Original Article

Comparison Between Imprint Cytology and Histopathology Results in Pleural Effusion Cases Undergoing Pleuroscopy

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Abstract

Background: Pleuroscopy is a valuable minimally invasive procedure for evaluating undiagnosed pleural effusion. Rapid diagnosis of malignancy is often needed to reduce procedure time and patient discomfort, particularly when pleurodesis is planned. Imprint cytology is a quick and simple method, though underutilized in pleuroscopy practice in Indonesia. This study aimed to compare the diagnostic yield of imprint cytology and histopathology in pleural effusion cases undergoing pleuroscopy.

Methods: This retrospective observational study was conducted from August to November 2024 and included patients with pleural effusion who underwent diagnostic pleuroscopy. Pleural biopsies were taken using forceps. Imprint cytology was performed by directly smearing the biopsy tissue onto slides, followed by staining. Histopathology was done using standard tissue processing.

Results: Of the 25 patients who underwent pleuroscopy, 14 met the inclusion criteria. Pleuroscopic findings varied, with the most common being mass lesions (35.7%), followed by multiple nodules (21.4%) and sago-nodules (14.3%). Histopathology revealed malignancy in 10 patients (71.4%) and non-malignant in 4 (28.6%). Imprint cytology detected malignancy in 12 patients (85.7%) and non-malignant findings in 2 patients (14.3%).

Conclusion: Imprint cytology offers a rapid and reliable diagnostic method during pleuroscopy, particularly in resource-limited settings. It may facilitate early detection of malignancy and support timely clinical decision-making.

Keywords: cytopathology, lung malignancy, pleural effusion, pleuroscopy, rapid diagnosis

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Submitted: November 11th, 2025
Accepted: April 28th, 2026
Published: May 15th, 2026

J Respirol Indones. 2026
Vol. 46 No. 2: 91-8
https://doi.org/10.36497/jri.v46i2.1111

INTRODUCTION

Pleural effusion builds up from an imbalance between hydrostatic pressure and oncotic pressure in the capillaries, pleural space, and the lymphatic system. It can be classified as transudative or exudative based on its chemical composition, per Light's criteria.[1] A pleural effusion is an exudate if at least one of the following criteria is met: 1) protein concentration in effusion divided by serum protein concentration >0.5; 2) lactate dehydrogenase (LDH) concentration in effusion >200 IU; LDH concentration in effusion divided by serum LDH concentration >0.6.[2]

In high-resource countries, the common causes of pleural effusions in adults are cardiac failure, malignancy, and pneumonia. In contrast, in low-resource countries, tuberculosis (TB) and parapneumonic effusions are more prevalent. Patients with a non-malignant pleural effusion have a one-year mortality in the range of 25% to 57%.[1,2]

Medical thoracoscopy, or pleuroscopy, is an important diagnostic method for evaluating pleural abnormalities, particularly in cases of undiagnosed pleural effusion, whether malignant (MPE) or benign (BPE).[3] Histopathological examination of pleural biopsy specimens obtained through pleuroscopy is the diagnostic gold standard, but it often requires several days for processing and evaluation, potentially delaying clinical decision-making.[4]

Rapid on-site evaluation (ROSE) using imprint cytology is a technique commonly used for transbronchial needle aspiration samples, enabling

immediate cytological assessment. ROSE offers the advantage of enabling real-time differentiation between malignant and benign pleural effusions at the bedside, potentially improving biopsy positivity rates and allowing prompt determination of whether a patient is suitable for pleurodesis.[4]

A retrospective cohort study conducted by Wang et al in China demonstrated that ROSE of touch-imprint samples obtained during pleuroscopy had high accuracy in distinguishing benign from malignant lesions.[5] However, pleuroscopy services are generally limited to tertiary care centers in major cities in Indonesia, typically led by pulmonologists with interventional training.

The use of imprint cytology during pleuroscopy procedures for pleural effusion has not yet been widely explored in Indonesia. Therefore, this study was conducted to evaluate the diagnostic profile and agreement between imprint cytology and histopathology in patients with pleural effusion undergoing pleuroscopy.

METHODS

This retrospective observational study aimed to evaluate the diagnostic profile and agreement between imprint cytology and histopathology in patients with pleural effusion undergoing pleuroscopy. The study was conducted at Persahabatan General Hospital, Jakarta, Indonesia, from August to November 2024. Eligible participants were patients with pleural effusion who underwent diagnostic pleuroscopy at Persahabatan General Hospital and met both inclusion and exclusion criteria. Due to the retrospective nature of the study and the use of anonymized data, both ethical clearance and informed consent requirements were waived.

