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Original Research Article

COMPARATIVE DIAGNOSTIC EFFICACY OF CYTOLOGY SMEAR, CELL BLOCK, AND CLOSED PLEURAL BIOPSY IN SUSPECTED MALIGNANT PLEURAL EFFUSION

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ABSTRACT

Background: Malignant pleural effusion (MPE) requires definitive cytological or histological confirmation for prognostication and treatment planning. Conventional cytology offers limited sensitivity; cell block technique and closed pleural biopsy may provide superior diagnostic yield. This study aimed to compare the diagnostic yield of conventional cytology smear, cell block preparation, and closed pleural biopsy in patients with suspected MPE at an Indian tertiary care centre.

Materials and Methods: This prospective observational study enrolled 60 consecutive patients with suspected MPE at Government General and Chest Hospital, Hyderabad, India, over 18 months (January 2023–June 2025). Each enrolled patient was subjected to diagnostic thoracentesis incorporating conventional cytology smear and cell block preparation, followed by closed pleural biopsy using Cope's needle. Diagnostic yield, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated. Comparisons used the chi-square and McNemar tests.

Results: Mean age was 58.17 ± 11.55 years; 51.7% were female. Closed pleural biopsy demonstrated the highest diagnostic yield (53.3%, 32/60), followed by cell block (48.3%, 29/60) and conventional cytology (18.3%, 11/60) ($p < 0.001$). Among nine patients (15%) with inconclusive cell block results, pleural biopsy confirmed malignancy in all cases. Conventional cytology demonstrated sensitivity of 12.5%, specificity 75%, PPV 36.4%, NPV 42.9%, and diagnostic accuracy 41.7%.

Conclusion: Closed pleural biopsy may offer superior diagnostic yield compared with cytology-based methods in suspected MPE, particularly when cell block results are inconclusive. A stepwise diagnostic approach, simultaneous cytology and cell block at initial thoracentesis, with selective biopsy for non-diagnostic cases may be pragmatic in resource-constrained settings. External validation in adequately powered multicentre cohorts is warranted.

Keywords: Malignant pleural effusion, Cytology, Cell block, Pleural biopsy, Diagnostic yield.

INTRODUCTION

Among cancer patients, pleural involvement manifesting as malignant effusion complicates roughly one in seven case and signals advanced disease, with reported median survival ranging from 3 to 12 months depending on the primary tumor type.[1,2] Establishing a definitive tissue or cytological diagnosis is essential for prognostication, selection of targeted therapy, and avoidance of unnecessary empirical treatment.[3] The British Thoracic Society (BTS) guidelines recommend initial pleural fluid cytology as the first diagnostic step, with further invasive procedures reserved for non-diagnostic cases.[4,5]

Conventional pleural fluid cytology, while simple and minimally invasive, demonstrates widely variable sensitivity (13–79%) across published series, with particularly poor performance in mesothelioma and certain adenocarcinomas.[6,7] Cell block technique involving centrifugation, formalin fixation, and paraffin embedding of pleural fluid sediment has emerged as a valuable adjunct. The technique preserves tissue architecture and enables immunohistochemistry (IHC) for tumor subtyping, with some series reporting positivity rates exceeding 90%[8,9,10]. However, diagnostic performance depends on fluid volume, cellularity, and preparation technique.[11]

When cytological methods fail, closed pleural biopsy using Cope or Abrams needles offers tissue diagnosis without requiring thoracoscopy. Although medical thoracoscopy and image guided biopsy are preferred in resource-rich centers, closed biopsy remains widely practiced in low- and middle-income countries due to accessibility, lower cost, and bedside feasibility [4,12]. In the Indian context, where tuberculosis and malignancy frequently coexist as causes of exudative effusions, selecting the optimal diagnostic approach requires balancing sensitivity, safety, and resource availability.[13]

Despite the availability of these three modalities, few prospective studies have directly compared their diagnostic performance within the same patient cohort in Indian tertiary care settings. The present investigation was designed to assess and compare the diagnostic yield of conventional cytology smear, cell block preparation, and closed pleural biopsy in patients presenting with suspected MPE.

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study was conducted at the Department of Pulmonary Medicine at

Government General Chest Hospital, in Hyderabad, Telangana, India, over an 18-month period (January 2023–June 2025). Ethical clearance for this work was obtained from the Institutional Review Board and following the ethical principles set out in the Declaration of Helsinki. Prior to any study procedure, each participant provided written informed consent.

Study population: Sixty consecutive patients aged ≥18 years presenting with unilateral or bilateral pleural effusion clinically suspected to be malignant were enrolled. Inclusion criteria comprised: (a) exudative pleural effusion by Light's criteria;[3] (b) clinical or radiological suspicion of malignancy (history of known primary, weight loss, lymphadenopathy, or suspicious imaging features); and (c) adequate effusion volume for diagnostic sampling. Exclusion criteria included: bleeding diathesis, empyema, trapped lung on imaging, patient refusal, or contraindications to pleural biopsy.

