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Pleural Fluid and Bronchoalveolar Lavage Cytology in Patients With Lung Lesions and Pleural Effusion: A Prospective Paired-Cytology Study

Devanshi Gosai [1], Khusbu Chhaya [1], Vidhi Jain [1], Aman Jain [2]

1. Pathology, Sumandeep Vidyapeeth (Deemed to be University), Vadodara, IND 2. Pathology, Smt. B. K. Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth (Deemed to be University), Vadodara, IND

Corresponding author: Devanshi Gosai, gosaidevanshi.1011@gmail.com

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Abstract

Background

Lung lesions with pleural effusion often have overlapping clinical and radiological features that make malignancy difficult to distinguish from tuberculosis and other benign disease. Pleural fluid cytology is a minimally invasive first-line test, but its sensitivity is limited, and bronchoalveolar lavage (BAL) cytology may detect abnormalities missed on pleural fluid alone. In this exploratory, single-centre, prospective paired-cytology study, the primary objective was to compare the agreement of pleural fluid, BAL, and combined (OR-rule) cytology with a composite clinical, radiological, and microbiological reference that included the index cytology; secondary objectives were inter-test concordance and clinico-pathological associations.

Methods

This prospective observational study was conducted in the Department of Pathology of a tertiary care hospital over 18 months after ethics committee approval. Seventy patients with suspected lung lesions and pleural effusion who underwent both pleural fluid aspiration and bronchoscopy with BAL were enrolled by consecutive sampling after informed consent. Smears were stained with Papanicolaou, May-Grünwald-Giemsa, and haematoxylin and eosin; cell blocks with immunocytochemistry were prepared where indicated. A specimen was cytology-positive only when malignant cells were identified; suspicious/atypical smears were indeterminate and counted as test-negative. Combined testing used an OR rule. The composite reference diagnosis incorporated the index cytology, so results are reported as agreement estimates with Wilson 95% CIs, Cohen's kappa, Fisher's exact test, and exact McNemar tests.

Results

Mean age was 53.96 ± 15.54 years, and 43/70 (61.4%) were male. Malignant disease was diagnosed in 24 (34.3%) and non-malignant disease in 46 (65.7%); tuberculosis (18/70, 25.7%) and adenocarcinoma (12/70, 17.1%) were the commonest diagnoses. Malignancy was associated with older age, male sex, and smoking (all $p < 0.05$). Pleural fluid and BAL cytology each showed 70.8% sensitivity (17/24; 95% CI 50.8-85.1%), 100% specificity (46/46; 95% CI 92.3-100%), and 90.0% agreement (63/70; 95% CI 80.8-95.1%). The combined strategy showed 87.5% sensitivity (21/24; 95% CI 69.0-95.7%) and 95.7% agreement (67/70; 95% CI 88.1-98.5%), with overlapping confidence intervals and unchanged specificity. Exact McNemar tests were not significant (pleural vs. BAL, 4 vs. 4 discordant cases, $p = 1.00$; combined vs. either test, 0 vs. 4, $p = 0.125$). Binary concordance between the two tests was 62/70 (88.6%; kappa 0.69, 95% CI 0.49-0.89); multi-category concordance was 56/70 (80.0%; kappa 0.58). Among the 24 malignant cases, 13 (54.2%) were positive on both tests, four (16.7%) on pleural fluid only, four (16.7%) on BAL only, and three (12.5%) on neither.

Conclusions

Pleural fluid and BAL cytology showed comparable standalone point estimates, and their combination showed higher point estimates, but differences were not statistically significant, and the 100% specificity is largely an artifact of the composite reference design. Because the reference diagnosis was not independent of the index tests, blinding was not documented, the sample was small, and itemised diagnoses differed by three patients from the disease-group classification (21 vs. 24 malignant), these findings are exploratory and hypothesis-generating. They await multicentre validation against an independent reference standard.

Categories: Pathology
Keywords: bronchoalveolar lavage, cytopathology, diagnostic accuracy, lung malignancy, pleural effusion, pleural fluid cytology, tuberculosis

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Introduction

Pulmonary diseases remain a major contributor to global morbidity and mortality, and accurate, timely distinction between malignant and non-malignant lung lesions is central to appropriate management and prognosis [1,2]. Cytological evaluation of respiratory specimens is frequently used as an initial investigation in this process because it is minimally invasive, low-cost, and rapid relative to tissue biopsy [3]. Among the available cytological specimens, pleural fluid and bronchoalveolar lavage (BAL) fluid are the two most frequently obtained in patients presenting with pleural effusion and suspected pulmonary pathology.

Pleural effusion is a common clinical problem that may result from malignancy, tuberculosis, pneumonia, or congestive heart failure, among other causes [4]. Cytological examination of pleural fluid is considered the first-line investigation for suspected malignant pleural effusion because of its high specificity, even though its sensitivity is only moderate [5,6]. Identification of malignant cells in pleural fluid provides direct evidence of pleural involvement and informs staging and treatment planning, but false-negative results occur because of low tumour cell shedding, sampling error, or technical limitations, and additional testing is often required [4,7].

BAL, performed via fiberoptic bronchoscopy, allows sampling of the lower respiratory tract and has an established role in diagnosing lung malignancy, opportunistic infection, and diffuse interstitial lung disease, particularly in patients unsuitable for more invasive biopsy procedures [8,9]. Cytological evaluation of BAL fluid has been reported to have high combined diagnostic accuracy for neoplastic and non-neoplastic pulmonary lesions [3].

Because pleural fluid cytology primarily reflects pleural cavity pathology, while BAL cytology reflects parenchymal and airway pathology, the two techniques provide complementary rather than redundant information [10]. In principle, correlating the two should reduce false-negative diagnoses and improve overall diagnostic confidence, but few prospective studies from tertiary care settings in India have directly compared their individual and combined performance alongside relevant clinical, radiological, biochemical, and microbiological correlates in the same cohort of patients.

The present study was therefore designed as an exploratory, hypothesis-generating, single-centre prospective paired-cytology study in patients attending a tertiary care hospital with lung lesions and pleural effusion. The objectives were as follows: (i) Primary objective: to compare the agreement of pleural fluid cytology, BAL cytology, and their combination (OR rule) with a composite reference classification of malignant versus non-malignant disease. (ii) Secondary objectives: (a) to characterise the concordance between the two cytological investigations and the pattern of cases detected by one test but not the other; and (b) to explore associations between clinico-pathological variables and malignancy.