Inclusion criteria were: 1) adult patients aged >18 years with pleural effusion confirmed by clinical symptoms and chest X-ray or thoracic ultrasound; 2) patients who underwent pleuroscopy at Persahabatan General Hospital; and 3) availability of both imprint cytology and histopathology results from pleural biopsy. The exclusion criterion was inconclusive histopathology results.

A total sampling method was used, and all eligible patients who underwent pleuroscopy in September and October 2024 were included. Nurses from the bronchoscopy unit prepared imprint cytology smears, while anatomical pathologists at Persahabatan General Hospital interpreted both histopathology and cytology slides. Clinical data were recorded, including name, age, sex, and presenting symptoms.

All patients underwent chest radiography and/or thoracic ultrasound within the 3 months preceding pleuroscopy to confirm the presence of pleural effusion and to guide the procedure. Laboratory evaluations and anesthetic assessments were completed before the pleuroscopy procedure. Bronchoscopy was performed as part of routine clinical evaluation to assess airway involvement and to exclude concomitant endobronchial pathology.

All pleuroscopes underwent debris removal and high-level disinfection (HLD) with 70% alcohol wipes before each use, where a rigid pleuroscope (HOPKINS Telescope 0° and 30°, Karl Storz) was used in all procedures. All procedures were performed in the operating theater under local anesthesia with mild sedation. After identifying the pleural fluid using thoracic ultrasound, the entry site was marked. Patients were positioned in the lateral decubitus position with the healthy lung dependent. The area was sterilized and draped under aseptic conditions. Local anesthesia was administered using 15–30 mL of 1% lidocaine, infiltrated through the skin, subcutaneous tissue, intercostal muscles, and parietal pleura.

A small skin incision (8–10 mm) was made, followed by blunt dissection into the pleural cavity using curved forceps. A blunt-tipped trocar was then inserted into the pleural space, and pleural fluid was gently aspirated using a catheter connected to a negative-pressure suction device. A rigid pleuroscope was introduced through the trocar, and systematic inspection of the pleural cavity was performed. Multiple pleural biopsies were taken from abnormal areas of the parietal pleura using biopsy forceps and underwent both histopathological and imprint cytology examinations of the pleura. All specimens were

labeled and sent to the Department of Anatomical Pathology at Persahabatan General Hospital.

One biopsy specimen by gently pressing tissue obtained from parietal pleural forceps biopsies onto glass slides, fixed in 95% alcohol, and sent for imprint cytology. The slides were stained using the Papanicolaou stain and examined microscopically. The remaining tissue samples were placed in 10% buffered formalin and sent for histopathological examination. No biopsy samples were taken from the visceral pleura or diaphragm. All pathological readings were performed by the on-duty pathologist on the day of the pleuroscopy procedure. Rapid on-site evaluation (ROSE) was not performed in this study.

After biopsy, an intercostal drainage (ICD) tube was inserted toward the apex of the pleural cavity under direct visualization. The tube was secured with sutures, and the incision site was dressed with sterile gauze, concluding the procedure. Post-procedure, patients were monitored in the recovery room. A post-pleuroscopy chest X-ray was performed in all patients to assess lung condition and confirm ICD placement.

For analytical purposes, the results were categorized into two groups: malignant and non-malignant findings. Malignancy refers to histopathological or cytological findings consistent with malignant cells, particularly adenocarcinoma. Non-malignant findings include granulomatous inflammation suggestive of infection (e.g., tuberculosis) and nonspecific inflammatory changes without evidence of malignancy. All data were presented in a table along with their actual counts for each variable and their percentages.

RESULTS

Of 25 patients, all had adequate histopathology results; however, 11 lacked corresponding imprint cytology results and were therefore excluded from the study. After applying the exclusion criteria, 14 patients were included as research subjects. All subjects were presented with dyspnea (100%) as the most common symptom. Additional respiratory and systemic symptoms are outlined in Table 1.