Diagnostic procedures

All enrolled patients underwent the following sequential procedures:

Thoracentesis and conventional cytology: Diagnostic thoracentesis was performed under aseptic conditions with ultrasound guidance for fluid localisation. A minimum of 50 mL of pleural fluid was aspirated. An aliquot was sent for conventional cytology smear preparation (Papanicolaou and Giemsa staining) and examined by an experienced cytopathologist.

Cell block preparation: A separate aliquot (minimum 20 mL) was processed using the formalin-fixed, paraffin-embedded cell block technique. Fluid was centrifuged, the sediment fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with haematoxylin and eosin. IHC was performed where indicated to determine tumour origin and subtype.

Closed pleural biopsy: Following thoracentesis, closed pleural biopsy was performed using Cope's needle under local anaesthesia. A minimum of four biopsy specimens were obtained from different sites along the parietal pleura. Specimens were fixed in formalin and processed for histopathological examination.

Outcome measures

The primary outcome was diagnostic yield, defined as the proportion of cases in which each modality yielded a definitive diagnosis of malignancy. Secondary outcomes included sensitivity, specificity, PPV, NPV, and overall diagnostic accuracy calculated against the composite reference standard (final clinical diagnosis based on all available pathological, radiological, and follow-up data).

Statistical analysis

Frequencies and percentages were used to summarise categorical data; continuous variables as mean ± standard deviation. Diagnostic yield comparisons between the three modalities were performed using the chi-square test and McNemar test for paired proportions. Sensitivity, specificity, PPV, NPV, and accuracy with 95% confidence intervals were calculated for each modality. Statistical significance was set at alpha = 0.05 throughout. Analysis was performed using SPSS version 26.0.

RESULTS

Baseline characteristics

Sixty patients were enrolled during the study period. The mean age was 58.17 ± 11.55 years (range 32–82 years). Female patients comprised 51.7% (31/60) of the cohort. Right-sided effusions predominated (70%, 42/60). Pleural fluid was haemorrhagic in 83.3% (50/60) of cases. Adenosine deaminase (ADA) levels were <40 IU/L in 78.3% (47/60). Fluid differential cell count revealed lymphocytic predominance in 86.7% (52/60) of patients. [Table 1]

Diagnostic yield comparison

Closed pleural biopsy demonstrated the highest overall diagnostic yield at 53.3% (32/60), followed by cellblock at 48.3% (29/60), and conventional cytology at 18.3% (11/60). The difference between modalities was statistically significant ($p < 0.001$). The incremental yield of cell block over conventional cytology was 30.0 percentage points, while biopsy provided an additional 5.0 percentage points over cell block. [Table 2]

Resolution of inconclusive cell block results

Among the nine patients (15%) in whom cell block yielded inconclusive results, closed pleural biopsy confirmed malignancy in all nine cases (100% resolution rate), suggesting that pleural biopsy may serve as a valuable complementary procedure when cell block fails to provide a definitive diagnosis.

Diagnostic accuracy of conventional cytology

Against the composite reference standard, conventional cytology smear demonstrated sensitivity of 12.5%, specificity of 75%, PPV of 36.4%, NPV of 42.9%, and overall diagnostic accuracy of 41.7%. [Table 3]

Procedure-related complications

Closed pleural biopsy was associated with a higher frequency of minor procedural complications compared with simple thoracentesis. No major life-threatening complications or procedure-related mortality occurred in either group. Detailed complication analysis is reported separately in a companion publication.

Table 1: Baseline Demographic and Pleural Fluid Characteristics (N = 60)

Parameter	Value
Age (years), mean ± SD	58.17 ± 11.55
Female, n (%)	31 (51.7)
Right-sided effusion, n (%)	42 (70.0)
Hemorrhagic fluid, n (%)	50 (83.3)
ADA < 40 IU/L, n (%)	47 (78.3)
Lymphocytic predominance, n (%)	52 (86.7)

ADA = adenosine deaminase; SD = standard deviation.

Table 2: Diagnostic Yield of Three Modalities (N = 60)

Modality	Positive for malignancy, n (%)	Inconclusive, n (%)	Negative/Non-diagnostic, n (%)
Conventional cytology	11 (18.3)	—	49 (81.7)
Cell block	29 (48.3)	9 (15.0)	22 (36.7)
Closed pleural biopsy	32 (53.3)	—	28 (46.7)

$p < 0.001$ (chi-square test for overall comparison).

Table 3: Diagnostic Performance of Conventional Cytology Smear

Parameter	Value (%)
Sensitivity	12.5
Specificity	75.0
Positive predictive value	36.4
Negative predictive value	42.9
Diagnostic accuracy	41.7

DISCUSSION

The present investigation compared the diagnostic efficacy of three modalities, conventional cytology, cell block, and closed pleural biopsy, in 60 patients with suspected MPE at an Indian tertiary care centre. Closed pleural biopsy appeared to offer the highest diagnostic yield (53.3%), with cell block (48.3%) providing a substantial improvement over conventional cytology (18.3%) [14,15].

