

Diagnostic Accuracy of Cell Block versus Conventional Cytological Smear in Malignant Pleural Effusion: A Comparative Study

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Abstract

Background: Malignant pleural effusion (MPE) is a common oncological complication that requires accurate diagnosis to guide appropriate management. Cytological smears are widely used; however, they have variable sensitivity. The cell block technique has emerged as a potentially superior diagnostic tool due to its better preservation of cellular architecture and compatibility with ancillary testing.

Objective: This study aims to compare the diagnostic utility of the cell block technique with the conventional cytological smear in detecting MPE, using histopathology as the gold standard.

Methods: This cross-sectional study was conducted at the Institute of Tuberculosis and Chest Medicine, Mayo Hospital, Lahore. One hundred and thirty-eight patients, aged 18 to 75 years, with probable malignant pleural effusion were enrolled. Pleural fluid specimens were subjected to both conventional cytology and cell block analysis. All patients subsequently received a pleural biopsy for histological validation. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated using SPSS version 27.0.

Results: Cytology demonstrated a sensitivity of 65.82%, specificity of 86.44%, PPV of 86.67%, NPV of 65.38%, and overall diagnostic accuracy of 74.64%. The cell block technique demonstrated a significantly higher sensitivity (89.87%), specificity (94.92%), PPV (95.95%), NPV (87.50%), and overall diagnostic accuracy (92.03%) ($p=0.002$).

Conclusion: The cell block technique is more effective than conventional cytological smears in diagnosing malignant pleural effusion, offering higher sensitivity, specificity, and diagnostic accuracy.

Key words: Malignant pleural effusion (MPE), cytology, cell block, pleural biopsy, sensitivity, specificity, diagnostic accuracy.

Introduction

Malignant pleural effusion (MPE) is characterized by the accumulation of pleural fluid containing malignant cells, which can be identified through cytological analysis or verified via pleural biopsy. This condition constitutes a substantial clinical issue and is frequently associated with advanced-stage cancer.¹

MPE affects approximately 20% of cancer patients, including those with primary pleural malignancies like mesothelioma and secondary metastases from lung, breast, and ovarian neoplasms.² Other malignancies that contribute include lymphomas, ovarian carcinoma, and gastrointestinal cancers. Patients frequently present with dyspnea, cough, and chest pain; however,

some cases are identified incidentally during imaging conducted for unrelated indications. Given its association with advanced cancer, prompt and

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Received: 26 February 2026, Accepted: 02 May 2026

Published: 17 July 2026

Authors Contribution

KG & MY conceptualized the project. WM, AWG & FM did the data collection. KG, AWG & MR did the literature search. KG, MY & WM performed the statistical analysis, drafting, revision & writing of manuscript. FM also did the editing and proof reading.

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accurate diagnosis of MPE is crucial for effective patient management.³

Pleural fluid cytology remains the first-line investigation because it is minimally invasive and easy to perform. However, the diagnostic sensitivity of a standard cytological smear varies widely typically from 40% to 90% depending on factors such as tumor type, pleural tumor burden, sample adequacy, primary lesion site, and laboratory expertise.⁴ Conventional smear techniques are insufficient for extensive ancillary testing, such as immunohistochemistry, which is often required to identify the primary tumor site or differentiate reactive mesothelial cells from malignant cells. Consequently, a false-negative cytology result may necessitate more invasive diagnostic procedures, such as an image-guided pleural biopsy or thoracoscopy, thereby increasing patient discomfort, healthcare costs, and procedural risks.^{5,6}

The cell block technique has become a valuable adjunct to traditional cytology in the evaluation of MPE. In the cell block technique, the residual sediment obtained after pleural fluid centrifugation is processed into paraffin-embedded blocks, similar to conventional histopathological specimens.⁷ This method preserves architectural patterns, increases cellular yield, and minimizes cell dispersion. Sections obtained from the paraffin block can be stained with hematoxylin and eosin (H&E) and analyzed using immunohistochemistry (IHC), thereby improving diagnostic accuracy.⁸