Table 1. Baseline clinical and pleural fluid characteristics of study subjects (n=14)

Characteristics	n	%
Baseline Clinical		
Age, mean [median (min-max)	50,29 [48 (24 – 86)]	
Gender		
Male	5	35.7
Female	9	64.3
Smoking status		
Active smoker	4	28.6
Passive smoker	4	28.6
Ex-smoker	1	7.1
Non-smoker	5	35.7
Symptoms		
Non-productive cough	8	57.1
Productive cough	5	35.7
Hemoptysis (coughing blood)	3	21.4
Chest pain	8	57.1
Dyspnea (shortness of breath)	14	100
Fever	3	21.4
Weight loss	9	64.3
Night sweats	5	35.7
History of Anti-Tuberculosis Treatment (OAT)		
Previous TB treatment	0	0.0
No history of TB treatment	8	57.1
Currently undergoing TB treatment	6	42.9
Pleural Fluid		
Initial Diagnosis		
Malignancy	12	85.7
Infection	2	14.3
Side of Pleural Effusion		
Right	8	57.1
Left	5	35.7
Bilateral	1	7.1
Pleural Fluid Color		
Serosanguinous	5	35.7
Serohemorrhagic	9	64.3
Type of Pleural Fluid		
Transudate	0	0.0
Exudate	14	100
Pleural Fluid Adenosine Deaminase (ADA)		
<40 U/L	7	50.0
≥40 U/L	3	21.4
No ADA result available	4	28.6
Pleural Fluid Cytology Before Pleuroscopy		
Malignant cells detected	0	0.0
No malignant cells detected	10	71.4
No cytology examination performed	4	28.6

Most patients (85.7%) were initially suspected of having malignancy, while the remaining were presumed to have infection. Right-sided pleural effusion was more common (57.1%). All cases met

Light's criteria for exudative effusion. The characteristics of pleural effusion, fluid adenosine deaminase (ADA) levels, and pre-pleuroscopy cytology are also summarized in Table 1.

Bronchoscopy was performed as part of a routine clinical evaluation to assess airway involvement. The most frequent finding was compression stenosis (57.1%), likely reflecting extrinsic airway compression due to underlying pleural or parenchymal disease. Full bronchoscopic findings are listed in Table 2.

Table 2. Characteristics of bronchoscopic findings and pleuroscopic findings

Characteristic	n	%
Bronchoscopic Findings		
Normal	3	21.4
Edematous mucosa	2	14.3
Compression stenosis	8	57.1
Infiltrative nodule	1	7.1
Pleuroscopic Operator Visualization		
No abnormality detected	0	0.0
Irregular pleural surface	1	7.1
Infiltrative mucosa	1	7.1
Minimal nodules	1	7.1
Sago-like nodules	2	14.3
Multiple nodules	3	21.4
Single mass	1	7.1
Multilobulated mass	5	35.7
Pleural Cavity Septations		
Septated	5	35.7
Non-septated	9	64.3

On the other hand, pleuroscopic visualization showed a variety of surface abnormalities, with multilobulated masses being the most common (35.7%), followed by multiple nodules and sago-like appearances. Pleural cavity septations were observed in 35.7% of patients. Details of pleuroscopic findings are also presented in Table 2.

Representative pleuroscopic images from malignant and tuberculosis cases are shown in Figure 1. In Figure 1.1, the histopathology results show metastatic adenocarcinoma, while the imprint cytology results show adenocarcinoma. In Figure 1.2, the histopathology results show granulation tissue with nonspecific inflammation, while the imprint cytology results show chronic granulomatous inflammation, possible TB.

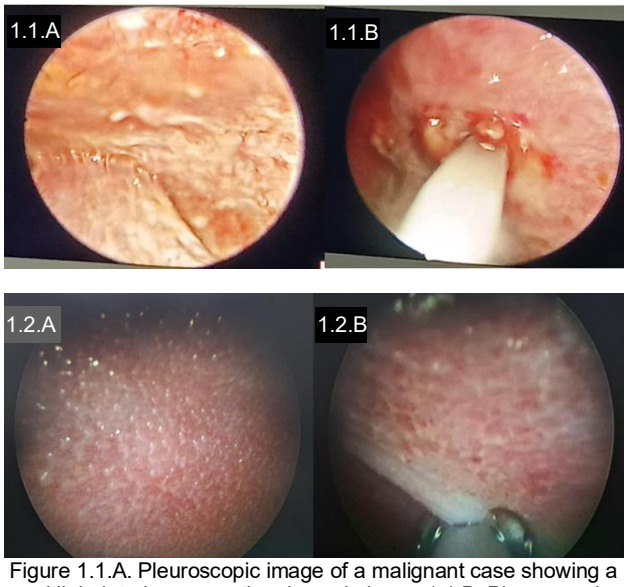

Figure 1.1.A. Pleuroscopic image of a malignant case showing a multilobulated mass on the visceral pleura; 1.1.B. Pleuroscopic image of a malignant case showing forceps biopsy of a parietal pleural nodule; 1.2.A. Pleuroscopic image of a tuberculosis case showing multiple sago-like nodules on the parietal pleura; 1.2.A. Pleuroscopic image of a tuberculosis case showing forceps biopsy.

