB and MT in patients with undiagnosed exudative pleural effusions. Eligible patients were selected (based on Light's criteria), and those with specific comorbidities or contraindications (such as patients >80 years or less than 18 years of age, bleeding diathesis/coagulopathy, recent myocardial infarction within 4 weeks, acute or chronic renal failure, uncontrolled diabetes mellitus, and hemodynamic instability) were excluded.

Details of ultrasound-guided pleural biopsy and medical thoracoscopy

Ultrasound-guided pleural biopsy

Localization of the site for CPB was done by USG chest (phased-array probe, 5-1 MHz). Areas of pleural thickening more



than 10 mm were preferred for biopsy (Figure 1a and b). Utmost care was taken to pursue a site of entry at least 6 cm away from the vertebra's spinous process and on the lower rib's upper border. A maximum of two sites for CPB were chosen. 2% of lignocaine was infiltrated into the skin, subcutaneous tissues, rib, periosteum, and parietal pleura. Under real-time USG guidance, a manually operated 18-gauge Tru-cut biopsy needle was advanced till the parietal pleura was reached. At this point, the biopsy needle was actuated to launch the specimen notch forward. USG and color Doppler of the biopsy site(s) were performed after the procedure to exclude any pneumothorax or bleeding. Complications were treated according to standard protocol.

Medical thoracoscopy

MT was performed utilizing the Olympus LTF-Type 160 semi-rigid thoracoscope. The scope has a 22 cm proximal rigid insertion shaft with a 5 cm flexible tip and a 2.8 mm internal working channel to introduce forceps and other accessories. While the patient was lying in the lateral decubitus position with the affected side up, the site of entry was marked with USG. All the patients were monitored using a pulse oximeter, a blood pressure monitor, and nasal prongs were applied at a flow rate sufficient to maintain saturation above 95%. 2% lignocaine was infiltrated into the skin, subcutaneous tissues, rib, periosteum, and parietal pleura. A 1.5-2 cm skin incision parallel to the rib was made under aseptic conditions at the marked site. After that, blunt dissection of the subcutaneous tissue was done with straight artery forceps till the pleura was punctured. At this point, the trocar and cannula were inserted. The trocar was removed, and the pleural fluid was drained using a 16-French suction catheter. After drainage of the pleural fluid, a thoracoscope was introduced, and an inspection of the pleura, along with a video recording, was done. Afterward, biopsy forceps were introduced, and biopsy pieces were obtained from areas of pleural irregularity. A 24-French intercostal drainage tube was inserted, and the insertion site was covered aseptically with gauze pieces and a sticky bandage. Complications were treated according to standard protocol.

Statistical analysis

The categorical variables were presented in the form of numbers and percentages. On the other hand, the quantitative data were presented as the mean $\pm$ standard deviation and median with 25th and 75th percentiles (interquartile range). The data normality was checked by using the Shapiro-Wilk test. In the cases in which the data were not normal, we used nonparametric tests. The following statistical tests were applied to the results: i) the comparison of the quantitative and not normally distributed variables was analyzed using the Mann-Whitney Test, and quantitative and normally distributed variables were analyzed using the independent *t*-test. The association of pleural nodularity/Pleural thickening(cm) with the final diagnosis was analyzed using analysis of variance; ii) the comparison of the qualitative variables was analyzed using the Chi-Square test. If any cell had an expected value of less than 5, Fisher's exact test was used.

The final analysis was done using Statistical Package for Social Sciences (SPSS) software, developed by IBM (Chicago, USA), version 25.0. For statistical significance, a *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 136 patients with exudative pleural effusions were screened for inclusion in the study. After applying inclusion and exclusion criteria, 50 patients aged ≥ 18 years with undiagnosed exudative pleural effusion (as per Light's criteria) were included in the study. A total of 25 patients underwent USG-guided CPB, and 25 underwent MT. In our study, the mean age was 57.56 ± 11.54 years for the USG-CPB group and 57.32 ± 14.16 years for the MT group. There was a male preponderance (66%). Table 1 shows the baseline demographic characteristics of the study population.