Conventional cytology performance

The low sensitivity of conventional cytology (12.5%) observed in this study is consistent with reports from several centres. Kurniawan et al. reported cytology sensitivity of 13.63% in lung tumour patients,[16] while a large systematic review noted sensitivity ranging from 40% to 87% depending on tumour type and fluid volume.[6] The particularly low sensitivity in our cohort may reflect the high proportion of haemorrhagic effusions (83.3%), which can obscure malignant cells, as well as potential sampling limitations inherent to a single cytological preparation. Arnold et al. reported initial cytology sensitivity of 75% in a retrospective cohort, though this included repeat sampling.[17] The variability across studies underscores that cytology performance depends substantially on case-mix, fluid processing techniques, and cytopathologist experience.[7]

Cell block superiority over conventional cytology

Cell block preparation yielded a substantially higher diagnostic rate (48.3%) compared with conventional

cytology (18.3%), representing an incremental gain of 30 percentage points. This finding aligns with multiple published series demonstrating cell block superiority. Betty et al. reported cell block sensitivity of 97% versus 59% for conventional smear in lung cancer patients.[18] Patil et al., in a large Indian series of 500 cases, found cell block positivity of 96% compared with 42% for cytology.[9] Chandanwale et al. similarly demonstrated that cell block detected malignancy in 23.6% versus 10.4% by conventional smear.[19] The architectural preservation afforded by the cell block technique facilitates pattern recognition and enables IHC, which appears particularly valuable for determining tumour origin and subtype.[8,11]

However, 15% (9/60) of cell block preparations yielded inconclusive results, likely attributable to low cellularity or extensive necrosis. This limitation has been acknowledged in prior literature and highlights that cell block, while superior to conventional smear, may not entirely obviate the need for tissue biopsy [8,20].

Role of closed pleural biopsy

Closed pleural biopsy demonstrated the highest diagnostic yield (53.3%) and notably resolved all nine inconclusive cell block cases. This observation supports the continued utility of closed biopsy in resource-constrained environments where thoracoscopy may be unavailable.[4,12] Maskell et al., in a randomised controlled trial, demonstrated that even CT-guided cutting-needle biopsy offered only marginal improvement over Abrams needle biopsy for malignant disease (sensitivity 87% vs 47%), suggesting that closed biopsy retains a role when image guidance is limited.[21] Rani et al. similarly reported that pleural biopsy identified more malignant cases than cell block in a 50-patient comparative study.[22]

The BTS 2023 guidelines acknowledge that while thoracoscopy offers the highest diagnostic yield for MPE, closed biopsy remains acceptable in settings where thoracoscopy is not readily available, particularly for diffuse pleural disease.[5] The modest difference between biopsy (53.3%) and cell block (48.3%) in our cohort suggests that cell block may serve as a reasonable initial tissue-equivalent modality before proceeding to biopsy.

Stepwise diagnostic approach

The present data suggest that a stepwise approach beginning with conventional cytology and cell block simultaneously during initial thoracentesis, followed by closed pleural biopsy for non-diagnostic or inconclusive cases may optimise diagnostic yield while minimising unnecessary invasive procedures. The finding that all inconclusive cell block cases were resolved by biopsy supports the complementary nature of these modalities. Batool et al. demonstrated that combining cytology, cell block, and IHC achieved sensitivity exceeding 92%,[11] reinforcing the value of multimodal assessment. Combining approaches has been advocated by several authors as a strategy to reduce indeterminate results and expedite treatment initiation. [10,23]

Contextual considerations

The predominance of haemorrhagic effusions (83.3%), lymphocytic predominance (86.7%), and low ADA levels (<40 IU/L in 78.3%) is consistent with a population in which malignancy was the principal diagnostic consideration. In the Indian context, where tuberculosis remains prevalent, the combination of low ADA, lymphocytic predominance, and haemorrhagic fluid may serve as a clinical pointer toward malignancy and guide the decision to pursue cell block and biopsy early.[13,24]

Limitations

Several limitations warrant consideration. First, the sample size of 60 patients limits statistical power and precision of diagnostic accuracy estimates; findings should therefore be interpreted as hypothesis generating. Second, the single-centre design may limit generalisability to settings with different case-mix or resource availability. Third, the composite reference standard, while pragmatic, may introduce incorporation bias. Fourth, operator experience with Cope's needle biopsy and variability in cell block preparation technique may influence reproducibility. Fifth, the incremental value of repeat cytology or IHC was not assessed systematically across all cases. External validation in adequately powered multicentre cohorts will be necessary to confirm these preliminary observations.

CONCLUSION

Using a prospective observational design in 60 patients with suspected MPE, closed pleural biopsy appeared to offer the highest diagnostic yield (53.3%), followed by cell block (48.3%) and conventional cytology (18.3%). Cell block preparation provided a substantial improvement over conventional cytology and may serve as a valuable initial diagnostic tool. Closed pleural biopsy appears particularly useful when cell block results are inconclusive. A stepwise diagnostic approach incorporating simultaneous cytology and cell block at initial thoracentesis, with selective closed biopsy for non-diagnostic cases may be a pragmatic strategy in resource-constrained settings. These observations call for external validation in adequately powered multicentre cohorts.

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