This reference classification is multi-modal (clinical, radiological, microbiological, and cytological findings, with histological confirmation in only 4 of 70 patients) and includes the index cytology results themselves, so the study is subject to incorporation bias; its estimates are therefore reported as agreement rather than diagnostic accuracy.

Materials And Methods

Study design and setting

This prospective observational study was conducted in the Department of Pathology at Smt. B.K. Shah Medical Institute and Research Centre (SBKS MI & RC), Dhiraj Hospital, Piparia, Vadodara, Gujarat, India, a tertiary care teaching hospital with dedicated cytopathology, histopathology, microbiology, radiology, and bronchoscopy services. The study was carried out over a period of 18 months. The study was designed a priori as exploratory (agreement with the composite reference, inter-test concordance, and the observed BAL-only detection proportion, without a confirmatory hypothesis). The primary and secondary objectives are listed at the end of the Introduction. A prospective observational design was chosen to allow real-time, unbiased recording of cytological findings and clinical outcomes without any therapeutic intervention. Reporting followed the Standards for Reporting Diagnostic Accuracy Studies (STARD) 2015 guidance where information was available; items that could not be fully verified against the study protocol (participant flow with exclusions, formal blinding procedures, and sample-size parameters specific to a paired-comparison objective) are identified explicitly below and in the Limitations.

Ethical considerations

The study was approved by the Institutional Ethics Committee of Sumandeep Vidyapeeth University prior to commencement (ethics approval no: SVIEC/UN/MEDI/BNPD24/JAN/25/277). Written informed consent was obtained from all participants (or their legal guardians) prior to enrolment.

Study population

Patients of all age groups presenting with clinically or radiologically suspected lung lesions and pleural effusion, from whom both a pleural fluid sample and a BAL fluid sample were obtained as part of their

diagnostic work-up, were eligible for inclusion. Patients with inadequate or autolysed cytological specimens, incomplete clinical or laboratory data, or who did not provide consent were excluded. A consecutive sampling technique was used; all eligible patients presenting during the study period were enrolled until the pre-calculated sample size was reached. Using a standard sample-size formula for estimating a proportion (Z = 1.96 for 95% confidence, based on the expected prevalence of lung lesions and an acceptable margin of error), a minimum sample of 70 patients was calculated and achieved; the specific prevalence and margin-of-error values entered into the formula were not recorded in the study protocol and cannot be stated, and the calculation was for prevalence estimation, not for the paired comparison. Enrolled patients were categorised into a malignant lung lesion group (cytological and, where available, histopathological evidence of malignancy) and a non-malignant lung lesion group (inflammatory, infectious, or other benign final diagnosis). The overall study workflow, from enrolment through sample collection, cytological processing, and composite final diagnosis, is summarised in Figure *1*. The composite reference classification was assigned at final diagnosis by integrating the clinical, radiological, microbiological, and cytological findings described above, with histology where available (4/70); the identity and number of the clinicians or pathologists who assigned it, and whether they knew the index cytology results, were not recorded in the protocol, and the index cytology contributed to the classification.

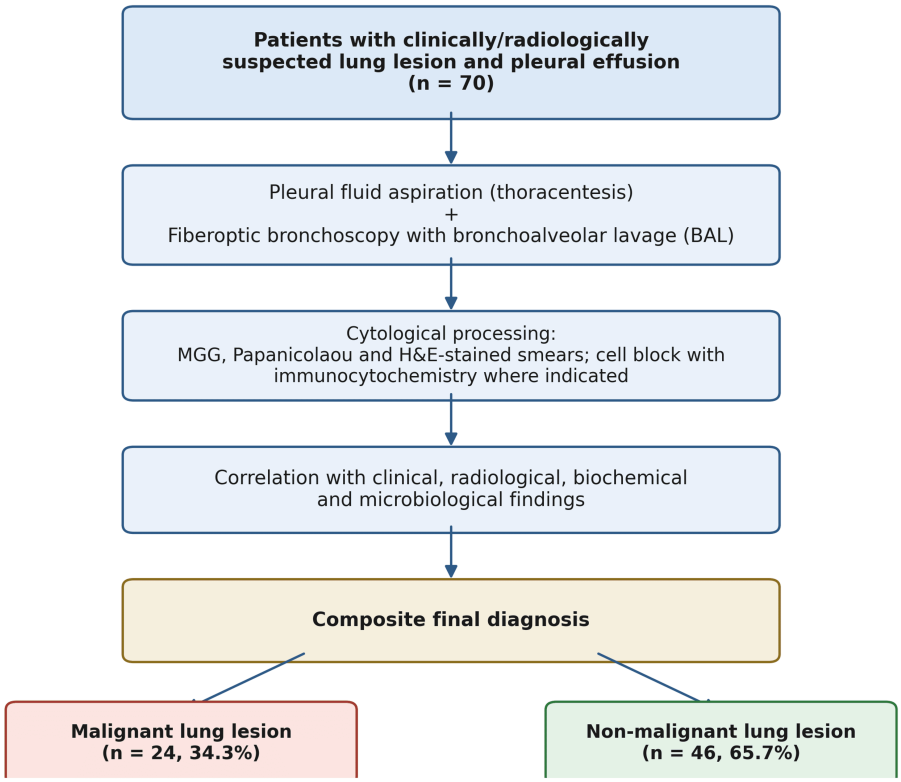


FIGURE 1: Overview of the study workflow from patient enrolment to composite final diagnosis

Flow diagram summarising patient enrolment, paired sample collection (pleural fluid aspiration and bronchoalveolar lavage), cytological processing, and correlation with clinical, radiological, biochemical, and microbiological data leading to the composite final diagnosis.

BAL, bronchoalveolar lavage; MGG, May-Grünwald-Giemsa; H&E, haematoxylin and eosin.

Importantly, the composite reference diagnosis used to calculate agreement incorporated cytological findings from the index tests themselves (pleural fluid and/or BAL cytology) rather than resting on an independent reference standard such as histopathology for every patient; independent histopathological or tissue confirmation was documented as an outcome for only 4 of 70 patients (5.7%) during the study period (recorded as "biopsy confirmed" in the outcome data), all other patients being classified by composite clinical, radiological, cytological, and/or microbiological criteria. This is a source of potential incorporation bias, discussed further in the Limitations, and means the agreement estimates reported here should be interpreted as a measure of agreement between cytological and composite clinical criteria rather than validation against a fully independent gold standard.