Discordant cases between histopathology and imprint cytology are illustrated in Figure 2. In Figure 2.1, the histopathology results show chronic granulomatous pleuritis, while the imprint cytology results show metastatic adenocarcinoma. In Figure 2.2, the histopathology results show no malignancy, while the imprint cytology results show non-small cell lung carcinoma (NSCLC), suggestive of adenocarcinoma.

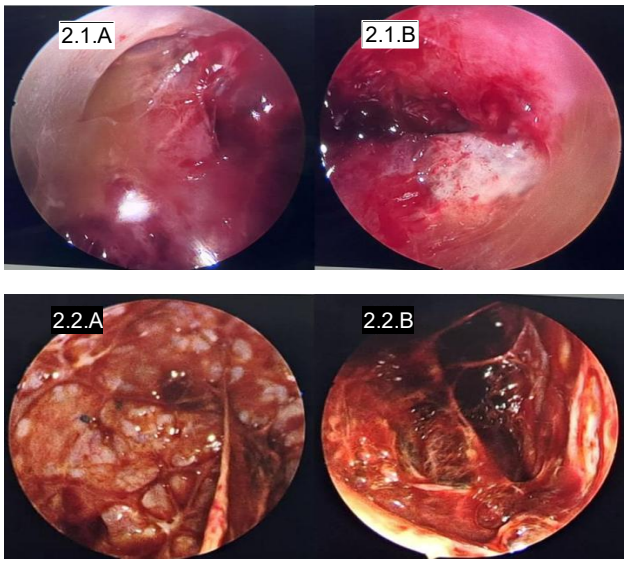

Figure 2.1.A. Pleuroscopic image from a discordant case (subject 6) showing septated parietal pleura; 2.1.B. Pleuroscopic images from a discordant case (subject 6) showing irregular nodules with serohemorrhagic fluid; 2.2.A. Pleuroscopic image from a discordant case (subject 7) showing irregular pleural surface; 2.2.B. Pleuroscopic image from a discordant case (subject 7) showing fibrinous septations with serohemorrhagic fluid.

Table 3. Descriptions of pleuroscopic operator findings and microscopic anatomical pathology from both histopathology and imprint cytology

Subject	Pleuroscopic Findings	Histopathology Conclusion	Imprint Cytology Conclusion
1	White sago-like nodules on the parietal pleura and white nodules on the visceral pleura	Chronic pleuritis	No malignant cells detected
2	Nodules on both parietal and visceral pleura	Metastatic adenocarcinoma	Metastatic adenocarcinoma
3	Infiltrative mucosa on the parietal pleura	Adenocarcinoma	Adenocarcinoma
4	Multiple red, easily bleeding nodules	Metastatic adenocarcinoma	Adenocarcinoma
5	Multiple nodules on both parietal and visceral pleura	Papillary adenocarcinoma	Adenocarcinoma
6	Irregular nodules on the parietal pleura	Chronic granulomatous pleuritis	Metastatic adenocarcinoma
7	Irregular pleural surface	No malignant cells detected	Metastatic adenocarcinoma
8	Multilobulated mucosa over the entire parietal pleura	Papillary and solid metastatic adenocarcinoma	Adenocarcinoma
9	Multilobulated visceral pleura with nodules on the diaphragm	Metastatic adenocarcinoma	Adenocarcinoma
10	Mass on the parietal pleura	Adenocarcinoma	Adenocarcinoma
11	Multilobulated mucosa on the parietal pleura	Metastatic adenocarcinoma	Adenocarcinoma
12	Multilobulated appearance of the parietal pleura	Metastatic adenocarcinoma	Adenocarcinoma
13	Both the visceral and parietal pleura appeared multilobulated, with nodules on the diaphragm.	Metastatic adenocarcinoma	Metastatic adenocarcinoma
14	Multiple evenly distributed sago-like nodules	Granulation tissue with nonspecific inflammation	Chronic granulomatous inflammation, suspicious for tuberculosis

All malignancies diagnosed by anatomical pathology in this study were NSCLC, specifically adenocarcinoma. No cases of pleural mesothelioma were identified in this study. This finding may reflect the relatively low incidence of mesothelioma in this setting. However, mesothelioma remains an important differential diagnosis in patients with pleural effusion, particularly in cases with nonspecific pleuritis. Therefore, it should still be considered in clinical evaluation, and an appropriate histopathological and immunohistochemical assessment is necessary when suspected. Detailed descriptions of pleuroscopic operator findings and microscopic anatomical pathology from both histopathology and imprint cytology are presented in Table 3.

