Original Article

The diagnostic yield of closed needle pleural biopsy in exudative pleural effusion: a retrospective 10-year study

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Background: Pleural effusion is a common presentation in clinical practice. About 40% of exudative pleural effusion is unable to be diagnosed through thoracentesis, and closed pleural biopsy (CPB) is needed. This study was designed to investigate the diagnostic yield of CPB in exudative pleural effusion.

Methods: This was a retrospective 10-year study of patients with unexplained exudative pleural effusion who underwent CPB in two centers. Malignant pleural effusion (MPE) was diagnosed when there was histopathological evidence of pleural tissue, pulmonary tissue, or pleural fluid. Tuberculous pleural effusion (TPE) was confirmed when granuloma or coagulative necrosis was observed in pleural tissue, Ziehl-Neelsen acid-fast staining was positive, or adenosine deaminase (ADA) in pleural effusion was higher than 35IU with clinical symptoms of TB orγ-interferon increased with symptoms of TB.

Results: A total of 644 patients were enrolled, of which 479 were specifically diagnosed (217 patients with TPE and 262 patients with MPE). The sensitivity of CPB in the diagnosis of MPE was 51.5%. Among the pathological types of MPE, lung adenocarcinoma accounted for 77.9% (204/262) of cases, making up the largest proportion. The sensitivity of CPB for diagnosing TPE was 68.7%.

Conclusions: CPB has a relatively high sensitivity in the diagnosis of exudative pleural fluid, especially in relation to tuberculous lesions. CPB could provide an alternative technique in clinical practice, especially for basic hospital units without thoracoscopy.

Keywords: Closed pleural biopsy (CPB); tuberculous pleural effusion (TPE); malignant pleural effusion (MPE); sensitivity

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Introduction

A pleural effusion is defined as an abnormal accumulation of pleural fluid within the pleural space, commonly classified as either transudative or exudative (1), which can be differentiated by thoracocentesis and biochemical analysis. However, approximately 40% of exudative pleural effusion cannot be diagnosed by thoracocentesis, creating the need for pleural biopsy or thoracoscopy (2).

Closed pleural biopsy (CPB), which was first reported by De Francis in 1955, has become a common method of obtaining pleural tissue for the diagnosis of pleural diseases (3). Copes and Abrams's needles were the most popular CPB needles after practical modification (4,5). CPB is a simpler and inexpensive technique that can be regularly carried out in hospitals at different levels. The complications of CPB mainly include pneumothorax, chest pain, vasovagal syncope, and hemothorax (6,7). Previous studies have demonstrated that while CPB has lower diagnostic accuracy, it also has lower rates of complications than thoracoscopy (8,9).

Thoracoscopy, with its high level of diagnostic accuracy, has been recognized as the gold standard for diagnosing pleural lesions (10). However, according to the results of different studies, the sensitivity of thoracoscopy is only approximately 90% to 95% (8,9). Therefore, CPB is still considered as an essential method to diagnose exudative pleural effusion owing to its practicability and safety in pleural diseases. This study was performed to assess the efficiency of CPB in the diagnosis of exudative pleural effusion at Nanjing Jinling Hospital and Nanjing Jiangning Hospital of China in the past decade.

Methods

This was a double-center retrospective study of patients with undiagnosed pleural effusion who underwent CPB (*Figure 1*) in Nanjing Jinling Hospital and Nanjing Jiangning Hospital in the ten-year period from January 01, 2008, to July 30, 2018. Thoracentesis and biochemical analyses were carried out for patients with unidentified pleural effusion. Light's criteria were used to distinguished exudative from transudative pleural effusion. For unknown exudative pleural effusion, tuberculosis and malignancy were diagnosed as follows: (I) tuberculous pleural effusion (TPE) was diagnosed if one of the following applied: granuloma was found by histopathology; Ziehl-Neelsen acid-fast staining was positive; adenosine deaminase (ADA)
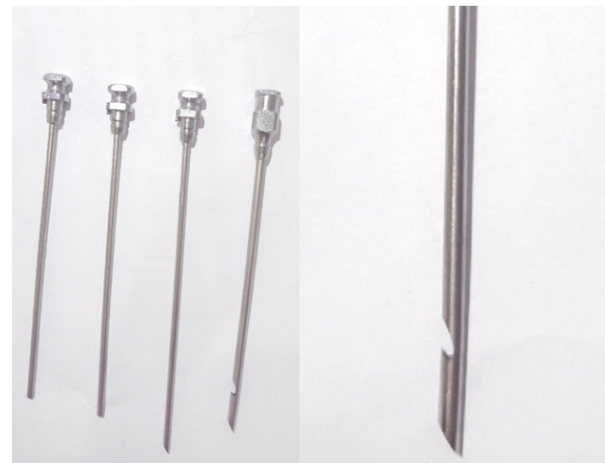

