

The diagnostic value of liquid-based cytology of pleural fluid in malignant pleural effusion: A prospective study

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ABSTRACT

Introduction: Pleural effusion (PE) is commonly observed in clinical practice. Conventional smear (CS), cell block (CB), and liquid-based cytology (LBC) of pleural fluid are used to guide the diagnosis of malignant pleural effusion (MPE). However, the effectiveness of these cytological techniques, whether used alone or in combination, is still not well established. **Methods:** A prospective study was conducted from October 2019 to May 2020 at the Department of Pulmonary Medicine, Cho Ray Hospital (Ho Chi Minh City, Vietnam). Suspected MPE patients were investigated by simultaneous cytological methods (CS, CB, and LBC) of pleural fluid and pleural tissue histopathology. The study included 47 patients with MPE, confirmed by pleural tissue pathology as the gold standard. The study compares the sensitivity of the three cytological methods. **Results:** Out of 69 patients suspected of MPE, 47 were confirmed to have MPE through histopathological analysis of pleural biopsy. The average age of the study participants was 62.6 years, with 44.7% being male. The sensitivity of LBC and CB, LBC and CS, and CB and CS did not significantly differ, with p-values of 0.546, 0.789, and 0.606, respectively (McNemar test). Combining two of the three cytological methods (CS, CB, LBC) significantly enhances the sensitivity in diagnosing MPE compared to using a single method alone, except for the combination of CB and LBC versus LBC alone. The study has limitations, including the exclusion of non-MPE pleural effusion cases, which means the specificity of the cytological methods could not be calculated. Additionally, the limited number of patients should be taken into consideration, and caution is advised when interpreting the study results. **Conclusions:** The study concludes that CS, CB, and LBC methods have similar sensitivity in diagnosing MPE. Combining any two methods improves diagnostic sensitivity compared to using a single method, although CB and LBC together do not surpass LBC alone. Clinicians should consider combining cytological techniques to optimize the diagnostic sensitivity of MPE.

Key words: Malignant pleural effusion, conventional smear, cell block, liquid-based cytology, sensitivity

INTRODUCTION

Pleural effusion (PE) is frequently encountered in clinical practice and affects more than 0.3% of the population annually¹. Common etiologies of PE include heart failure, malignant pleural effusion (MPE), parapneumonic effusion, and pulmonary embolism². Identifying malignant cells in pleural fluid is warranted if the initial diagnosis suspects MPE. Pleural fluid cytology testing includes three methods: conventional smear (CS), cellblock (CB), and liquid-based cytology (LBC).

Although LBC was developed later than CS and CB^{3,4}, numerous investigations have demonstrated that LBC is capable of diagnosing malignant disorders as effectively as, or even better than, other cytological methods in various specimen types, including sputum⁵, fine-needle aspiration of thyroid lesions⁶, bronchoalveolar lavage⁷, transbronchial needle aspi-

ration⁸, and pleural fluid^{9,10}. In clinical practice, it is essential to use CS, CB, and LBC of pleural fluid to guide the diagnosis of MPE. However, the diagnostic efficacy remains unclear whether these cytological methods are used individually or in combination. This study aimed to compare the diagnostic value of these cytological methods when performed separately or in combination for diagnosing MPE.

METHODS

A prospective study was conducted from October 2019 to May 2020 at the Department of Pulmonary Medicine, Cho Ray Hospital (Ho Chi Minh City, Vietnam). Patients suspected of having MPE were identified based on a history of lung cancer or other malignancies, smoking, and prolonged symptoms over several weeks, such as cough, chest pain, dyspnea, hemoptysis, weight loss, or chest imaging showing PE

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with a suspicious lung mass. Suspected MPE patients admitted to the hospital were included in the study, and simultaneous cytological methods (CS, CB, and LBC) of pleural fluid and pleural tissue histopathology were performed. Finally, the study included 47 patients with MPE, confirmed by pleural tissue pathology as the gold standard.

Inclusion Criteria

The study included patients fulfilling all of the following criteria: i) aged 18 years or older, ii) consenting to participate in the study, iii) having a confirmed diagnosis of MPE through pleural tissue histopathology obtained via blind pleural biopsy, and iv) undergoing all three cytological methods, including CS, CB, and LBC.