No significant differences were observed in the distribution of CT chest findings between patients undergoing USG-guided CPB and those undergoing MT (Table 2). No significant difference was observed in the mean $\pm$ standard deviation of pleural nodularity or

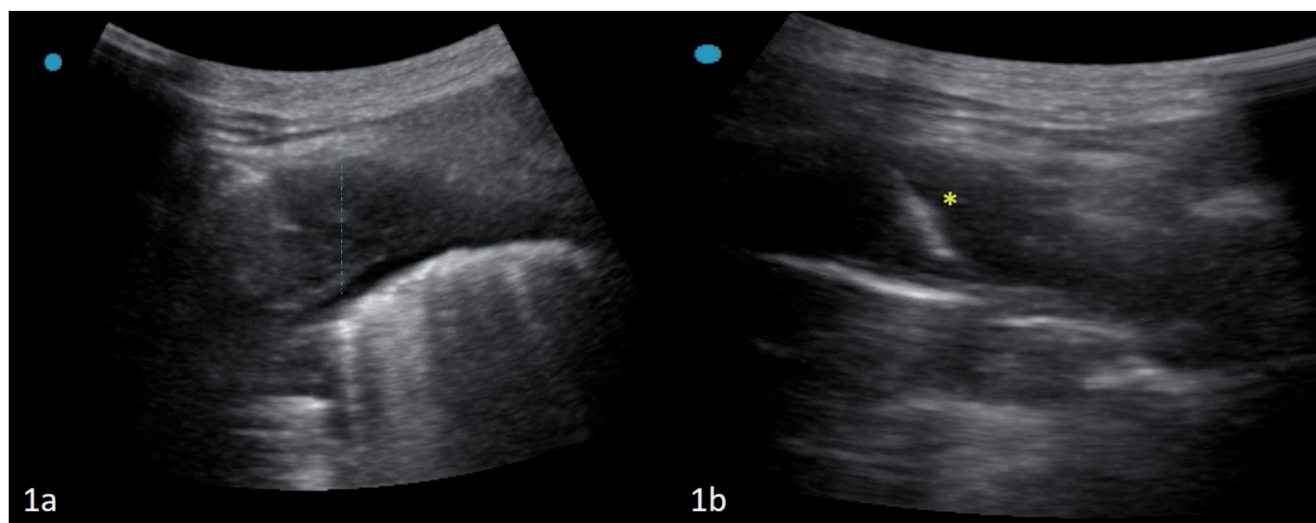


Figure 1. a) Localization of the pleural-based lesion (blue dashed line represents the pleural thickness); b) ultrasound-guided pleural biopsy (yellow asterisk represents the biopsy needle).

thickening between patients undergoing USG-guided CPB and those undergoing MT (Figure 2).

No significant differences were observed in pleural fluid investigations between patients undergoing USG-guided CPB and those undergoing MT. Both the USG-guided pleural biopsy and MT groups achieved a diagnostic yield of 92%, despite fewer biopsy specimens being taken in the USG-guided CPB group (4.52 ± 0.65) compared to the MT group (7.8 ± 1) ($p < 0.0001$).

Discussion

While image-guided or assisted needle biopsies and MT have significantly enhanced the diagnostic accuracy for pleural diseases, the primary challenge now is to improve the success rate of the initial procedure. This would help minimize costs, complications, and hospital burden, as well as enhance patient comfort. The key lies in identifying the most appropriate method for each patient. In other words, a strategy that recommends the sequence and preference of needle biopsy or MT based on the patient's specific pleural pathology would be beneficial.

The mean age of participants in our study was similar across both groups, with a male predominance observed, consistent with findings from previous studies by Maturu *et al.* and Durgesheswar *et al.* [7,8]. In terms of smoking status, our study found a higher proportion of reformed smokers compared to the study by Durgesheswar *et al.* [8].

Consensus in the literature exists that MT is the most effective procedure for the invasive diagnosis of pleural disease. In MT, the samples are obtained under direct visual observation. Therefore, the diagnostic sensitivity is notably high, about 95%, and the procedure has a very low complication rate; the major complication rate is $< 3\%$ [9-12]. The British Thoracic Society (BTS) guidelines on pleural dis-

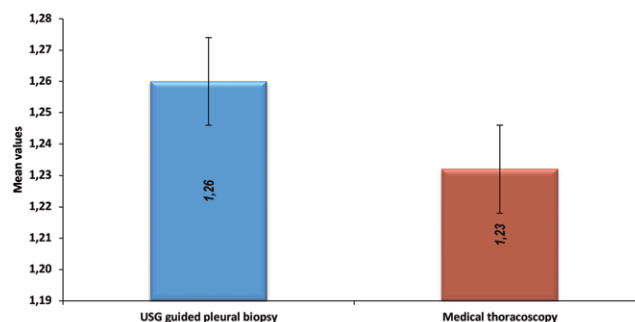


Figure 2. Comparison of pleural nodularity/pleural thickening(cm) between the ultrasound (USG)-guided pleural biopsy group and the medical thoracoscopy (MT) group. No significant difference was observed in the mean $\pm$ standard deviation of pleural nodularity or thickening between patients undergoing USG-guided closed pleural biopsy and those undergoing MT.