Figure 1 Pleural biopsy needle.

in pleural effusion was higher than 35IU with clinical symptoms of TB or γ-interferon increased with symptoms of TB, or mycobacterium tuberculosis could be cultured from pleural effusion or pleural tissue; (II) malignant pleural effusion (MPE) was confirmed when histopathological evidence was obtained by pleural biopsy, pneumocentesis, fibrobronchoscopy, surgery, or pleural fluid cytology.

Results

Overall, a total of 730 patients with exudative pleural fluid who underwent CPB at Nanjing Jinling Hospital and Nanjing Jiangning Hospital in China were included (*Figure 2*). Eighty-six cases were excluded because of inadequate samples or unavailable biopsy results. Of the 644 eligible candidates, 479 (74.4%) patients received a specific diagnosis. Malignancy accounted for the etiology in most cases (262/644, 40.7%), followed by tuberculosis (217/644, 33.7%).

The demographic characteristics of patients with a specific diagnosis in both hospitals included age, sex, smoker or not, and the side and color of effusion. Protein, glucose, and ADA levels were also collected (*Table 1*). The average age of the patients was 54.7 years, and 305 males and 174 females were included.

As shown in *Tables 2,3*, the sensitivity of CPB in detecting MPE and TPE was 51.5% and 68.7%, respectively. The specificity and positive predictive value of CPB for MPE and TPE were both 100%, whereas the negative predictive value was 63.1% and 79.4% in MPE and TPE, respectively.
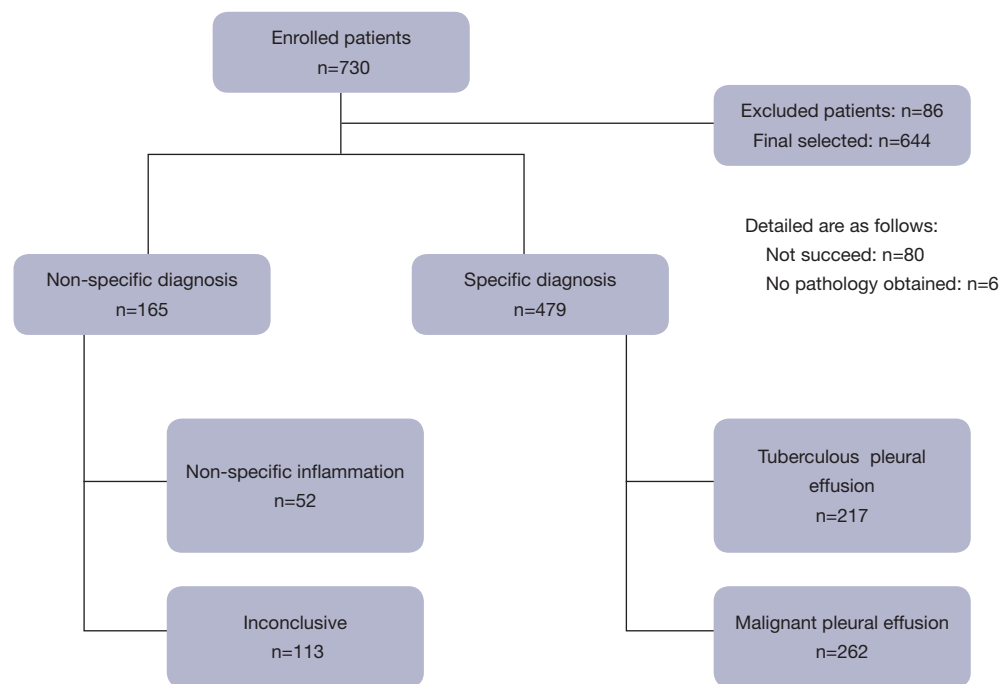
Figure 2 Results of closed pleural biopsy.

Table 1 Patients' demographic characteristics in Jinling and Jiangning hospital

Characteristics	Total	Male	Female
Number	479	305	174
Mean age (years)	54.7	54.7	54.5
Smoker			
Yes/no	178/297	170/132	7/165
Side of effusion			
Left	201	123	78
Right	245	166	79
Bilateral	32	15	17
Color of effusion			
Yellow/hemorrhagic	323/144	–	–
Pleural fluid			
Protein (g/L)	47.3	–	–
Glucose (mmol/L)	5.6	–	–
ADA (U/L)	32.5	–	–

The diagnostic yields of similar studies are also listed in *Table 4*.