Exclusion Criteria

Patients with the following characteristics were excluded: i) contraindications for blind pleural biopsy, ii) undergoing cancer treatment with chemotherapy, radiotherapy, or targeted therapy, and iii) a known diagnosis of pleural cancer (either primary or metastatic) in their medical history.

Conventional Smear

The pleural fluid was divided into two portions with a minimum volume of 5 mL each. One portion was smeared and stained with methylene blue, then observed under a light microscope to determine the number of red blood cells and nucleated cells. The remaining portion was centrifuged, smeared, and stained with Wright-Giemsa stain, and then observed under a light microscope to identify atypical cells suspected of malignancy.

Cellblock

To perform the CB method, at least 60 mL of pleural fluid should be used. The fluid was allowed to sit for 8-10 hours, after which the supernatant was removed, and the cell sediment was distributed into small tubes. The tubes were centrifuged at 2000 rpm for 10 minutes, the supernatant was discarded, and the sediment was fixed in 10% formalin at 60°C for about 2 hours. After the formalin was discarded, the cell block was removed, wrapped in paper, and placed into a plastic mold. The mold was then processed according to routine histology procedures (paraffin embedding), sections 3-5 μm thick were cut, stained with hematoxylin-eosin, and immunohistochemical staining was performed if needed.

Liquid-Based Cytology

The minimum amount of pleural fluid required to perform the LBC method was set at 20 mL. After the sample was centrifuged, the supernatant was discarded, and the cell components at the bottom were collected. To wash the sample, 30 mL of CytoLyt® solution was added, and another round of centrifugation was conducted. If the cell components were clean and clear, they were transferred to a container with PreservCyt® solution for stabilization. The sample was stabilized for 15 minutes before it was processed using the ThinPrep® 2000 processor (Hologic, USA).

Pleural Tissue Pathology

At least three pleural tissue samples obtained through blind pleural biopsy were fixed in 10% formalin and embedded in paraffin. The specimens were stained with Hematoxylin-Eosin. Immunohistochemical staining was performed if needed to differentiate malignant cells from mesothelial cells.

Cytological and Histopathological Report

Pleural fluid CS results were interpreted by a cytologist with over 5 years of experience and were reported as positive if abnormal or suspicious malignant cells were detected. Pleural fluid CB results were interpreted by a pathologist with over 3 years of experience and were reported as positive if abnormal, suspicious malignant, or cancer cells were detected. Additionally, pleural fluid LBC results were also read by a pathologist with over 3 years of experience, with positive results reported if abnormal or suspicious malignant cells were identified. All physicians interpreting the cytological and histopathological results were completely blinded to the clinical information and the results of other methods.

Statistical Analysis

The statistical analysis was performed using Stata version 14 (StataCorp). Quantitative variables with a normal distribution were represented as mean \pm standard deviation (SD), whereas those with a non-normal distribution were shown as medians. Qualitative variables were expressed as percentages. The sensitivity of CS, CB, and LBC was calculated. The McNemar test was used to compare paired data proportions in the same population. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

We enrolled 69 patients suspected of having MPE, of whom 47 were definitively diagnosed with MPE based

on histopathological examination of pleural biopsy specimens for inclusion in the final analysis. The study population had a mean age of 62.6 years, with 44.7% being male. Detailed information is shown in **Table 1**.

The Value of Cytological Methods

DISCUSSION

Our study simultaneously applied three cytological methods to the pleural fluid specimen to compare their sensitivity in detecting cancer cells against the gold standard of histopathological examination. The results indicate that combining two of the three cytological methods (CS, CB, LBC) significantly improves the sensitivity in diagnosing MPE compared to using a single method alone (except for the combination of CB + LBC compared to LBC alone).