Histopathological analysis results of forceps biopsies revealed malignancy in 10 subjects (71.4%) and non-malignant in 4 subjects (28.6%). Meanwhile, imprint cytology detected malignancy in 12 subjects (85.7%) and infection in 2 subjects (14.3%).

On the other hand, Figure 3.1 shows the imprint cytology of a malignant case, while Figure 3.2 illustrates the imprint cytology of a tuberculosis case. Imprint cytology images from the two discordant cases are not available, as the cells on the slides were processed for EGFR mutation analysis.

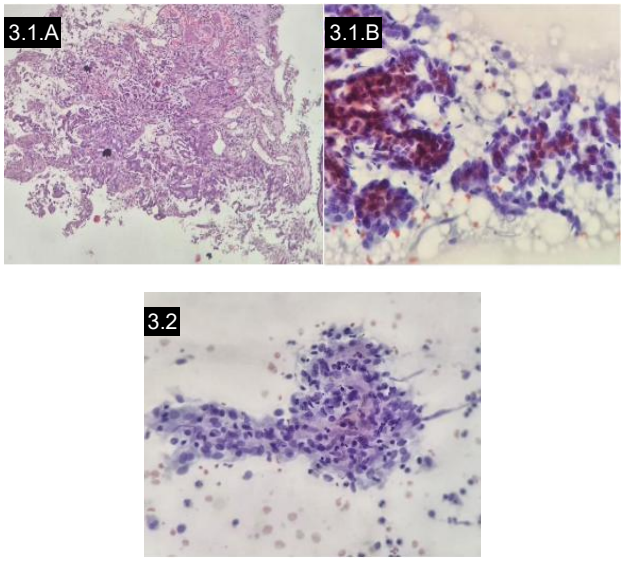

Figure 3.1. Malignant features from a microscopic image of imprint cytology in a malignant case (subject 9) with an imprint cytology diagnosis of NSCLC, adenocarcinoma type, are shown in (A) hematoxylin-eosin staining with 100× magnification, and (B) Papanicolaou-stained with 400× magnification;
3.2 Microscopic image of imprint cytology in a tuberculosis case (subject 14) with a cytological diagnosis of tuberculosis that was Papanicolaou-stained at 400× magnification, revealing the presence of epithelioid cells.

This study also identified two cases with discordant histopathology and imprint cytology results. In subject 6, as much as 0.5 cc of fragmented tissue revealed fibrotic connective tissue with chronic inflammatory cells and epithelioid cells, interpreted as chronic granulomatous pleuritis, possibly due to tuberculosis. However, imprint cytology showed leukocytes, macrophages, and clusters of pleomorphic, hyperchromatic cells with prominent nucleoli—suggestive of metastatic carcinoma, likely

adenocarcinoma. Pleuroscopic findings in this case included a septated parietal pleura with irregular nodules in the posterior region and serohemorrhagic pleural fluid.

In subject 7, as much as 2 cc of fragmented tissue contained blood clots, fibrin, and mesothelial cells, with no malignant cells identified on histopathology. In contrast, imprint cytology revealed clusters of round-to-oval nuclei with coarse chromatin and prominent nucleoli—suggestive of NSCLC, likely adenocarcinoma. Pleuroscopic findings included an irregular pleural surface with extensive fibrinous septations, which were released during the procedure, along with serohemorrhagic pleural fluid.

These two cases were handled by different operators and assistants. Then, both patients with discordant diagnoses were presented to a multidisciplinary team (MDT) meeting that included pulmonologists, radiologists, thoracic surgeons, anatomical pathologists, and other relevant specialists. The final diagnosis for both patients was malignancy (adenocarcinoma), and treatment was administered based on their EGFR mutation status, which in both cases was negative.

DISCUSSIONS

This study confirms that pleuroscopy is a valuable and safe diagnostic procedure for undiagnosed pleural effusion, even in elderly patients. Radiological imaging plays an important role in evaluating pleural effusion and guiding pleuroscopy. However, a detailed correlation between radiological findings and pleuroscopic features was not analyzed in this study.