Sample collection

Pleural fluid was collected by thoracentesis under aseptic precautions into sterile, labelled containers; BAL fluid was collected by flexible fiberoptic bronchoscopy, instilling sterile normal saline into the selected broncho-pulmonary segment and aspirating the lavage fluid into sterile collection traps. An optimal volume of 20-30 mL was collected for routine cytology, increased to 30-50 mL where cell block preparation was anticipated. Samples were transported to the laboratory within two hours where possible; when immediate processing was not feasible, samples were refrigerated at 4°C and processed within 24-48 hours. Heparin or EDTA was added to haemorrhagic or high-protein specimens to prevent clotting. The volume of saline instilled during bronchoscopy, the lung segment(s) lavaged, and a minimum acceptable recovery volume or cell count were not recorded in the study protocol.

Sample processing and cytological interpretation

After gross examination (volume, colour, consistency, and clot formation), approximately 10-15 mL of each specimen was centrifuged at 2000 rpm for 10 minutes, and the sediment was used for smear preparation. At least two smears were prepared from each sample - one air-dried smear stained with May-Grünwald-Giemsa (MGG) and one wet-fixed smear (95% ethanol) stained with Papanicolaou (PAP) stain; haematoxylin and eosin (H&E) staining was used where required. Cell blocks were prepared from adequately cellular sediment or fibrin clot material using 10% neutral buffered formalin fixation and routine paraffin processing, enabling immunocytochemistry (ICC) where indicated (i.e., when malignant or suspicious cells required lineage or primary-site characterisation). All slides and cell block sections were examined independently by experienced cytopathologists and categorised as malignant, suspicious for malignancy, benign/inflammatory, or inadequate/non-diagnostic, with assessment of cellularity, nuclear atypia, background inflammatory cells, necrosis, haemorrhage, and mucin. Specimen adequacy was judged on cellularity and preservation (reported as adequate, moderate, or cell-rich); inadequate or non-diagnostic specimens were excluded at enrolment. The BAL segment was the broncho-pulmonary segment selected by the bronchoscopist; formal selection criteria were not recorded in the protocol. A formal procedure for resolving interpretive disagreement between cytopathologists was not documented. Smears were prepared directly from the centrifuged sediment. Antibody clones, dilutions, and positive/negative control slides used for ICC were not recorded in the protocol.

Index test definitions and reference standard

Each specimen was classified using a single prespecified binary rule: a test was scored positive only when malignant cells were identified. Smears reported as suspicious for malignancy or showing atypical cells were classified as indeterminate and, in the 2 × 2 analyses, were counted in the test-negative group; they were not pooled with positive results. For combined testing, a patient was classified as cytology-positive if either the pleural fluid or the BAL specimen was positive under this rule (OR rule). This differs from the descriptive breakdown of cytomorphological patterns, in which categories were not mutually exclusive. All slides and cell block sections were examined independently by experienced cytopathologists (their number was not recorded). Whether the reporting cytopathologist(s) were blinded to the paired specimen result and to clinical and radiological information was not recorded, so interpretation of the two specimens cannot be assumed to be independent of each other or of clinical context (see Limitations).

Clinical and laboratory correlates

Clinical parameters (age, sex, smoking status, presenting complaints, and symptom duration), radiological findings, pleural fluid biochemistry (protein, adenosine deaminase (ADA), and total leukocyte count (TLC)), microbiology (acid-fast bacilli (AFB) smear, culture, and CBNAAT/GeneXpert), and immunocytochemical or ancillary markers (TTF-1, p40, synaptophysin, CK7, and calretinin) were recorded and correlated with cytological findings and final diagnosis. Final diagnosis, disease category (malignant/non-malignant), hospital stay, and clinical outcome were also recorded. Tuberculosis is itemised as a separate diagnostic category, although it is classified within the non-malignant group, because it was the commonest final diagnosis in this cohort and, in a tuberculosis-endemic setting, the principal clinical and cytological mimic of malignancy in lung lesions with pleural effusion; separating it allows readers to see how many non-malignant cases it contributes to the specificity denominator. Tuberculosis diagnoses drew on AFB smear, culture, and/or CBNAAT/GeneXpert together with clinical and radiological correlation; itemised criteria for other non-malignant diagnoses were not specified in the protocol (see Limitations). Pleural fluid ADA cut-off values and any formal decision algorithm for final classification in patients without histology were not documented in the protocol.

Statistical analysis

The prespecified primary analysis was the agreement of pleural fluid cytology, BAL cytology, and combined (OR-rule) testing with the composite reference classification of malignancy. Associations involving clinico-pathological variables and concordance detail are secondary, exploratory analyses reported descriptively rather than as confirmatory findings. Data were entered in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and analysed using IBM SPSS Statistics for Windows, Version 31 (Released 2025; IBM Corp., Armonk, NY, USA). Descriptive statistics (mean, standard deviation, frequency, and percentage)

summarised demographic and clinical data. The chi-square test was used to assess association between categorical variables; small-subgroup comparisons (e.g., rare tumour subtypes, selected 2 × 2 comparisons) were analysed using Fisher's exact test given the modest expected cell counts involved. The unpaired t-test compared means between the malignant and non-malignant groups; the skewness of biochemical markers such as ADA and TLC is noted as a limitation of the parametric comparison. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall agreement of pleural fluid cytology and BAL cytology, individually and combined, were calculated against the composite reference diagnosis - termed agreement rather than diagnostic accuracy, for the reasons given in Limitations; 'agreement' is used uniformly for these reference-based estimates, and 'concordance' only for the comparison between the two index tests - with 95% confidence intervals derived using the Wilson score method given the small sample and boundary (100%) proportions involved. Agreement between pleural fluid and BAL cytology was quantified using Cohen's kappa (κ) on two bases: (i) a strict binary basis (malignant cells identified versus not; observed agreement 62/70) and (ii) a multi-category basis using the original cytological categorisation of each specimen, in which suspicious/atypical, benign/inflammatory, and negative results are separate categories (observed agreement 56/70; the individual categories were not itemised in the available dataset); given the paired design, the exact McNemar test (two-sided binomial test on discordant pairs) was applied to the paired dichotomous outcomes, computed from the aggregate overlap counts. A small number of secondary pleural fluid-BAL parameter associations were explored but are reported narratively rather than as correlation coefficients because the specific coefficient and ordinal-variable coding require prespecification in a future analysis. Multiple comparisons were not corrected for; secondary associations should accordingly be regarded as hypothesis-generating. A two-tailed p-value <0.05 was considered nominally statistically significant throughout.

Results

Seventy patients meeting the inclusion criteria were enrolled over the study period. The mean age of the study population was 53.96 ± 15.54 years (range 24-80 years), and the largest proportion of patients (17/70, 24.3%) were aged 46-55 years (Table *1*). Males constituted 61.4% (n=43/70) of the cohort, and smoking history was almost equally distributed between current smokers (22/70, 31.4%), ex-smokers (24/70, 34.3%), and never-smokers (24/70, 34.3%) (Table *1*).