Numerous studies have demonstrated that the cell block method is superior to the conventional cytological smear for detecting malignant pleural effusions. Patil et al. reported a significantly higher diagnostic yield with the cell block technique (96%) compared to conventional cytology (42%).⁹ Similarly, Mariedina and Betty reported a sensitivity of 97% for cell block analysis compared to 59% for conventional cytological smears, while maintaining an identical specificity.¹⁰ Rani et al. demonstrated a high degree of concordance between cell block results and histopathological biopsies, reinforcing its utility as a reliable diagnostic tool.¹¹ Similarly, Matreja et al. reported that the sensitivity and specificity of conventional cytological smears were 69.2% and 95.0%, respectively, whereas those of the cell block technique were 92.3% and 99.2%, respectively.¹² In addition, Güldaval et al. reported that the cell block technique yielded a sensitivity and specificity of 59.2% and 100.0%, respectively.¹³

Although promising evidence supports the superiority of the cell block technique, local data comparing its diagnostic performance with conventional cytological smears within our population remain limited. Variations in laboratory

protocols, patient demographics, and regional disease trends necessitate the validation of diagnostic methods within specific healthcare settings. This study aimed to evaluate and compare the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the cell block technique and conventional cytology in the diagnosis of malignant pleural effusion, utilizing histopathology as the gold standard. The cell block technique was hypothesized to exhibit significantly higher sensitivity, specificity, and overall diagnostic accuracy compared to conventional cytological smears.

Methods

This cross-sectional analytical study was conducted at the Institute of Tuberculosis and Chest Medicine, Mayo Hospital, Lahore from October 2025 to February 2026. Patients aged 18-75 years of either gender presenting with unexplained exudative pleural effusion characterized by an adenosine deaminase (ADA) level < 33 IU/L, hemorrhagic fluid, or clinical and radiological features suggestive of MPE were included. Patients with transudative effusions, suspected tuberculous effusions (ADA 33-83 IU/L), bilateral effusions secondary to systemic comorbidities, or coagulopathy (INR ≥ 1.5) were excluded.

A total of 138 patients were enrolled using a non-probability convenience sampling method after obtaining written informed consent. The sample size was calculated using a 95% confidence level and 10% absolute precision, assuming a 40.0% disease prevalence, an anticipated sensitivity of 59.2%, and an anticipated specificity of 87.0%.^{10,13} The margin of error was 13.0% for sensitivity and 8.0% for specificity.

Written informed consent was obtained from all participants prior to enrollment, and they were free to withdraw from the study at any moment before completion. To

The demographic and clinical characteristics of the participants including age, gender, symptom duration, smoking status, and radiological findings were recorded. Following evaluation through baseline investigations, including a complete blood count and coagulation profile, all participants underwent diagnostic thoracentesis under aseptic conditions using local anesthesia with 2% xylocaine. Approximately 100–150 mL of pleural fluid was collected and divided for conventional cytological smear and cell block preparation.

For the conventional cytological smear, 10 mL of pleural fluid was centrifuged at 2500 rpm for

15 minutes. The supernatant was discarded, and the remaining sediment was used to prepare the smears. Following air-drying, the slides were stained using Leishman-Giemsa stain and evaluated by a consultant pathologist under light microscopy. The remaining pleural fluid was also spun at 2500 rpm for 15 minutes for the cell block technique. Following centrifugation and removal of the supernatant, the residual pellet was combined with 250 μ L of pooled plasma and 250 μ L of thromboplastin (Uniplastin), then incubated for two minutes to form a cohesive cell button. The cell button was placed in a cassette, fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, and sectioned at a thickness of 4 μ m using a microtome. The sections were stained and evaluated under light microscopy by a consultant histopathologist.

