Original Article

A comparative diagnostic yield among cytologic examination, cell block and closed pleural biopsy in exudative pleural effusion

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Background: Cytology, cell block, and closed pleural biopsy are the initial investigations for exudative pleural effusion. However, the study of the diagnostic yield of the combination of methods is limited. The objective is to compare the diagnostic yield of cytology, cell block, and closed pleural biopsy with that of cytology and cell block.

Methods: A retrospective cross-sectional study was conducted between 1 January 2014 and 31 March 2020 at Srinagarind Hospital, Thailand. The study included subjects with undiagnosed pleural effusion who had cytology, cell block, and closed pleural biopsy results.

Results: The study included 175 subjects with exudative pleural effusions. One hundred and thirty-eight malignant pleural effusions (78.9%) and 34 tuberculous pleural effusions (19.4%) were diagnosed. One hundred and forty-two patients could be diagnosed by either method. Cytology, cell block, and closed pleural biopsy had 40.6%, 36.0%, and 58.3% diagnostic yields, respectively. Compared with cytology alone, 49.1% of the diagnostic yield was increased with cytology and cell block (P<0.001) and 81.1% with closed pleural biopsy, cell block, and cytology (P<0.001). In malignant pleural effusions, cytology, cell block, and closed pleural biopsy yielded 51.4%, 45.7%, and 56.5%, respectively. Combining the three methods increased to 85.5% compared with cytology alone (P<0.001). Seventeen patients (10%) had complications associated with thoracentesis and closed pleural biopsy, of which 6.9% resulted in pneumothorax.

Conclusions: A combination of closed pleural biopsy, cell block, and conventional cytology provided favorable diagnostic yields in patients with exudative pleural effusion.

Keywords: Cytology; cell block; closed pleural biopsy; exudative pleural effusion

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Introduction

Exudative pleural effusion is a common problem in clinical practice. Malignant pleural effusion and tuberculous pleural effusion are the common etiologies of exudative pleural effusions. Thailand is one of the countries with high tuberculosis burdens, according to World Health Organization's reports. The estimated tuberculosis burden in Thailand was 155 cases per 100,000 population (1). Tuberculous pleuritis is the common extrapulmonary tuberculosis, which accounts for 4–10% of total tuberculosis (2). The differentiation between malignant pleural effusion and tuberculosis can be challenging, especially in areas of high tuberculosis burden, since both diseases present with similar clinical and radiological features (3).

The cell block technique is used for non-gynecologic fluid analysis. After removing the supernatant, sediment is processed and embedded in tissue blocks, which are cut and stained as in histology. According to some studies, adding cell block to conventional cytology increases the diagnostic yield of malignancy (4-7). Furthermore, cell block and cytology had a low diagnostic yield for pleural infections (7). A closed pleural biopsy is commonly used to investigate patients with exudative pleural effusions. Based on previous studies, the diagnostic yield of closed pleural biopsies ranges from 34–86% (8-11). There was a 43–59% diagnostic yield for malignant pleural effusions (9,11,12), while there was a 67–80% diagnostic yield for tuberculous pleural effusions (13,14). Closed pleural biopsy is more feasible and cost-effective than thoracoscopy for diagnosing tuberculous pleural effusion; previous guidelines recommended that closed pleural biopsy be performed for exudative pleural effusions in areas with high tuberculous infection rates (15). Complications of closed pleural biopsy include pneumothorax, haemothorax, and rare death. Despite closed pleural biopsy having a lower diagnostic yield than cytology when used with adjunct cytology, closed pleural biopsy increased diagnostic yield when it was combined with cytology (8,11,16,17).

In our center, conventional cytology, cell block, and closed pleural biopsy are the initial studies used for patients with exudative pleural effusion. To date, limited studies have investigated the diagnostic yield of a combination of these three. Hence, this study aimed to compare the combination of conventional cytology, cell block and closed pleural biopsy with conventional cytology for diagnostic yield. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1006/rc).

Highlight box

Key findings

- A combination of conventional cytology, cell block, and closed pleural biopsy increases diagnostic yield in exudative pleural effusion.

What is known and what is new?

- Adding a cell block or closed pleural biopsy to conventional cytology has improved diagnostic yield in exudative pleural effusion.
- We demonstrate that simultaneously performing three methods as the investigation for patients who present with exudative pleural effusion can increase diagnostic yield compared with either method alone.

What is the implication, and what should change now?