Parameter	Category	n (%) / Value
Age (years)	Mean ± SD (range)	53.96 ± 15.54 (24-80)
Age category	18-25 years	3 (4.3%)
	26-35 years	12 (17.1%)
	36-45 years	9 (12.9%)
	46-55 years	17 (24.3%)
	56-65 years	14 (20.0%)
	>65 years	15 (21.4%)
Sex	Male	43 (61.4%)
	Female	27 (38.6%)
Smoking status	Current smoker	22 (31.4%)
	Ex-smoker	24 (34.3%)
	Never smoker	24 (34.3%)

TABLE 1: Age and demographic profile of the study population (n=70)

The most common presenting complaints were wheeze (24/70, 34.3%), haemoptysis and sputum production (20/70, 28.6% each), and cough (18/70, 25.7%) (Table *2*), and the mean duration of symptoms before presentation was 99.34 ± 52.84 days (range 10-176 days), with wide variability across patients. Radiologically, a peripheral lung mass with pleural effusion was the commonest pattern (10/70, 14.3%), followed by pleural nodularity, upper lobe cavity, pleural infiltrates, and bronchiectatic change with effusion (7/70, 10.0% each) (Table *2*), consistent with a case-mix comprising both malignant and infective/inflammatory pathology. Pleural effusion was left-sided in 26/70 (37.1%), right-sided in 22/70 (31.4%), and bilateral in 22/70 (31.4%) of patients.

Parameter	Category	n (%) / Value
Duration of symptoms (days)	Mean ± SD (range)	99.34 ± 52.84 (10-176)
Chief complaint	Wheeze	24 (34.3%)
	Haemoptysis	20 (28.6%)
	Sputum production	20 (28.6%)
	Cough	18 (25.7%)
	Chest pain	17 (24.3%)
	Night sweats	17 (24.3%)
	Dyspnoea	16 (22.9%)
	Fatigue	14 (20.0%)
	Fever	11 (15.7%)
	Weight loss	11 (15.7%)
Predominant radiological pattern	Peripheral lung mass with effusion	10 (14.3%)
	Pleural nodularity with effusion	7 (10.0%)
	Upper lobe cavity with effusion	7 (10.0%)
	Pleural effusion with infiltrates	7 (10.0%)
	Bronchiectasis changes with effusion	7 (10.0%)
	Hilar mass with collapse and effusion	6 (8.6%)
	Fibronodular infiltrates with effusion	6 (8.6%)
	Hyperinflation with infective infiltrates	6 (8.6%)
	Cavitary lesion with effusion	6 (8.6%)
	Consolidation with effusion	5 (7.1%)
	Mild free pleural effusion	4 (5.7%)
	Diffuse interstitial shadows, minimal effusion	3 (4.3%)
Pleural effusion side	Left	26 (37.1%)
	Right	22 (31.4%)
	Bilateral	22 (31.4%)

TABLE 2: Clinical presentation and radiological findings

Pleural fluid was predominantly exudative, with a mean protein concentration of 4.45 ± 0.72 g/dL. Mean pleural fluid ADA was 36.89 ± 25.77 U/L, and mean TLC was 2282.89 ± 1195.42/cumm (Table *3*), both showing wide variation consistent with the heterogeneous disease spectrum. Turbid and serous fluid were the commonest gross appearances (16/70, 22.9% each), followed by haemorrhagic and straw-coloured fluid (14/70, 20.0% each).

Parameter	Category	n (%) / Value
Fluid appearance	Turbid	16 (22.9%)
	Serous	16 (22.9%)
	Haemorrhagic	14 (20.0%)
	Straw-coloured	14 (20.0%)
	Serosanguinous	10 (14.3%)
Protein (g/dL)	Mean ± SD (range)	4.45 ± 0.72 (3.0-5.9)
ADA (U/L)	Mean ± SD (range)	36.89 ± 25.77 (10-95)
Total leukocyte count (/cumm)	Mean ± SD (range)	2282.89 ± 1195.42 (356-4174)

TABLE 3: Pleural fluid gross appearance and biochemical parameters

ADA, adenosine deaminase

On pleural fluid cytology, malignant cells were identified in 17/70 (24.3%) of patients and cells suspicious for malignancy in a further 7/70 (10.0%); the remainder showed negative, lymphocyte-predominant, granulomatous, mixed inflammatory, reactive mesothelial, or neutrophil-predominant patterns (Table *4*). BAL cytology showed a closely comparable distribution, with malignant cells in 17/70 (24.3%) and atypical cells in 7/70 (10.0%) of patients, while reactive bronchial cells (15/70, 21.4%), AFB positivity (9/70, 12.9%), and fungal elements (5/70, 7.1%) reflected the substantial infective/inflammatory component of the cohort (Table *4*).

Test	Cytomorphological feature observed	n (%)
Pleural fluid cytology	Positive for malignant cells	17 (24.3%)
	Suspicious for malignancy	7 (10.0%)
	Negative for malignant cells	20 (28.6%)
	Reactive mesothelial cells	10 (14.3%)
	Mixed inflammatory cells	8 (11.4%)
	Granulomatous inflammation	7 (10.0%)
	Lymphocyte-predominant exudate	6 (8.6%)
	Neutrophil-predominant smear	3 (4.3%)
BAL cytology	Positive for malignant cells	17 (24.3%)
	Reactive bronchial cells	15 (21.4%)
	AFB positive	9 (12.9%)
	Negative for malignant cells	8 (11.4%)
	Atypical cells	7 (10.0%)
	Inflammatory smear	7 (10.0%)
	Necrotic inflammatory smear	6 (8.6%)
	Fungal elements seen	5 (7.1%)
BAL cellularity	Moderate	28 (40.0%)
	Cell rich	24 (34.3%)
	Adequate	18 (25.7%)

TABLE 4: Pleural fluid and BAL cytomorphological features observed (non-mutually-exclusive descriptive categories)

Rows sum to more than n = 70 (pleural fluid 78, 111.5%; BAL 74, 105.7%) because these are non-mutually exclusive descriptive cytomorphological patterns, not a per-patient classification (see Methods for detail); not used in the diagnostic-accuracy analysis.