The etiological classification for MPE is set out in *Table 5*. The most frequent histopathological type of MPE was pleural metastasis of pulmonary adenocarcinoma (204/262), followed by pulmonary squamous cell carcinoma (11/262), and small cell lung cancer (11/262). Lymphoma and mesothelioma accounted for 3.4% (9/262) and 2.3% (6/262) of MPEs, respectively. Other histopathological types are also listed in *Table 5*.

Table 6 shows the pleural fluid parameters of both the TPE group and the MPE group. There were significant differences in ADA, protein, and glucose between the groups. The mean values of ADA and protein in the TPE group were 48.83 U/L and 50.12 g/L, respectively, which were higher than the ADA and protein levels in the MPE group (15.09 U/L and 45.38 g/L, respectively). However, the MPE group had higher glucose levels (6.13 mmol/L) compared to the TPE group (5 mmol/L). LDH was slightly higher in malignant diseases than tuberculous lesions, although there were no significant

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Table 2 Closed pleural biopsy results, diagnosed as malignancy*

Indicators	Gold standard		
	Positive	Negative	Total
CPB			
Positive	135	0	135
Negative	127	217	344
Total	262	217	579
Test performance indicator			
Sensitivity (%)			
a/(a+c) =135/262	–	51.5%	–
Specificity (%)			
d/(b+d) =217/217	–	100%	–
Positive predictive value (%)			
a/(a+b) =135/135	–	100%	–
Negative likelihood ratio (%)			
d/(c+d) =217/344	–	63.1%	–

*, malignancy included lung cancer, mesothelioma, hematological malignancy and metastatic carcinoma. a: true-positive results; b: false-positive results; c: false-negative results; d: true-negative results.

Table 3 Closed pleural biopsy results, diagnosed as tuberculosis

Indicators	Gold standard		
	Positive	Negative	Total
CPB			
Positive	149	0	149
Negative	68	262	330
Total	217	262	479
Test performance indicator			
Sensitivity (%)			
a/(a+c) =149/217	–	68.7%	–
Specificity (%)			
d/(b+d) =262/262	–	100%	–
Positive predictive value (%)			
a/(a+b) =149/149	–	100%	–
Negative likelihood ratio (%)			
d/(c+d) =262/330	–	79.4%	–

a: true-positive results; b: false-positive results; c: false-negative results; d: true-negative results.

Discussion

Since 1955, CPB has become a popular technique for diagnosing exudative pleural effusion (4). We performed a double-center retrospective analysis of the diagnostic yield of CPB in patients with exudative pleural fluid. The sensitivity of CPB for diagnosing TPE was significantly higher than for diagnosing MPE in our study. The relatively lower yield for MPE is due to the scarce, irregular, and patchy distribution of tumor invasion of the pleura, which can be improved by locating the focus through ultrasound or CT. The sensitivity for diagnosing MPE by CPB in our study was lower than that reported in some previous studies (11,14,18,19) but higher than that published by other teams (6,15,20,21). The diagnostic sensitivity of CPB in MPE ranged from 33.9% to 82.4%, which might be related to the technical level of operation or number of biopsies, for example. The diagnostic yield of CPB for TPE ranges from 60% to 95% according to previous reports (19,22-25). In our study, the sensitivity for TPE was 68.7%, which is

consistent with previous studies.

While the specificity of CPB achieved 100% in both tuberculous and malignant pleural fluid, which is comparable with previous results (6,11,14,19,21), the positive predictive value was 100% in both TPE and MPE in our study, while the negative predictive value was lower (63.1% and 79.4% in the MPE and TPE groups, respectively). The reasons for MPE varied. Lung adenocarcinoma was the most frequent etiology, accounting for 77.7%, followed by pulmonary squamous carcinoma and small cell lung cancer, which each accounted for 4.1% of MPE cases. Mesothelioma and tumors of other systems, such as thymoma, lymphoma, metastatic carcinoma, made up the remaining etiologies.