Table 1. Comparison of demographic parameters between the ultrasound-guided closed pleural biopsy group and the medical thoracoscopy group.

Parameters	Ultrasound-guided pleural biopsy (n=25)	Medical thoracoscopy (n=25)	p
Age (median in years)	60 (49-65 year)	56 (53-66 year)	0.948
Age (mean $\pm$ standard deviation)	57.56 $\pm$ 11.54	57.32 $\pm$ 14.16	
Age (Range)	19-75	19-85	
Gender (male), n (%)	18 (72)	15 (60)	0.37
Gender (female), n (%)	7 (28)	10 (40)	
Nonsmoker, n (%)	8 (32)	14 (56)	0.253
Reformed smoker, n (%)	12 (48)	8 (32)	
Current smoker, n (%)	5 (20)	3 (12)	
No co-morbidities, n (%)	19 (76)	18 (72)	0.747
Systemic hypertension, n (%)	3 (12)	4 (16)	1
Coronary artery disease, n (%)	1 (4)	1 (4)	1
Chronic obstructive pulmonary disease, n (%)	4 (16)	2 (8)	0.667
Diabetes mellitus, n (%)	1 (4)	2 (8)	1

Table 2. Comparison of computed tomography chest between the ultrasound-guided closed pleural biopsy group and the medical thoracoscopy group.

Computed tomography chest	Ultrasound-guided pleural biopsy (n=25), n (%)	Medical thoracoscopy (n=25), n (%)	Total n (%)	p
Bilateral pleural effusion with pleural based nodules	8 (32)	5 (20)	13 (26)	0.514
Left pleural effusion with pleural based nodules	5 (20)	5 (20)	10 (20)	
Right pleural effusion with pleural nodules	11 (44)	15 (60)	26 (52)	
Right pleural effusion with pleural thickening	1 (4)	0 (0)	1 (2)	
Total	25 (100)	25 (100)	50 (100)	



ease (2023) state that diagnostic accuracy appears to be higher with MT pleural biopsy when compared with image-guided CPB. However, this statement was based on low-quality evidence. So, BTS guidelines recommend that thorascopic or image-guided pleural biopsy may be used depending on the clinical indication and local availability of techniques [13]. MT also presents the advantage of facilitating a potentially definitive therapeutic intervention (*i.e.*, talc poudrage pleurodesis) for patients with recurrent symptomatic effusion simultaneously. However, the cost is slightly higher, and the procedure time is longer than that of needle biopsy [14]. Studies have shown that the diagnostic sensitivity of image-guided or image-assisted pleural biopsy is higher for pleural thickening, pleural nodular lesions, and pleural-based masses [15-20]. In a study by Zhang *et al.* [21], a pleural thickness of ≥ 3 mm independently predicted diagnostic accuracy, 85.2% vs. 61.0%. The authors pointed out that it is important to detect focal thickening, pleural nodules or masses with imaging examination before biopsy to increase the accuracy of diagnosis. Similar results were also found in a prospective randomized study [16]. In patients with only pleural effusion, the diagnostic sensitivity of pleural biopsies performed with either a cutting needle or an Abrams needle was significantly lower than in patients with pleural thickening or a lesion accompanying pleural effusion (56.5% vs. 93.7% for Abrams needle; 42.9% vs. 80% for cutting needle) [16]. In a prospective, randomized study by Metintas *et al.*, the sensitivity of needle biopsy was 82% in patients with a pleural thickening of <1 cm compared with 95% in patients with a pleural thickening of ≥ 1 cm [10]. In another study by Metintas *et al.*, in which the method of sampling was decided by examining the CT scan findings of the patients, considering that it could increase the success of the methods, the diagnostic accuracy of MT was found to be 95.2%. The same rate was 90.2% for a needle biopsy. The sensitivity of the entire workup was 92.4% [22]. In the work of Niu *et al.* [5], all patients demonstrated a pleural thickness of >5 mm, and the diagnostic accuracy of pleural needle biopsy using CT scan guidance was 89.2%. In their study, Bugalho *et al.* concluded that image-assisted needle biopsy is more likely to be diagnostic in pleural thickening of >10 mm [23]. In the prospective randomized study by Metintas *et al.* [24], the sensitivity of image-assisted-Abram needle pleural biopsy (69.7%) was significantly lower than that of MT (96.9%) in patients with only pleural effusion on CT imaging. However, no difference was found between

needle biopsy and MT in terms of sensitivity (88.1% vs. 95.4%) in the group with pleural thickening or lesion in addition to pleural effusion.