BAL, bronchoalveolar lavage; AFB, acid-fast bacilli

Microbiological evaluation was positive (AFB, CBNAAT, bacterial or fungal culture) in 38/70 (54.3%) of patients overall, and ancillary ICC (chiefly TTF-1 and p40) or GeneXpert testing was performed in 42/70 (60.0%) of cases to support tumour typing or confirm tuberculosis (Table *5*).

Parameter	Category	n (%)
Microbiology result	No growth	32 (45.7%)
	Bacterial culture positive	12 (17.1%)
	AFB detected	10 (14.3%)
	CBNAAT positive	8 (11.4%)
	Fungal culture positive	8 (11.4%)
IHC/ancillary test	Not required	28 (40.0%)
	GeneXpert positive	18 (25.7%)
	TTF-1 positive	12 (17.1%)
	p40 positive	7 (10.0%)
	Calretinin positive	3 (4.3%)
	Synaptophysin positive	1 (1.4%)
	CK7 positive	1 (1.4%)
Final diagnosis	Tuberculosis	18 (25.7%)
	Adenocarcinoma	12 (17.1%)
	Squamous cell carcinoma	7 (10.0%)
	Bronchiectasis	7 (10.0%)
	COPD with infection	6 (8.6%)
	Fungal infection	6 (8.6%)
	Parapneumonic effusion	5 (7.1%)
	Reactive effusion	4 (5.7%)
	Interstitial lung disease	3 (4.3%)
	Small cell carcinoma	1 (1.4%)
	Metastatic carcinoma	1 (1.4%)
Disease group	Malignant	24 (34.3%)
	Non-malignant	46 (65.7%)

TABLE 5: Microbiology, ancillary testing, and final diagnosis

AFB, acid-fast bacilli; IHC, immunohistochemistry; COPD, chronic obstructive pulmonary disease

Based on composite cytological and clinical evaluation, 24 patients (34.3%) were categorised as having malignant lung disease and 46 (65.7%) as having non-malignant disease. Tuberculosis (18/70, 25.7%) was the single commonest final diagnosis, followed by adenocarcinoma (12/70, 17.1%), squamous cell carcinoma and bronchiectasis (7/70, 10.0% each), COPD with infection and fungal infection (6/70, 8.6% each), parapneumonic effusion (5/70, 7.1%), reactive effusion (4/70, 5.7%), interstitial lung disease (3/70, 4.3%), and small cell or metastatic carcinoma (1/70, 1.4% each) (Table *5*). The itemised diagnoses in Table *5* include 21 malignant entities (12 adenocarcinoma, 7 squamous cell, 1 small cell, and 1 metastatic) and 49 non-malignant entities, whereas the disease-group classification contains 24 malignant and 46 non-malignant patients; this three-patient difference could not be reconciled from the available aggregate data and requires verification against patient-level records. All agreement analyses use the disease-group classification (24 vs 46), and malignant-subtype percentages should be interpreted with this discrepancy in mind.

Malignant disease showed statistically significant associations with several demographic and clinical variables (Table *6*).

Variable	Malignant (n=24)	Non-malignant (n=46)	Statistic	p-value
Mean age (years)	62.3 ± 12.4	49.6 ± 14.2	t=5.11	<0.001*
Male sex, n (%)	19 (79.2%)	24 (52.2%)	Fisher's exact	0.039*
Current/ex-smoker, n (%)	20 (83.3%)	26 (56.5%)	Fisher's exact	0.034*
Age <40 years, n (%)	0 (0.0%)	18 (39.1%)	Fisher's exact	<0.001*
Pleural fluid protein (g/dL)	4.83 ± 0.48	4.07 ± 0.61	t=5.32	<0.001*
Haemorrhagic/serosanguinous fluid, n (%)	10 (41.7%)	14 (30.4%)	Fisher's exact	0.429
Positive microbiology, n (%)	0 (0.0%)	31 (67.4%)	Fisher's exact	<0.001*
Hospital stay (days)	10.8 ± 3.6	9.9 ± 4.1	t=1.27	0.208

TABLE 6: Association between clinico-pathological variables and disease group

*Statistically significant (p<0.05). Percentages for categorical rows use common denominators: the malignant (n=24) and non-malignant (n=46) column totals. Continuous variables are mean ± SD (unpaired t-test); categorical comparisons use Fisher's exact test on 2x2 tables. Positive microbiology is 31/46 here, as in the source analysis, whereas Table 5 gives 38/70 positive overall; this discrepancy of seven patients could not be reconciled without patient-level data

Patients with malignancy were significantly older than those with non-malignant disease (62.3 ± 12.4 vs. 49.6 ± 14.2 years, p<0.001), and no malignant case occurred below the age of 40 years (0/24 malignant vs 18/46 non-malignant, Fisher p<0.001). Malignant patients were more often male (19/24, 79.2% vs 24/46, 52.2%; p=0.039) and current or ex-smokers (20/24, 83.3% vs 26/46, 56.5%; p=0.034) than non-malignant patients. Malignant effusions also had significantly higher pleural fluid protein (4.83 ± 0.48 vs. 4.07 ± 0.61 g/dL, p<0.001); haemorrhagic or serosanguinous appearance was not significantly more frequent (10/24, 41.7% vs 14/46, 30.4%; p=0.429). Conversely, tuberculosis was strongly associated with elevated pleural fluid ADA (75.4 ± 13.2 U/L vs. 22.1 ± 7.8 U/L in non-tuberculous cases, p<0.001; Table *7*), and a positive microbiological result was found exclusively among non-malignant cases (0/24 vs 31/46, p<0.001). Hospital stay did not differ significantly between malignant and non-malignant groups (10.8 ± 3.6 vs. 9.9 ± 4.1 days, p=0.208).

Parameter	Tuberculous (n=18)	Non-tuberculous (n=52)	Statistic	p-value
Pleural fluid ADA (U/L)	75.4 ± 13.2	22.1 ± 7.8	t=11.88	<0.001*

TABLE 7: Pleural fluid ADA in tuberculous versus non-tuberculous cases

Values are mean ± SD (unpaired t-test). Tuberculous cases are the 18 patients with a final diagnosis of tuberculosis; non-tuberculous cases are the remaining 52 patients (malignant and other non-malignant diagnoses). *Statistically significant (p<0.05).

ADA, adenosine deaminase

Agreement estimates for pleural fluid cytology and BAL cytology in relation to malignancy, using the prespecified malignant-cells-positive criterion (Methods) and evaluated individually and in combination against the composite reference diagnosis, are summarised in Table *8* (with 95% confidence intervals), Table *9* (underlying 2x2 counts), and Table *10* (exact overlap among malignant cases); these are reported as exploratory findings rather than validated diagnostic-accuracy figures, for the reasons given in Methods.