- Thoracentesis for conventional cytology and cell block, accompanied by closed pleural biopsy, should be considered particularly prior to pleuroscopy, especially in areas with a high burden of tuberculosis.

Methods

Study design

A retrospective cross-sectional study was conducted between 1 January 2014 and 31 March 2020 at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Human Research Ethics committee, Khon Kaen University (approval No. HE631246). Informed consent was waived due to the retrospective nature of this study. Participants older than 18 with pleural effusion clinically consistent with an exudative pleural profile, who had undergone thoracentesis closed pleural biopsy were recruited. Thoracocentesis and closed pleural biopsy were performed under ultrasound guidance. Patients with pre-procedural diagnoses of certain causes, such as transudative pleural effusion, chylothorax, pseudo chylothorax, haemothorax, and pseudo exudative pleural effusion, were excluded.

Procedure

Ultrasonography-guided thoracentesis and closed pleural biopsy were performed under local anesthesia. The

amount of pleural fluid obtained was approximately 200 mL. An analysis of the pleural fluid included differential cell counts, total protein levels, lactate dehydrogenase (LDH), adenosine deaminase (ADA), gram stain, acid-fast bacilli (AFB), aerobic culture, mycobacterial culture, and polymerase chain reaction testing of *Mycobacterium tuberculosis* (MTB) [GeneXpert for *Mycobacterium tuberculosis* and rifampicin resistance (MTB/RIF)]. A closed pleural biopsy was performed with an Abrams needle. At least four pieces of specimen were obtained for pathological study under 10% formalin fixation, and two pieces were obtained for mycobacterium culture.

Cytologic and cell block examination

A 15-mL sample of pleural fluid was centrifuged under 2,500 rpm. Then, the supernatant was removed. For cytological examination, the smear was stained with Papanicolaou staining. For the examination of cell blocks, pleural fluid was centrifuged at 1,600 rpm for 10 minutes. Afterward, the supernatant was re-centrifuged at 1,600 rpm for 5 minutes. The final supernatant was melted with BIO-OPTICA agar media under the microwave; 1–2 droplets of the specimen were transferred to a sediment tube, shaken with a vortex, and frozen for 1 hour. The specimen was transferred into a tissue cassette and processed with a formalin-fixed paraffin-embedded tissue protocol as follows: embedding, sectioning ribbons, and hematoxylin-eosin staining. The pathologist evaluated the visible nucleate neoplastic cells for a percentage cellularity estimation under a ×40 magnification light microscope. The diagnosis was made by examination of cytologic slides and cell block slides under the compound light microscope (Olympus BX-43, Olympus Corporation, Tokyo, Japan).

Definition

The diagnostic yield of cytologic examination and cell block was defined as a diagnosis established by the presence of malignancy. The diagnostic yield of closed pleural biopsy was defined as the presence of malignancy, chronic granulomatous inflammation, positive AFB stain, or the isolation of MTB from tissue.

Data collection

Demographic information and laboratory results were collected from the patient's medical record. Using the Picture Archiving and Communication System (PACS), chest radiographic findings were obtained. Age, sex, body mass index (BMI), symptoms, underlying diseases, smoking history, chest radiographic findings, thoracentesis profile results, and complications of pleura-related procedures were recorded. Statistical analysis of the data was performed using Stata after it had been stored in a Redcap database.

Statistical analysis

An estimation of the population is based on a study by Báez-Saldaña *et al.* (10) with a 95% confidence interval and 0.10 precision. The sample size is 113, with an anticipated dropout rate of 10%. Categorical data were presented as numbers and percentages. Normal-distributed continuous data's mean and standard deviation (SD) were presented. The median and interquartile range (IQR) were presented for non-normally distributed data. Category data was compared using the Chi-squared and Fisher's exact test, depending on the data type. Mann-Whitney *U* test was used to compare nonparametric data. McNemar's Chi-squared test was used to analyze diagnostic yield. The statistical analysis was performed with Stata version 10.1 (StataCorp, Texas, USA).

Results

One hundred and seventy-five patients with suspected exudative pleural effusion underwent thoracentesis and closed pleural biopsy. One hundred and forty-two patients were diagnosed using those methods, and 33 patients required alternative diagnostic methods. One hundred and thirty-eight patients (78.9%) were diagnosed with malignant pleural effusions. One hundred and seven patients (61.1%) had pleural metastasis from lung cancer. Specifically, metastatic adenocarcinomas were the most common malignancy (82 patients, 46.9%). The demographics of the subjects and the final diagnosis are shown in *Table 1*.