In our study, 88% of participants in the USG-guided CPB group were diagnosed with malignant pleural effusion, compared to 72% in the MT group. The overall diagnostic yield was 92% for both methods (Table 3), which is consistent with results from Durgeswar *et al.* and Chang *et al.* [8,25]. The high diagnostic yield in our study can be credited to the benefits of USG guidance, which enables real-time imaging and the precise identification of biopsy sites.

According to the results of our study and the other studies described herein, we suggest that thorax CT imaging of patients with undiagnosed pleural effusion should be examined carefully before biopsy. Image-guided pleural biopsy should be performed if pleural thickening or a localized lesion is present on the pleura, accompanied by effusion on CT imaging and within reach of the needle. MT should be performed in patients with only an effusion or with a lesion that the needle cannot reach on CT imaging. Also, MT can be used as the second procedure in patients who remain undiagnosed after image-guided pleural biopsy. This approach can save time, reduce hospital workload, and be cost-effective.

Strengths of our study include a pragmatic study design. Our study also investigated the relation between the diagnostic yield and the number of biopsy specimens obtained. This study brings important points to notice, as there is a scarcity of comparative studies between USG-guided pleural biopsy and MT in India.

Limitations of our study are a small sample size, a single-center study, lack of blinding due to the nature of the interventions. The pleural nodularity or thickness cut-off taken in this study was set at 10 mm; further studies are needed to evaluate the utility of both biopsy methods with a lower cut-off.

Our findings suggest that USG-guided CPB is a suitable alternative to MT in diagnosing undiagnosed exudative pleural effusion, especially in patients with pleural thickening or nodularity exceeding 10 mm on radiological imaging. Despite fewer biopsy samples being taken in the USG-guided CPB group, the diagnostic yield remained similar in both groups. This approach can streamline diagnosis and treatment, ultimately improving patient outcomes. Further studies, particularly randomized controlled trials with a lower cut-off for pleural nodularity or thickening, are needed to comprehensively evaluate diagnostic yield.

Table 3. Summary of all the diagnoses in the ultrasound-guided closed pleural biopsy group and the medical thoracoscopy group.

Final diagnosis	Ultrasound-guided pleural biopsy (n=25), n (%)	Medical thoracoscopy (n=25), n (%)	Total n (%)	p
Acute inflammation	0 (0)	1 (4)	1 (2)	0.383
Adenocarcinoma	5 (20)	8 (32)	13 (26)	
Ewing's sarcoma	1 (4)	0 (0)	1 (2)	
Moderately differentiated keratinizing squamous cell carcinoma	1 (4)	0 (0)	1 (2)	
Non-small cell carcinoma	8 (32)	5 (20)	13 (26)	
Non-specific inflammation	2 (8)	1 (4)	3 (6)	
Poorly differentiated keratinizing squamous cell carcinoma	1 (4)	0 (0)	1 (2)	
Poorly differentiated non-keratinizing squamous cell carcinoma	2 (8)	1 (4)	3 (6)	
Small cell carcinoma	1 (4)	3 (12)	4 (8)	
Tuberculosis	1 (4)	5 (20)	6 (12)	
Undifferentiated carcinoma	3 (12)	1 (4)	4 (8)	
Total	25 (100)	25 (100)	50 (100)	



Conclusions

USG-guided CPB is a suitable alternative to MT in diagnosing undiagnosed exudative pleural effusion, especially in patients with pleural thickening or nodularity exceeding 10 mm on radiological imaging. More studies, particularly randomized controlled trials with a lower cut-off for pleural nodularity or thickening, are needed to comprehensively evaluate diagnostic yield.

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Received: 16 January 2025; Accepted: 20 January 2025; Early view: 18 March 2025.

Contributions: all the authors were involved in the literature search, planning, conducting, writing the original manuscript draft and editing. All the authors have agreed with the submitted manuscript. Dr Rohit Kumar is the corresponding author and guarantor for all.

Conflict of interest: the authors declare that they have no conflicts of interest regarding the current study.

Ethics approval and consent to participate: this study received ethical clearance from the institute ethical committee (IEC/VMMC/SJH/Thesis/9/2022/CC-13), dated 6/10/2022.

Informed consent: obtained.

Patient consent for publication: written informed consent has been obtained from all patients for the publication of the data.

Availability of data and materials: data and materials are available from the corresponding author upon request.

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