Parameter	Pleural fluid cytology	BAL cytology	Combined (pleural OR BAL positive)
Sensitivity (95% CI)	70.8% (50.8-85.1%)	70.8% (50.8-85.1%)	87.5% (69.0-95.7%)
Specificity (95% CI)	100.0% (92.3-100%)	100.0% (92.3-100%)	100.0% (92.3-100%)
Positive predictive value (95% CI)	100.0% (81.6-100%)	100.0% (81.6-100%)	100.0% (84.5-100%)
Negative predictive value (95% CI)	86.8% (75.2-93.5%)	86.8% (75.2-93.5%)	93.9% (83.5-97.9%)
Overall agreement with reference classification (95% CI)	90.0% (80.8-95.1%)	90.0% (80.8-95.1%)	95.7% (88.1-98.5%)

TABLE 8: Agreement between pleural fluid cytology, BAL cytology, combined testing, and the composite reference classification of malignancy, with 95% confidence intervals

95% CIs were calculated using the Wilson score method. A specimen was scored positive only when malignant cells were identified (suspicious/atypical results were classified as indeterminate and excluded from this primary 2 × 2 analysis; see Table 9 and Methods). Combined testing used an OR rule (positive if either specimen was positive). The raw counts (n) underlying every percentage in this table - true positives, false positives, false negatives, and true negatives for each row - are given in full in Table 9.

BAL, bronchoalveolar lavage

Test	Reference-positive (malignant)	Reference-negative (non-malignant)	Total
Pleural fluid cytology positive	17	0	17
Pleural fluid cytology negative	7	46	53
BAL cytology positive	17	0	17
BAL cytology negative	7	46	53
Combined (OR rule) positive	21	0	21
Combined (OR rule) negative	3	46	49

TABLE 9: Underlying 2x2 tables of agreement between pleural fluid cytology, BAL cytology, combined testing, and the composite reference classification (n=24 reference-positive, n=46 reference-negative)

In each "positive" row, the reference-positive column is the TP count and the reference-negative column is the FP count; in each "negative" row, the reference-positive column is the FN count and the reference-negative column is the TN count. Counts are derived arithmetically, not extracted from patient-level data (Methods, Limitations). The malignant-case overlap between the two tests is nonetheless exactly determined; see Table 10.

TP, true positive; FP, false positive; FN, false negative; TN, true negative; BAL, bronchoalveolar lavage

Detection pattern	n (of 24 malignant cases)	Derivation
Positive on both pleural fluid and BAL cytology	13	Pleural TP + BAL TP - Combined (OR) TP = 17+17-21
Positive on pleural fluid cytology only	4	Pleural TP - Both = 17-13
Positive on BAL cytology only	4	BAL TP - Both = 17-13
Negative on both tests (neither detected malignancy)	3	24 - Combined (OR) TP = 24-21

TABLE 10: Overlap of malignant-case detection between pleural fluid and BAL cytology among the 24 reference-positive (malignant) patients

Unlike Table 9, this overlap is exact (not an assumption): 17+17-21=13, by inclusion-exclusion on the three reported margins. The BAL-only cell (n=4) is the source of the '4 additional malignant cases' in Results. Patient identity, subtype, and clinical characteristics within each cell are not available and require patient-level records (Limitations).

TP, true positive; BAL, bronchoalveolar lavage

Both tests independently showed identical point estimates: sensitivity 70.8% (17/24; 95% CI 50.8-85.1%), specificity 100.0% (46/46; 95% CI 92.3-100%), PPV 100.0% (17/17; 95% CI 81.6-100%), NPV 86.8% (46/53; 95% CI 75.2-93.5%), and overall agreement 90.0% (63/70; 95% CI 80.8-95.1%). When pleural fluid and BAL cytology were interpreted together using an OR rule, point-estimate sensitivity was higher at 87.5% (21/24; 95% CI 69.0-95.7%), NPV at 93.9% (46/49; 95% CI 83.5-97.9%), and agreement at 95.7% (67/70; 95% CI 88.1-98.5%), while specificity (46/46) and PPV (21/21) point estimates remained 100.0%. Exact McNemar tests on the paired outcomes were not significant (pleural fluid versus BAL, p=1.00; combined strategy versus either single test, p=0.125).

On the strict binary basis (malignant cells identified versus not), pleural fluid and BAL cytology were concordant in 62/70 patients (88.6%; 13 positive on both and 49 negative on both) and discordant in 8/70 (11.4%), giving Cohen's kappa 0.69 (95% CI 0.49-0.89; expected agreement 63.2%), i.e. substantial agreement. On the multi-category basis using the original cytological categorisation (Table *11*), concordance was lower, 56/70 (80.0%), with 14/70 (20.0%) discordant and kappa 0.58 (moderate agreement), because suspicious/atypical, benign/inflammatory and negative results are counted as separate categories. The multi-category kappa could not be recomputed from the aggregate data. As shown precisely in Table *10*, four of the 24 malignant cases had an unequivocally positive (malignant cells identified, not suspicious/atypical) BAL cytology result with a negative pleural fluid cytology result under the primary analysis definition; conversely, four had a positive pleural fluid result with a negative BAL result (pleural-only), 13 were positive on both tests, and three were positive on neither. The BAL-only detection represents 4/24 (16.7%) of malignant cases.

Parameter	Value
Binary basis: concordant cases	62/70 (88.6%)
Binary basis: discordant cases	8/70 (11.4%)
Binary basis: expected agreement	63.20%
Binary basis: Cohen's kappa (95% CI)	0.69 (0.49-0.89)
Multi-category basis: concordant cases	56/70 (80.0%)
Multi-category basis: discordant cases	14/70 (20.0%)
Multi-category basis: expected agreement	52.60%
Multi-category basis: Cohen's kappa	0.58
Multi-category concordance, malignant/suspicious pleural cytology	21/24 (87.5%)
Multi-category concordance, benign/inflammatory pleural cytology	35/46 (76.1%)
Malignant cases with unequivocally positive BAL cytology but negative pleural fluid cytology (BAL-only; see Table 10), n	4
Observed BAL-only detection proportion among malignant cases	4/24 (16.7%)

TABLE 11: Concordance and observed BAL-only detection proportion between pleural fluid and BAL cytology

Concordance between pleural fluid and BAL cytology was numerically higher for malignant/suspicious pleural cytology (21/24, 87.5%) than for benign/inflammatory pleural cytology (35/46, 76.1%), but this difference was not statistically significant (Fisher's exact test p = 0.352). This is an observed detection proportion in this cohort, not an independently validated incremental diagnostic yield: it depends on the same non-independent composite reference classification discussed throughout (Methods, Limitations), and the exact McNemar test on the discordant pairs (4 pleural-only vs 4 BAL-only) was not significant (p = 1.00); patient-level confirmation of the four BAL-only cases was not performed.