There are several mechanisms leading to PE associated with malignancies, which can be categorized into four main groups: PE due to the local effects of the tumor (*e.g.*, lymphatic obstruction, atelectasis from bronchial obstruction), PE due to the systemic effects of the tumor (*e.g.*, pulmonary embolism, hypoalbuminemia), and PE as a complication of radiation or chemotherapy (*e.g.*, methotrexate, cyclophosphamide)¹¹. However, not all cases of PE in malignancies involve the presence of cancer cells in the pleural fluid or on the pleural surface. The authors suggest that the primary mechanism leading to MPE is the tumor's increased secretion of vascular endothelial growth factor (VEGF) and the resultant increased vascular permeability^{12,13}. In cases where lung cancer metastasizes to the pleura, it is classified as M1 in the TNM (tumor, node, metastasis) staging system, which negatively impacts prognosis. Therefore, identifying pleural cancer is crucial for determining the treatment strategy and prognosis for the patient¹⁴. In practice, pleural fluid cytology testing demonstrates higher sensitivity compared to pleural tissue histopathology obtained through blind pleural biopsy. This is due to several factors: **a)** approximately 50% of pleural metastatic cancers do not involve the parietal pleura¹⁵, **b)** the biopsy is conducted at a single site, and **c)** the biopsy is performed blindly¹¹. Thus, enhancing the sensitivity of pleural fluid cytology through the combination of methods such as CS, CB, and LBC can improve diagnostic accuracy. This approach may reduce the need for blind pleural biopsy, an inherently more invasive procedure.

Unlike CS and CB methods, which have been widely applied in medical practice, LBC is a more recent development. However, numerous studies on various

types of specimens have shown that LBC may offer superior diagnostic capabilities compared to CS and CB^{8,10,16,17}. LBC offers several advantages, including the creation of a thin, uniform layer of cells without overlapping or obscuring factors such as artifacts or blood and preserving cellular morphology. Additionally, LBC provides representative and incidental sampling, which helps reduce the time required for result interpretation^{18,19}. Our study demonstrates that the sensitivity of CS, CB, and LBC in diagnosing MPE does not show a statistically significant difference. However, combining two of the three cytological methods significantly improves sensitivity in diagnosing MPE compared to using a single method alone (except for the combination of CB + LBC compared to LBC alone). The advantages of LBC mentioned above, along with the findings of this study, which demonstrate that LBC has higher sensitivity than CB and that the combination of CB and LBC does not further increase sensitivity compared to LBC alone, suggest the potential superiority of LBC over CB in diagnosing MPE.

Table 1: Clinical and laboratory characteristics of the study population (n = 47)

Variables	Normal value	n (%)	Mean ± SD
Age (years)			62.6 ± 12.7
Male		21 (44.7)	
Female		26 (55.3)	
History of cancer			
Lung cancer		7 (14.9)	
Non-lung cancer		2 (4.3)	
Symptom			
Fever		0 (0.0)	
Dyspnea		35 (74.5)	
Cough		28 (59.6)	
Chest pain		27 (57.4)	
Hemoptysis		3 (6.4)	
Weight loss		7 (14.9)	
Location of pleural effusion on chest X-ray			
Right side		19 (40.4)	
Left side		21 (44.7)	
Both sides		7 (14.9)	
Cellular components of pleural fluid			
Lymphocyte > 50%		30 (63.8)	
Eosinophil > 10%		2 (4.3)	
Serum total protein (g/dL)	6–8		6.1 [5.7–6.6]
Pleural fluid protein (g/dL)	<1.5		4.2 [3.7–4.8]
Serum LDH (U/L)	140–280		266 [216–387]
Pleural fluid LDH (U/L)			638 [327–1084]
Pleural fluid ADA (U/L)			9.9 [6.2–13.5]
Exudates pleural effusion bases on Light’s criteria, n (%)			47 (100%)

Abbreviations: IQR: interquartile range, SD: standard deviation, LDH: lactate dehydrogenase, ADA: adenosine deaminase.

Table 2: Sensitivity of cytological methods in diagnosing malignant pleural effusion (n = 47)

Methods	Sensitivity, n (%)	p ^a
CS	27 (57.4)	0.606 ^b
CB	24 (51.1)	0.546 ^c
LBC	27 (57.4)	0.789 ^d
CS + CB	33 (70.2)	0.041 (when compared with CS) 0.008 (when compared with CB)
CS + LBC	34 (72.3)	0.023 (when compared with LBC) 0.023 (when compared with CS)
CB + LBC	31 (66.0)	0.134 (when compared with LBC) 0.023 (when compared with CB)
CS + CB + LBC	36 (76.6)	0.083 (when compared with CS + CB) 0.157 (when compared with CS + LBC) 0.025 (when compared with CB + LBC)

Abbreviations: CS: conventional smear, LBC: liquid-based cytology, CB: cell block. ^aMcNemar test. ^bp-value when comparing CS and CB. ^cp-value when comparing LBC and CB. ^dp-value when comparing LBC and CS. Values with p < 0.05 are highlighted in bold.