Subsequently, all patients underwent pleural biopsy via pleuroscopy conducted by a consultant pulmonologist under procedural sedation with midazolam and local anesthesia utilizing 4% xylocaine. During the procedure, vital signs and oxygen saturation were constantly monitored. Eight to ten pleural tissue samples were collected and preserved in formalin for histopathological examination, considered the gold standard for diagnosis. The histopathologists performing the cytology and cell block analyses were blinded to the findings of the other modalities and also the biopsy. Data were recorded and analyzed using SPSS version 27.0. Quantitative variables like age and the duration of symptoms were presented as mean $\pm$ standard deviation. Qualitative variables, including gender, smoking status, cytology results, and cell block findings, and histopathology results, were shown as frequencies and percentages. A 2 $\times$ 2 contingency table was created for each diagnostic method to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The Chi-square test was employed to evaluate the diagnostic performance of conventional cytology in comparison to cell block techniques. A *p*-value of under 0.05 was regarded as statistically significant.

Results

A total of 138 patients were included in the study, with a mean age of 54.58 $\pm$ 13.14 years and a predominance of males, 56.5% (*n* = 78). Smokers comprised 54.3% (*n* = 75) of the participants, and the mean duration of symptoms was 7.63 $\pm$ 2.89 weeks. Radiologically, massive pleural effusion was observed in 28.3% (*n* = 39), and moderate pleural effusion was present in 31.2% (*n* = 43). Pleural

effusion with pleural nodules and pulmonary mass were present in 22.5% (*n* = 31) and 18.1% (*n* = 25) of the participants, respectively (Table 1).

Cytological examination found that 60 cases (43.5%) were malignant and 78 cases (56.5%) were benign. The analysis of the cell block showed that 74 cases (53.6%) were malignant, and 64 cases (46.4%) were benign. Histopathological examination indicated the highest malignancy rate, with 79 cases (57.2%) identified as malignant and 59 cases (42.8%) as benign (Table-2).

Table 1: Demographic and clinical data of the participants.

Variables		Value
Age (years), Mean $\pm$ S.D.		*54.58 $\pm$ 13.14
Duration of symptoms (weeks), Mean $\pm$ S.D.		*7.63 $\pm$ 2.89
Gender	Male	**78 (56.5)
	Female	**60 (43.5)
Smoking status	Smoker,	**75 (54.3)
	Non-smoker	**63 (45.7)
Radiological findings	Moderate pleural effusion	**43 (31.2)
	Massive pleural effusion	**39 (28.3)
	Pleural effusion with pulmonary mass	**25 (18.1)
	Pleural effusion with pleural nodules	**31 (22.5)

*Mean $\pm$ SD, ***n* (%)

Table 2: Diagnostic results of cytology, cell block, and histopathology.

Diagnostic Modality	Benign <i>n</i> (%)	Malignant <i>n</i> (%)
Cytology	78 (56.5)	60 (43.5)
Cell Block	64 (46.4)	74 (53.6)
Histopathology	59 (42.8)	79 (57.2)

Cell block showed superior diagnostic efficacy to cytology. Cytology had a sensitivity of 65.82% and a specificity of 86.44%. It also had a PPV of 86.67%, an NPV of 65.38%, and an overall diagnostic accuracy of 75.00%. Cell block, on the other hand, had a much higher sensitivity (89.87%) and specificity (94.92%). It also had a PPV of 95.95%, an NPV of 87.50%, and a diagnostic accuracy of 92.03%. A statistically significant correlation was observed for cytology ($\chi^2 = 13.80$, *p* = 0.0002) (Table-3).

Among the 79 malignant cases confirmed on histopathology, adenocarcinoma was the most common, 15.9% (*n* = 22). This was followed by breast carcinoma 15.2% (*n* = 21), squamous cell carcinoma 12.3% (*n* = 17), and small cell carcinoma 10.1% (*n* = 14). Lymphoma was the least common malignancy 3.6% (*n* = 5) (Table-4).