BAL, bronchoalveolar lavage

Several pleural fluid and BAL parameters (cytology category, TLC and cellularity, ADA and tuberculosis-associated BAL findings, and protein and BAL cytology status) showed nominally significant positive associations in secondary, exploratory testing not corrected for multiple comparisons. Because the correlation method and variable coding underlying these associations could not be specified with confidence, they are reported here narratively rather than as a numeric results table, and should be treated as hypothesis-generating pending a re-analysis with a prespecified, documented method.

Radiology-cytology correlation was rated strong in 31/70 (44.3%) of cases, moderate in 28/70 (40.0%), and weak in 11/70 (15.7%), without a significant difference between malignant and non-malignant groups (χ^2 = 1.12, p = 0.571), indicating that imaging correlation was broadly useful across both disease categories rather than being specific to malignancy.

Discussion

This prospective, exploratory study examined the individual and combined relationship of pleural fluid and BAL cytology to a composite diagnosis of malignancy in 70 patients with lung lesions and pleural effusion at a tertiary care hospital. The principal finding was that, while pleural fluid cytology and BAL cytology each showed identical point estimates in isolation (70.8% sensitivity (17/24), 100.0% specificity (46/46), and 90.0% agreement (63/70)), applying the OR rule to combine them produced a higher observed detection proportion in this dataset (87.5% sensitivity (21/24) and 95.7% agreement (67/70)), with the specificity point estimate unchanged at 100.0% (46/46). This should not be read as evidence that the combined strategy is a superior diagnostic approach: the OR rule mechanically tends to trade specificity for sensitivity by construction, and because the reference diagnosis itself was not independent of these cytological results, the unchanged specificity point estimate is not reassuring evidence against that trade-off - it may simply reflect the same incorporation bias discussed above. The 100% specificity is therefore largely an artefact of the composite reference design rather than an intrinsic measure of diagnostic accuracy. These findings are compatible with, but do not establish, the hypothesis that the two tests provide complementary information, a hypothesis also broadly consistent with the substantial binary agreement (κ=0.69) and moderate multi-category agreement (κ=0.58) observed between them. The wide, overlapping confidence intervals, particularly around sensitivity, reflect the small number of malignant cases (n=24), and the exact McNemar tests (p=1.00 and p=0.125) did not show a statistically significant difference between strategies, so whether the difference in point estimates is statistically or clinically meaningful has not been established.

The mean age of 53.96 ± 15.54 years and the predominance of the 46-55 year age group in this cohort are consistent with the recognised increase in both malignant and infective pulmonary disease with advancing age. Malignancy occurred exclusively in patients aged 40 years and older and was significantly associated with older age (62.3 vs. 49.6 years, p<0.001), a pattern comparable to that reported by Sareen and Pandey, who found BAL cytology sensitivity of 72.69% and specificity of 100% for suspected lung malignancy in a similarly adult population [11].

Male predominance (43/70, 61.4%) and a significantly higher proportion of malignancy among males (19/43, 44.2%) than females (5/27, 18.5%, Fisher p=0.039) in the present cohort mirror findings from several Indian cytology series and a pattern also reported in other cytology series from this region, though this study did not directly measure tobacco pack-years or occupational exposure and so cannot establish the reason for this association. Raj et al. similarly reported a marked male preponderance (male:female ratio 15:1) among cytologically diagnosed lung cancers in a comparable Indian cohort, with adenocarcinoma as the commonest cytomorphological subtype and squamous cell carcinoma predominantly centrally located [12], while Davidson et al. emphasised that BAL cytology is informative across sexes for both neoplastic and non-neoplastic disease and requires careful clinical correlation regardless of patient sex [13].

Smoking status (current, ex-, or never-smoker) was associated with malignancy in the present study (10/22, 45.5% of current smokers; 10/24, 41.7% of ex-smokers; and 4/24, 16.7% of never-smokers had malignant disease; Fisher p=0.034 for current/ex-smokers versus never-smokers); that is, smoking category was statistically associated with malignancy in this cohort. Pack-years, duration of smoking, occupational and passive exposure were not measured, so no causal or risk-factor inference is drawn. Sareen and Pandey similarly reported a 27.3% false-negative rate for BAL cytology in their series, cautioning that suspicious lesions - particularly in smokers - may require more than a single cytological modality for confident exclusion of malignancy [11]. Boddapati et al. reported an even lower BAL sensitivity of 31.25% (with specificity preserved at 100%), reinforcing that BAL cytology should not be relied upon in isolation when pleural fluid cytology, imaging, or biopsy are available as adjuncts [14].

Pleural fluid biochemistry provided useful supportive information in this cohort. Malignant effusions had significantly higher protein concentrations than non-malignant effusions (4.83 vs. 4.07 g/dL, p<0.001), a difference that is compatible with, though not direct evidence of, greater pleural membrane involvement in malignant disease; as Porcel et al. have noted, however, protein elevation reflects an exudative process in general and is not, by itself, specific for malignancy, so it is best interpreted alongside cytology and other pleural fluid parameters [15]. Pleural fluid ADA, in contrast, showed a much more disease-specific pattern: tuberculous effusions had markedly higher ADA than non-tuberculous effusions (75.4 vs. 22.1 U/L, p<0.001), reaffirming the established role of ADA as a supportive biochemical marker for tuberculous pleuritis, particularly when interpreted alongside AFB smear, culture, and GeneXpert/CBNAAT results, as also reported by Tayal and Bhale in their series of 48 BAL specimens with a substantial tuberculosis component (18%) [16].

The overall point estimate of agreement with the composite reference classification for pleural fluid cytology (63/70, 90.0%) observed here is numerically comparable to previously reported diagnostic-accuracy figures for pleural fluid and BAL cytology. Ghildiyal et al. reported 81.48% sensitivity and 93.33% specificity for cytological evaluation of pulmonary lesions across neoplastic and non-neoplastic categories [3], while Sareen and Pandey reported BAL sensitivity of 72.69% and specificity of 100% for lung malignancy [11], figures numerically similar to the 70.8% sensitivity and 100.0% specificity point estimates for BAL cytology in the present study. However, these comparisons should be interpreted cautiously: the cited studies may differ from the present study in patient population, sampling method, malignancy prevalence, reference-standard construction, and cytology technique, and any of these differences could account for the numerical similarity or difference observed, independent of true test performance.