A study involving 278 patients with MPE compared the sensitivity of LBC and CB methods in diagnosing MPE. The study found that the sensitivity of LBC and CB was 61.2% and 61.9%, respectively, with no statistically significant difference ($p = 0.89$), similar to the results of our study. The specimen processing was performed using the ThinPrep® 2000 processor (Hologic). However, the simultaneous combination of both LBC and CB methods significantly improved the diagnostic sensitivity compared to using each method alone¹⁰. In a 2018 study by Woo involving 862 patients with PE, the sensitivity of LBC, CB, and the combination of LBC and CB were 81.3%, 94.3%, and 98.3%, respectively. The specimen processing was performed using the CellprepPlus® processor (Biodyne, South Korea)²⁰. The sensitivity of LBC and CB in our study is comparable to that reported by Assawasaksakul (57.4% vs. 61.2% for LBC and 51.1% vs. 61.9% for CB), with both studies utilizing the same LBC technique (ThinPrep® 2000 processor, Hologic)¹⁰. However, Woo's study reports significantly higher sensitivity for both LBC and CB, which can be attributed to differences in study design. Woo's study diagnosed MPE using cytology as the gold standard, whereas our study used pleural biopsy pathology as the gold standard. Additionally, variations in the LBC processing equipment may also contribute to these differences in sensitivity²⁰. Another study has also shown no significant difference between modified LBC and CytoRich Red preservatives in diagnosing malignant effusion, similar to the results of our study²¹.

Combining all three cytological methods shows the highest sensitivity in diagnosing MPE, with a sensitivity of 76.6%. However, this higher sensitivity is not statistically significant when compared to the use of only CS combined with CB or CS combined with LBC. The simultaneous use of all cytological methods may aid increase the detection of cancer cells in pleural fluid, which can explain the highest sensitivity observed when combining all three methods. However, due to the small sample size in our study, the difference is not yet clear.

Our study has several limitations. Firstly, we did not determine the origin of the cancer cells present in the pleura, which restricts our ability to assess the impact of different types of cancer on the sensitivity of cytological methods²². Secondly, we did not analyze the correlation between the volume of pleural fluid used in CB and LBC. Previous research has indicated that the diagnostic accuracy of LBC for bronchoalveolar lavage fluid improves with an increased volume of fluid tested⁷. Thirdly, since this study was conducted

at a single center with a small sample size and without calculating the minimum sample size or performing a power analysis, the results of this study should be applied with caution, and selection bias may occur. Finally, our study did not include cases with diagnoses of PE other than MPE, thus limiting our ability to calculate the specificity of each method.

CONCLUSIONS

All three cytological methods for pleural fluid—CS, CB, and LBC—demonstrate comparable efficacy in diagnosing MPE. However, combining any two of these methods significantly enhances sensitivity for diagnosing MPE compared to using a single method, except for the CB and LBC combination, which does not show improved sensitivity over LBC alone. This underscores the benefit of using multiple cytological methods to enhance diagnostic accuracy. Clinicians should consider combining cytological techniques to optimize the diagnostic sensitivity for MPE while also taking into account factors such as processing time, test costs, and the expertise available at each medical facility.

ABBREVIATIONS

ADA: Adenosine Deaminase, **CB:** Cell Block, **CS:** Conventional Smear, **IQR:** Interquartile Range, **LBC:** Liquid-Based Cytology, **LDH:** Lactate Dehydrogenase, **MPE:** Malignant Pleural Effusion, **PE:** Pleural Effusion, **SD:** Standard Deviation

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AUTHOR'S CONTRIBUTIONS

NVH, NTLP, KND, NDM: Conceptualization, Methodology, Writing original draft preparation; NDM, NTN, TDV, DLQ: Visualization, Methodology, Software; KND, NDM, NTN: Data curation; NVH, NTLP, KND, NDM, NTN, TDV: Validation, Investigation; TDV, DLQ: Supervision. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present study obtained approval from the Ethical Review Committee, University of Medicine and Pharmacy at Ho Chi Minh City (No. 19458/HĐĐĐ-ĐHYD). All patients participating in the study signed informed consent.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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