Combining three methods results in a significantly higher diagnostic yield than cytology alone in cases of exudative pleural effusions. In malignant pleural effusion, the combination of three methods adds diagnostic yield when compared with cytology or the combination of cytology and cell block (85.5% in the combination of three methods, 62.3% in the combination of cytology and cell block, and 51.4% in cytology alone). The results are similar to those of pleural metastasis from lung cancer (89.7% using all three methods, 71.0% using cytology and cell block, and

Table 1 Demographic data of 175 study subjects who had diagnostic thoracentesis and closed pleural biopsy

Variables	Values
Age (years), mean ± SD	64.63±12.06
Male, n (%)	95 (54.3)
Side of pleural effusion, n (%)	
Unilateral (left)	69 (39.4)
Unilateral (right)	93 (53.1)
Bilateral	13 (7.4)
Amount of effusion, n (%)	
<1/4 of hemithorax	7 (4.0)
1/4–1/2 of hemithorax	55 (31.4)
>1/2–3/4 of hemithorax	52 (29.7)
>3/4 of hemithorax	61 (34.9)
Effusion profiles	
Pleural protein (g/dL), median (IQR)	4.9 (4.2–5.6)
Pleural/serum protein ratio, median (IQR)	0.7 (0.63–0.77)
Pleural LDH (U/L), median (IQR)	344.0 (245.75–779.5)
Pleural/serum LDH ratio, median (IQR)	1.57 (1.08–2.93)
Final diagnosis, n (%)	
Malignancy	138 (78.9)
Lung cancer	107 (61.1)
Small cell	5 (2.9)
Non-small cell	102 (58.3)
Adenocarcinoma	82 (46.9)
Squamous cell carcinoma	5 (2.9)
Neuroendocrine	1 (0.6)
Other cell type	14 (8.0)
Mesothelioma	3 (1.7)
Breast cancer	7 (4.0)
Colon cancer	4 (2.3)
Cholangiocarcinoma	4 (2.3)
Hematologic malignancy	3 (1.7)
Sarcoma	2 (1.1)
Head and neck	2 (1.1)
Ovarian cancer	1 (0.6)
Other	5 (2.9)
Tuberculous pleuritis	34 (19.4)
Inflammation	3 (1.7)

SD, standard deviation; IQR, interquartile range; LDH, lactate dehydrogenase.

58.9% using cytology alone). The diagnostic yield of each method is shown in *Table 2*.

Thirty-six patients (20.5%) had pleural effusion from an infectious cause. Thirty-four patients (19.4%) were diagnosed with tuberculosis pleuritis, 24 patients (70.6%) were diagnosed by closed pleural biopsy, and 10 patients (29.4%) used alternative diagnostic methods. Two patients with non-tuberculous mycobacterium infection could not be diagnosed by closed pleural biopsy.

The alternative diagnostic methods performed in non-diagnostic patients are shown in *Table 3*. A pleuroscopy was performed on 13 patients to provide the final diagnosis. In 17 patients (10%), complications occurred after thoracentesis and closed pleural biopsy. *Table 4* shows the complications of the diagnostic procedure.

Discussion

It has been observed that in clinical practice, particularly in areas with a high burden of tuberculosis, the most common causes of exudative pleural effusions are malignant pleural effusions and tuberculosis. As a result of our studies, we found that combining conventional cytology, cell blocks, and closed pleural biopsy methods would result in a higher diagnostic yield compared to single methods for exudative pleural effusion. A greater diagnostic yield is seen in metastasis pleural effusion caused by lung cancer, the most common cause. The results of our study suggest that thoracentesis and closed pleural biopsy can be performed simultaneously in patients with exudative pleural effusion because of their favorable diagnostic yield.

Diagnostic yield has been shown to increase when cell blocks are added to conventional cytology. According to Assawasaksakul's study, cell block was comparable to conventional cytology for metastasis pleural effusions from solid malignancies (63.2% in cell block, 64.4% in conventional cytology), but when both methods were combined, the diagnostic yield increased to 73.4%. This improvement was more pronounced in metastasis pleural effusion from lung cancer (7). In another study from Shivakumarswamy, cell block provided an additional 15% diagnostic yield when combined with conventional cytology (4). Our study demonstrates that combining both techniques increases the diagnostic yield of malignant pleural effusion by 10.4% when compared to either technique alone. As a result, the effect has been consistently observed in patients with metastasis pleural effusions from lung cancer.