As shown in *Table 6*, the ADA of pleural fluid in the TPE group was significantly higher than that in the MPE group, which demonstrated ADA to be an excellent parameter for distinguishing tuberculous from MPE. The sensitivity of ADA in the diagnosis of TPE in our study was 76.9%, slightly lower than the 91.9% sensitivity reported by Darooei *et al.* (26). The protein level in the TPE group was significantly higher than that in the MPE group, which is consistent with Valdés *et al.*' findings but opposite to Darooei *et al.*'s (26,27). Antonangelo *et al.* also

Table 4 Diagnostic yield of CPB in similar studies

References	Number	Malignant		Tuberculous	
		Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Zuberi et al. (11), 2016	94	82.4	100.0	93.9	100.0
James et al. (12), 2010	48	85.7	None	76.2	None
Al-Shimemeri et al. (13), 2003	116	41.7	100.0	68.6	100.0
Báez-Saldaña et al. (14), 2017	1,034	77.0	98.0	None	None
Pereyra et al. (15), 2013	575	59.2	100.0	92.0	100.0
Chakrabarti et al. (6), 2006	46	45.7	100.0	None	None
Jakubec et al. (16), 2014	208	63.1	100.0	None	None
Botana-Rial et al. (17), 2013	67	60.0	None	91.7	None
Present study	479	51.5	100.0	68.7	100.0

CPB, closed pleural biopsy.

Table 5 Etiological diagnosis for malignant pleural fluid in Jinling and Jiangning Hospital

Result	Number (%)
Malignant neoplasm	
Lung adenocarcinoma	204 (77.9)
Squamous carcinoma	11 (4.2)
Adenosquamous carcinoma	1 (0.4)
Small cell lung cancer	11 (4.2)
Giant cell lung cancer	1 (0.4)
Mesothelioma	6 (2.3)
Thymoma	3 (1.1)
Lymphoma	9 (3.4)
Plasma cell tumor	2 (0.8)
Other neoplasm	14 (5.3)
Total	262 (100.0)

Table 6 Pleural fluid parameters in TPE group and MPE group

Parameter	Malignant group	Tuberculous group	P value
ADA	15.09 (2 to 128)	48.83 (1 to 305)	<0.001
LDH	624.98 (73 to 14,104)	616.24 (92 to 7,131)	0.389
Protein	45.38 (0.5 to 101.4)	50.12 (16.5 to 67)	<0.001
Glucose	6.13 (0.1 to 42.7)	5 (0.1 to 16.4)	<0.001

TPE, tuberculous pleural effusion; MPE, malignant pleural effusion; ADA, adenosine deaminase; LDH, lactate dehydrogenase.

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reported higher protein concentration in patients with TPE compared with MPE (P<0.001) (28). In contrast, the glucose level was lower in the TBE group (mean: 5 mmol/L) compared to the MPE group (mean: 6.13 mmol/L). This did not correspond to the findings of a previous report by Darooei *et al.* and Herrera *et al.* (26,29).

This is double-center retrospective research with large samples, involving 479 patients who were specifically diagnosed. We demonstrated that the sensitivity of CPB for MPE and TPE was 51.5% and 68.7%, respectively. The results showed that CPB had a higher sensitivity in diagnosing TPE, whereas the diagnostic yield for MPE was relatively low. The main reason for this relatively low diagnostic yield was the non-uniform pleural involvement of primary diseases, which caused the failure of obtaining the focus through biopsy needle. More evidence showed that medical thoracoscopy and video-assisted thoracoscopic surgery played important roles in diagnosing pleural diseases with high sensitivity (9,30-33).

However, medical thoracoscopy and video-assisted thoracoscopic surgery are more invasive and expensive than CPB, and they are difficult to carry out in primary hospitals. Image-guided pleural biopsy is not popular, especially in primary hospitals, because it requires more equipment and a higher level of training for physicians. CPB is still widely performed in patients with undiagnosed pleural effusion at our institution for its advantages of simple manipulation, minimal trauma, minimal pain, low cost, and safety. It is still a valuable diagnostic procedure and should be performed for patients with undiagnosed pleural effusion in clinical practice.

Our study's most notable limitation was its retrospective nature. Furthermore, we excluded non-specific diagnoses, which might be malignancy or tuberculous, because we did not follow up with these patients to make a firm diagnosis. Another potential limitation is the inequality in the technical ability of different physicians. Nevertheless, the research included two centers and had a good sample size, which contributes to the quality of the study.

Conclusions

CPB has a higher sensitivity in the diagnosis of exudative pleural effusion, especially for tuberculous pleural diseases. For malignant pleural fluid, CPB showed a moderate diagnostic efficacy of over 50%. CPB could be a valuable technique in clinical practice, especially for basic-level hospitals.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.47). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethical Committee of the Affiliated Jinling Hospital of Nanjing University and the Affiliated Jiangning Hospital of Nanjing Medical University (DBNJ027). Written informed consent was obtained from all patients.

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