Table 3: Diagnostic performance of cytology and cell block.

Diagnostic Test	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy	Correlation	p-value
Cytology	65.82%	86.44%	86.67%	65.38%	74.64%	13.80	0.0002
Cell Block	89.87%	94.92%	95.95%	87.50%	92.03%		

Table 4: Histological types of malignancy. (n = 79)

Histopathology	N (%)
Adenocarcinoma	22 (15.9)
Breast carcinoma	21 (15.2)
Squamous cell carcinoma	17 (12.3)
Small cell carcinoma	14 (10.1)
Lymphoma	5 (3.6)

Discussion

MPE signifies an advanced stage of cancer and presents considerable diagnostic and treatment difficulties. Timely and precise diagnosis is essential for staging, prognosis, and directing oncological treatment. The current study revealed that the cell block technique exhibited significantly enhanced diagnostic efficacy relative to traditional cytological smear, achieving greater sensitivity (89.87% vs. 65.82%), specificity (94.92% vs. 86.44%), and overall diagnostic accuracy (92.03% vs. 74.64%) when compared to histopathology as the gold standard. These findings substantiate the increasing evidence that cell block preparation improves the diagnostic yield of pleural fluid evaluation.

Kumari et al. reported that the cell block method outperformed traditional smears, diagnosing 26 malignant cases compared to just 19 identified by the smears. Using histopathology as the gold standard, the cell block method demonstrated a sensitivity of (96.4%), a specificity of (98.3%), and a diagnostic accuracy of (98.1%). These results markedly surpass cytological smear, which had a sensitivity of (79.3%), a specificity of (97.7%), and an accuracy of (95.2%).¹⁴ Shivakumarswamy et al. also reported that in a comparative analysis of pleural fluid samples, the cell block demonstrated a statistically significantly higher diagnostic yield by an additional diagnosis of 15% of malignant cases than the conventional smear cytology. The cell block yielded a significantly higher cellular count than the alternative technique ((z-test, ($p = 0.038$)), ($p = 0.0021$)).¹⁵ Bhanvadia et al. assessed the utility of the cell block over the cytological smear for the cytodiagnosis of effusions. The cell block approach found 12 more malignant cases, which was an 8% increase in diagnostic yield compared to conventional cytology. There was a statistically significant difference between conventional cytology and cell block ($p < 0.001$).¹⁶

A significant obstacle in conventional cytology is the differentiation of reactive mesothelial cells from metastatic cancers. This challenge arises from pronounced mesothelial atypia caused by various serous membrane insults, coupled with the complex cytomorphology of certain malignancies, particularly well-differentiated adenocarcinomas.¹⁷ Artifacts from poor fixation, preparation, or staining make it even harder to make a diagnosis. While conventional smear cytology is less technically demanding than preparing paraffin sections, it lacks the tissue architecture essential for an accurate diagnosis. Furthermore, features such as reactive mesothelial proliferation, a high inflammatory cell count, and a lack of representative malignant cells complicate definitive identification on conventional smears.^{18,19}

The cell block has been considered a superior approach to conventional cytology, especially in pleural and ascitic fluids, where malignant cells typically signify metastatic illness. Cell block is exceptionally proficient at identifying glandular patterns and groups of cancer cells.²⁰ Like a cytological smear, the cell block technique is minimally invasive. By providing a higher diagnostic yield, it eliminates the need for more invasive tissue biopsies, thereby enhancing patient compliance, enabling early cancer detection, and reducing procedure-related morbidity and mortality. In contrast to conventional smear, cell block presents numerous benefits: maintenance of tissue architecture, capability for routine, special, and immunocytochemical labeling, less cellular dispersal, enhanced microscopic assessment despite bloody backdrops, and simplified long-term storage. "The cell block technique offers enhanced cellularity alongside superior architectural and nuclear preservation. It demonstrates cellular aggregates, papillary structures, and three-dimensional clusters with intact membranes and distinct chromatin. This markedly improves diagnostic sensitivity for malignancies, even in cases overlooked by conventional smears.²¹ It preserves essential architectural characteristics by converting pleural fluid sediment into paraffin-embedded sections. It also improves diagnostic yield by concentrating cells into a defined area, reducing sampling error, and increasing detection in low-cellularity specimens. Moreover, the application of IHC on cell block sections allows accurate