Bronchoscopy was included as part of the comprehensive respiratory evaluation to assess possible endobronchial involvement and to exclude alternative diagnoses. Although bronchoscopic findings were not directly correlated with pleural pathology in this study, they may reflect underlying airway compression or parenchymal disease associated with pleural processes.

The oldest subject in this study was 86 years old. All patients had exudative effusions per Light's criteria, in accordance with standard indications for pleuroscopy. Malignancy was the most common etiology (85.7%), which contrasts with studies from high TB burden areas such as Qatar, where TB predominated among pleuroscopy patients.[6] In this study, only two cases were diagnosed as infections, both confirmed through histopathology and imprint cytology.

Medical thoracoscopy is known as a high diagnostic yield. Diacon et al reported 100% histological sensitivity for TB by thoracoscopy, compared with 66% for closed needle biopsy.[7] These results support the reliability of pleuroscopy for direct tissue sampling, especially in challenging cases.

In this study, two patients were identified whose imprint cytology and histopathology results were discordant. In both cases, imprint cytology revealed adenocarcinoma, while histology showed only nonspecific inflammation or reactive changes. These findings suggest that imprint cytology may help identify malignancy when conventional biopsy yields are limited due to sampling error or fibrosis, as supported by Chandra et al, who noted better nuclear detail and fewer crush artifacts in cytological samples.[8]

The sensitivity of pleuroscopy for malignancy has been reported at 93–95%, superior to pleural fluid cytology (60%) and closed pleural biopsy (45%).[9] Cytology has also demonstrated high accuracy in distinguishing small-cell from NSCLC,[10] where studies such as those by Fischer et al highlight the diagnostic advantage of fine-needle aspiration and cytological analysis over core biopsy.[11]

In this study, all imprint cytology slides were stained using the Papanicolaou method, which allows for better visualization of cellular features such as keratinization and nuclear detail compared to hematoxylin-eosin (HE) staining. However, the interpretation of cytology also poses challenges. Reactive endobronchial cells, cohesive spindle or columnar cells, and scattered granulomas may mimic malignancy, leading to false positives. Additionally, tuberculosis remains a diagnostic confounder,

especially in endemic regions like Indonesia, where its cytomorphologic features can resemble malignancy.[12]

Imprint cytology and ROSE may support rapid intra-procedural diagnostic assessment and facilitate clinical decision-making. However, their role in guiding pleurodesis was not evaluated in this study.[13]

Bhaker et al compared intraoperative imprint cytology and frozen section (FS) in skeletal tumors and found that both methods had high diagnostic accuracy. While FS had slightly higher sensitivity, imprint cytology offered faster processing and better cost-efficiency.[13] Dutta et al reported a sensitivity of 89.5% and specificity of 82.5% for imprint cytology in soft tissue tumors,[14] while Delgado-Bocanegra et al found that imprint cytology is reliable for detecting macrometastases in breast cancer sentinel lymph nodes.[15]

Liao et al demonstrated that positive imprint cytology during ultrasound-guided core biopsies strongly correlated with true malignancy, thereby reducing the need for additional sampling. Integrating imprint cytology with histopathology improved the negative predictive value to 90%, compared to 79% for histology alone.[16]

In this study, imprint cytology enhanced diagnostic accuracy and allowed more timely recognition of malignancy. However, its use was limited by additional costs associated with slide preparation, staining, and interpretation. The absence of an on-site cytopathologist also hindered immediate assessment of specimen adequacy. These limitations need to be evaluated for the reduction of procedure time and patient comfort.

LIMITATION

The main limitations of this study are its small sample size and retrospective design, which may limit generalizability. The absence of detailed radiological correlation is another limitation. Additionally, this study did not include follow-up or survival data, limiting the assessment of long-term clinical outcomes. Therefore, further prospective studies with larger cohorts and longitudinal follow-up are warranted to validate these findings.

CONCLUSION

Imprint cytology performed during pleuroscopy demonstrated a higher diagnostic yield than histopathology and enabled more rapid detection of malignancy in patients with exudative pleural effusions. This technique may serve as a practical substitute for frozen section examination, particularly in settings where such facilities are unavailable or when pleuroscopic procedures require time efficiency. The combination of pleuroscopy and imprint cytology improves diagnostic yield and should be considered as a routine component of pleural effusion evaluation.

ACKNOWLEDGMENTS

The authors thank our colleagues for their support and guidance during the preparation of this manuscript. The authors carefully reviewed and edited the content to ensure its accuracy and clarity.

CONFLICT OF INTEREST

The authors declare no conflicts of interest that could influence the content of this manuscript.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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