The key contribution of the present study is the precise, arithmetically exact characterisation of overlap between pleural fluid and BAL cytology among the malignant cases (Table *10*): 13 of 24 malignant cases were positive on both tests, four on pleural fluid only, four on BAL only, and three on neither. This BAL-only detection (16.7% of malignant cases) is the basis for the higher point-estimate sensitivity of combined testing, but - as discussed above - whether this represents a real, generalisable gain in detection or is partly an artefact of how the reference diagnosis was constructed cannot be determined from the present analysis. With that caveat, the finding is at least directionally consistent with, and comparable in magnitude to, prior reports of complementary value between the two techniques. Nguyen-Dang et al. reported comparatively low BAL sensitivity (25.7% for liquid-based cytology and 15.4% for conventional smears) in their prospective series, illustrating that BAL cytology alone may still miss a substantial proportion of malignant cases and underscoring the value of combining it with pleural fluid assessment [17]. Egbuchiem et al. similarly emphasised that a negative pleural fluid cytology - and even a negative pleural biopsy - does not reliably exclude malignancy when radiological suspicion is high, and recommended that further diagnostic evaluation, including additional sampling modalities, be pursued in such cases [7]. Sheikh et al. likewise showed that combining BAL cytology with a second sampling modality (transbronchial needle aspiration/biopsy correlation) improved overall diagnostic yield compared with either investigation alone, broadly consistent with the complementary value of combined cytological sampling observed in the present cohort [18].

The moderate rather than near-perfect agreement observed here (binary κ=0.69 and multi-category κ=0.58) is biologically plausible: pleural fluid cytology reflects shedding of cells into the pleural space, which depends on direct pleural involvement, whereas BAL samples the bronchial and alveolar compartments directly and can detect malignant or atypical cells even when a tumour has not yet involved the pleura, or when pleural sampling is technically suboptimal. This mechanistic distinction likely explains why the two tests were discordant in 8/70 (11.4%) patients on the binary basis and 14/70 (20.0%) across the multi-category grading and why BAL contributed meaningfully to sensitivity even where pleural cytology alone would have been falsely reassuring.

Limitations

This study has several important limitations. First, the composite reference diagnosis was not independent of the index cytology tests, creating a risk of incorporation bias that may inflate specificity and PPV; independent histopathological confirmation was available for only 4 of 70 patients (5.7%), so these findings are better regarded as agreement estimates than validated diagnostic accuracy. Second, blinding of cytopathologists to each other's results and to clinical/radiological findings was not documented, so review bias cannot be excluded. Third, the descriptive cytomorphological categories in Table *4* are non-mutually-exclusive, and the itemised final diagnoses (21 malignant and 49 non-malignant entities) differ by three patients from the disease-group classification (24 vs 46); likewise, positive microbiology is 38/70 in the frequency table (Table *5*) but 31/46 non-malignant cases in the association analysis (Table *6*), a difference of seven patients; none of these could be reconciled against patient-level data, and they did not feed into the primary agreement analysis (Tables *8*-*10*). Fourth, the paired exact McNemar tests were computed from aggregate counts only and, with eight discordant pairs overall, are severely underpowered. Fifth, the sample size was calculated for prevalence estimation rather than diagnostic-accuracy precision, yielding wide confidence intervals (e.g. sensitivity 95% CI 50.8-85.1%) and inadequate power for individual tumour-subtype or prognostic-category conclusions. Sixth, multiple comparisons were not corrected for, so secondary associations (Table *6*, and the pleural fluid-BAL parameter associations discussed in Results) should be considered hypothesis-generating rather than confirmatory. Selection bias is also possible, because only patients in whom both a pleural fluid sample and a BAL sample were obtained and adequate were enrolled (inadequate specimens were excluded), so the cohort may over-represent patients fit for bronchoscopy and may not reflect all patients with effusion and lung lesions. Finally, as a single-centre study in a tuberculosis-endemic setting (tuberculosis accounted for 18/70, 25.7% of diagnoses), the specific numerical findings may not generalise to lower-prevalence populations, and limited follow-up precluded assessment of long-term outcomes or delayed diagnosis after initially negative cytology. Given these constraints, this dataset should be regarded as hypothesis-generating pending patient-level verification and, ideally, multicentre validation with an independent reference standard and STARD 2015 reporting.

Conclusions

In this exploratory, prospective, single-centre cohort of 70 patients from a selected tertiary-care population with lung lesions and pleural effusion, pleural fluid cytology and BAL cytology showed identical standalone point estimates (sensitivity 70.8% (17/24), specificity 100.0% (46/46), agreement 90.0% (63/70) for malignancy, using a prespecified malignant-cells-positive criterion), and their combined (OR-rule) interpretation showed a higher point-estimate sensitivity (87.5% (21/24)) and agreement (95.7% (67/70)) with the unchanged 100% specificity largely an artifact of the composite reference design rather than a measure of diagnostic accuracy and the differences not statistically significant, and with BAL cytology detecting four malignant cases not identified by pleural cytology alone. Malignant disease was associated with older age, male sex, and smoking status, while elevated pleural fluid ADA was associated with tuberculosis. Because the composite reference diagnosis incorporated the index cytological tests themselves rather than resting on a fully independent standard, and because confidence intervals around these estimates are wide given the modest number of malignant cases, these findings are not sufficient to support a specific practice recommendation and await multicentre validation against an independent reference standard, with documented blinding, paired statistical comparison, and STARD-compliant reporting. In the interim, this dataset offers a quantitative benchmark for the complementary detection pattern of combined pleural fluid and BAL cytology in a tuberculosis-endemic, tertiary-care setting, and a concrete illustration of how incorporation bias can shape apparent diagnostic accuracy when index tests contribute to their own reference standard - a methodological caution of value beyond this cohort alone.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Devanshi Gosai, Khusbu Chhaya, Vidhi Jain, Aman Jain

Acquisition, analysis, or interpretation of data: Devanshi Gosai, Khusbu Chhaya, Vidhi Jain, Aman Jain

Drafting of the manuscript: Devanshi Gosai, Khusbu Chhaya, Vidhi Jain, Aman Jain

Critical review of the manuscript for important intellectual content: Devanshi Gosai, Khusbu Chhaya, Vidhi Jain, Aman Jain

Supervision: Vidhi Jain

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. SVIEC - Sumandeep Vidyapeeth Institutional Ethical Committee issued approval SVIEC/UN/MEDI/BNPD24/JAN/25/277. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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