identification of tumor origin and better differentiation of malignancy. This is especially beneficial for differentiating reactive mesothelial cells from well-differentiated adenocarcinomas, where true acinar formation and mucin positivity indicate malignancy. By consolidating cells within a singular focus plane and maintaining histological patterns, the cell block bridges the gap between cytology and histology.²²

Adenocarcinoma emerged as the most common histological subtype in MPE patients, followed by breast carcinoma, squamous cell carcinoma, small cell carcinoma, and lymphoma. Saqib et al. evaluated the histology of thoracoscopic pleural biopsies. Adenocarcinoma was the predominant malignancy identified in pleural biopsy (57.8%), followed by poorly differentiated metastatic carcinoma (22.3%). The lung constituted the predominant main site (43.4%), with additional origins including the breast, ovary, and kidney. Other malignancies include lymphoma (4.8%), squamous cell carcinoma (4.8%), and small cell carcinoma (4.2%).²³ Agarwal et al. reported that primary cancers causing MPE were lung cancer (43.8%), lymphoma (12.9%), and breast cancer (11.6%). The histological diagnosis among the lung cancer cases was adenocarcinoma (45.9%), squamous cell carcinoma (14.1%), and small cell carcinoma (5.1%).²⁴ The histological spectrum identified in this study aligns with recognized oncological patterns in MPE and underscores the necessity for diagnostic methods that can accurately classify tumors. The diverse therapeutic strategies for adenocarcinoma, breast carcinoma, small cell carcinoma, and lymphoid malignancies render the ability of the cell block technique to maintain architectural integrity and facilitate immunohistochemical assessment clinically significant for targeted treatment.

Although cell block preparation requires more processing time and higher initial laboratory costs than conventional cytology, its improved diagnostic sensitivity reduces false-negative results. This minimizes the need for repeat procedures, ultimately lowering overall healthcare costs and patient morbidity. Furthermore, this technique is highly feasible in low-resource settings, as most of the equipment required for cell block preparation is already available in standard histopathology laboratories, requiring only minimal additional training for technicians. Therefore, the cell block technique represents a practical and scalable approach to improving diagnostic accuracy, particularly in resource-limited healthcare systems.

This study has some limitations that should be acknowledged. The study was performed at a

single tertiary care facility with a limited sample size, potentially constraining the applicability of the results to larger populations. The application of non-probability convenience sampling may have resulted in selection bias. Subgroup analysis by primary tumor type was not conducted, which may have yielded further insight into diagnostic performance across various malignancies. The study failed to assess cost-effectiveness, turnaround time, or long-term clinical results, which are critical variables in evaluating the practical implications of using the cell block approach in standard clinical practice.

Conclusion

Cell block demonstrated higher diagnostic accuracy than conventional cytological smear and may be considered as an adjunctive routine technique in evaluation of suspected malignant pleural effusion. Although conventional cytology is a simple and readily available initial investigation, its relatively diminished sensitivity may lead to false-negative results and postponed therapeutic measures. The cell block method, on the other hand, greatly improves diagnostic accuracy by preserving tissue structure, increasing cellularity, and enabling additional investigations such as immunohistochemistry, thereby facilitating more accurate tumor identification and guiding appropriate oncologic treatment.

Funding: None.

Availability of Data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: The Institutional Review Board of King Edward Medical University (KEMU), Lahore approved the study via letter no. no179/RC/KEMU, dated 25/02/2025.

Conflict of Interest: None declared.

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