In conventional cytology, even though the preparation

Table 2 Diagnostic yield of cytology, cell block, closed pleural biopsy, combination of cytology and cell block, and combination of three methods

Diagnosis	Cytology, n (%)	Cell block, n (%)	P value[†]	Closed pleural biopsy, n (%)	P value[‡]	Combination of cytology and cell block, n (%)	P value[§]	Combination of three methods, n (%)	P value[¶]
Total (n=175)	71 (40.6)	63 (36.0)	<0.001	102 (58.3)	0.75	86 (49.1)	<0.001	142 (81.1)	<0.001
Tuberculous pleuritis (n=34)	0 (0.0)	0 (0.0)	N/A	24 (70.6)	N/A	0 (0.0)	N/A	24 (70.6)	N/A
Malignant pleural effusion (n=138)	71 (51.4)	63 (45.7)	<0.001	78 (56.5)	0.96	86 (62.3)	<0.001	118 (85.5)	<0.001
Lung cancer (n=107)	63 (58.9)	58 (54.2)	<0.001	61 (57.0)	0.71	76 (71.0)	<0.001	96 (89.7)	<0.001
Non-pulmonary cancer (n=31)	8 (25.8)	5 (16.1)	0.09	17 (54.8)	0.69	10 (32.3)	<0.001	22 (71.0)	0.03

[†], cell block compared with cytology alone; [‡], closed pleural biopsy compared with cytology alone; [§], combination of cytology and cell block compared with cytology alone; [¶], combination of three methods compared with cytology alone. N/A, not available.

Table 3 Final diagnosis and diagnostic method for 33 non-diagnosis cases by cytology, cell block, and closed pleural biopsy

Final diagnosis	Diagnosis methods	Number
Malignant pleural effusion (n=20)		
Non-small cell lung cancer (n=9)	Pleuroscopy	6
	Bronchoscopy	2
	Lymph node biopsy	1
Small cell lung cancer (n=2)	Bronchoscopy	2
Non-pulmonary cancer (n=9)	Pleuroscopy	6
	Opened lung biopsy	1
	Imaging (primary tumor found and typical pleural metastasis findings from CT)	2
Inflammatory (n=13)		
Tuberculous pleural effusion (n=10)	Positive PCR for tuberculosis in sputum	2
	Positive mycobacterium culture from sputum	1
	Positive PCR for tuberculosis in pleural fluid	1
	Positive mycobacterium culture from pleural fluid	1
	ADA ≥30 IU/L and response to anti-tuberculosis medications	5
Non-tuberculous mycobacterium infection (n=2)	Pleuroscopy	1
	Lymph node biopsy and response to treatment	1
Pseudochylothorax (n=1)	Pleural chemistry	1

CT, computer tomography; PCR, polymerase chain reaction; ADA, adenosis deaminase.

Table 4 Complication of thoracentesis and closed pleural biopsy in 17 patients

Complication	Number (%)
Pneumothorax	12 (6.9)
Subcutaneous emphysema	9 (5.1)
Hemothorax	1 (0.6)
Need chest drainage	3 (1.7)

is simple, the main problem is the lack of tissue architecture. Distinguishing reactive mesothelial cells from metastatic neoplasms in malignant pleural effusions may be difficult. The cell block has a complementary material for morphologically evaluating preserved tissue architecture. Moreover, pathologists may be familiar with the hematoxylin and eosin stain, so the cell block provides more advantages over conventional cytology. However, a variety of fixative substances can affect the diagnostic yield, so no consensus exists about the best fixatives (18,19). In the present study, we used agar embedding for cell block, which is feasible and preserves tissue comparable to the histopathological examination of surgical tissue samples (20).

An ultrasound-guided closed pleural biopsy has a 40–70% diagnostic yield for detecting malignant pleural effusions. However, some studies have shown that blind closed pleural biopsy is less sensitive than conventional cytology. Since some types of malignant cells, such as adenocarcinoma from the lung, ovary, breast, or gastrointestinal tract, are susceptible to shredding into pleural effusions, cytology has the advantage of diagnosing malignant pleural effusions (21). Moreover, malignant pleura usually spreads in patches, blind closed pleural biopsy may not detect lesions (22). Ultrasound-guided pleural biopsy improves diagnostic yields over cytology alone in malignant pleural effusions. It detected thickening of the pleura or overt pleural abnormalities. In the absence of sonographic pleural abnormalities, targeting at the low supradiaphragmatic pleura was performed. Using Abram or Tru-cut without real-time ultrasound guidance provided additional diagnostic yields of 31% to 89.7% (23). Another prospective study shows that ultrasound-located pleural biopsy with Abram needle increased diagnostic yield from 60% to 77.4% (24). Moreover, adding closed pleural biopsy to cytology increases diagnostic yield from 57.6% to 64.7% (11). According to our study, adding closed pleural biopsy to cytology and cell block significantly increases the diagnostic yield of malignant pleural effusion and malignant pleural effusion from lung cancer to 85.5% and 89.7%, respectively. The diagnostic yield was favorable in our study since the primary site of metastasis pleural effusions was almost lung cancer. Previous studies demonstrated that closed pleural biopsy provides good diagnostic yield when performed on populations with a high prevalence of metastatic pleural effusions from lung cancer (10,25). Moreover, the prevalence of mesothelioma was low in our study. Mesothelioma is difficult to diagnose by either cytology or a pleural biopsy. Cytology's diagnostic yield is unreliable in malignant mesothelioma (26). There is a high degree of variability in the histologic patterns of malignant mesothelioma, which makes it difficult to differentiate it from other metastasis carcinomas or even reactive mesothelium.

It has been shown that closed pleural biopsy provides excellent diagnostic yields for tuberculous pleuritis. According to a 10-year retrospective study, closed pleural biopsy had a 68.7% diagnostic yield, higher than malignant pleural effusions (8). A retrospective study from Taiwan found that 74% of tuberculosis pleuritis cases were confirmed by granuloma detection by closed pleural biopsy, whereas only 39% of cases received positive tissue cultures (27). Our study's results suggest relevant outcomes regarding tuberculous pleuritis diagnosis. Pathological diagnosis by closed pleural biopsy yielded a diagnostic rate of 70.6%. However, only 32% of pleural mycobacterium tissue cultures yielded a positive diagnosis. Accordingly, tuberculous pleuritis is commonly caused by a delayed hypersensitivity reaction to MTB. Thus, paucibacili in the pleural space leads to a lower likelihood of a positive mycobacterium culture. Pleural biopsy provides better diagnostic yield because tuberculous pleuritis pathology tends to be diffuse.

With clinically exudative pleural effusion, closed pleural biopsy has an overall diagnostic yield of 33.9–49.9% (7,8). In our study, the diagnostic yield for closed pleural effusion was 58.3%. When combined with conventional cytology and cell block, the diagnostic yield was 81.1%. Both surgical and medical thoracoscopy offer excellent diagnostic yields due to the visualization of pleural pathology, which guides proper sampling, and adequate tissue is always obtained. However, thoracoscopy may not be available, particularly in primary care units. A disadvantage of thoracoscopy is a longer hospital stay and higher expenses. Combined with cytology and cell block, blind closed pleural biopsy provides a satisfying diagnostic yield and is more feasible.

In our study, closed pleural biopsy resulted in 12.5% complications, of which 6% were pneumothorax without death. According to previous studies, pneumothorax rates after pleural biopsy vary from 2.5% to 9.4%, depending on whether it is ultrasound-guided (8,10,24). Based on previous guidelines, pneumothorax was found 3–15% after pleural biopsy with Abram needles (15). Closed pleural biopsy did not result in major life-threatening complications.

Our study's strength is that it demonstrates the diagnostic yield of a combination of three methods when applied simultaneously in patients with clinically exudative effusion or suspicion of malignant pleural effusion or tuberculous effusion. Particularly when applied in areas with a high prevalence of tuberculosis. The limitation is that the majority of final diagnoses are malignant pleural effusions from lung cancer and tuberculous pleuritis, so these results may not be extrapolated to other causes of exudative pleural effusions, such as non-pulmonary cancer metastasis pleural effusion or mesothelioma.

Conclusions

Our study suggests that the use of conventional cytology, cell block, and closed pleural effusion simultaneously can be performed without major complications and is feasible. In patients with clinically exudative pleural effusion, this method provides a satisfactory diagnostic yield.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1006/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1006/coif). 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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Human Research Ethics committee, Khon Kaen University (approval No. HE631246). Informed consent was waived due to the retrospective nature of this study.

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