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Research Article

Clinicoradiological evaluation of Interstitial lung disease and its association with bronchoalveolar lavage cytology: a cross-sectional study

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ABSTRACT

Abstract: Background and objectives: Interstitial lung diseases are also known as diffuse parenchymal lung disease, indicating that the interstitium is not the only part of the lung affected. In our state, where pulmonary tuberculosis being the common respiratory disease, ILDs have received little attention, are often overlooked, and, hence get underdiagnosed. This study mainly aimed to evaluate the association of the clinicoradiological patterns with the bronchoalveolar lavage cytology of various types of ILD cases.

Methods: This is a cross-sectional analytical study that included patients with ILD of age > 18 years admitted to the Chest Ward was carried out in the Department of Respiratory Medicine from October 2022 to March 2024. Demographic, clinical, radiological and bronchoscopy evaluation data was collected. It was done using IBM SPSS software. Fisher Freeman Halton exact test was used to evaluate the association between categorical variables considering p value < 0.05 as statistically significant.

Results: The overall mean age was 46.08 ± 13.75 years with a female predominance. Shortness of breath (93.9%) & cough were the most common symptoms. Usual Interstitial Pneumonia (42.9%) is the most common pattern found in HRCT thorax followed by Nonspecific Interstitial Pneumonia (26.5%). The BAL cytology was inflammatory predominantly of mixed cellularity (38.8%). BAL cytology was correlated with various types of ILD & high-resolution computed tomography scan of thorax. All patients with UIP and organizing pneumonia pattern had an inflammatory BAL.

Interpretation and Conclusions: Our study revealed a significant association between HRCT patterns & BAL cytology. It has also shown a significant association between the types of ILD & BAL cytology. Thus, it can be concluded that BAL is a supportive diagnostic tool for clinical and radiological evaluation in selected ILD patients, especially in resource-limited settings.

Keywords*: Interstitial lung disease, BAL, HRCT thorax.*

INTRODUCTION

Interstitial Lung Disease (ILD) is a group of disorders characterized by different degrees of lung parenchymal fibrosis and inflammation sharing some similarities in the clinical, radiological, physiological, and pathological features. ILD is also known as diffuse parenchymal lung disease (DPLD), indicating that the interstitium is not the only part of the lung affected. [1] In our state, where pulmonary TB is a very common respiratory disease, ILDs have received little attention, are often overlooked, and, in turn, get underdiagnosed.

There is paucity of data available on ILD epidemiology, particularly in developing nations. Studies have indicated that the overall incidence and prevalence of ILD have been increasing over the past few decades with an incidence rate of 32

per 100,000 annually in men and 26 per 100,000 annually in women. Similarly, the prevalence of ILD is higher in males (81 per 100,000 annually) compared to women (67 per 100,000 annually). [1]

According to the India ILD Registry by Singh S et al. [2], Hypersensitivity pneumonitis (HP) was the predominant form of ILD, followed by Connective Tissue Disease-associated ILD (CTD-ILD) & idiopathic pulmonary fibrosis (IPF). Another study done in India by Dhooria S et al. [3] (PGI Registry) found that Sarcoidosis was the most common sub-type of ILD, IPF being the second most common, and third most common was CTD-ILD. However, IPF and sarcoidosis were found to be the most common ILDs in North America and Europe. [4] ILD is associated with significant mortality and morbidity leading to reduced quality of life. In the United States, ILD accounted for 0.39% of the total Disability-Adjusted Life Years (DALYs) and 0.73% of the overall number of deaths. Both males and females had a rise in age-specific DALYs rates and mortality rates with increasing age. [5]

Progressive shortness of breath and persistent cough are the main presenting symptoms of the patients with ILD. They are often diagnosed by evidence of lung infiltrates on chest imaging, altered lung function, and impaired gas exchange. When the disease advances and severe fibrosis occur, it leads to prolonged hypoxemia. This causes the development of pulmonary hypertension and malfunction of the right side of the heart. [6]

There have been attempts to better assess the airways, collect tissue, and treat different respiratory disorders since late 19th century. As a result, bronchoalveolar lavage (BAL), endobronchial, and transbronchial forceps biopsies emerged one after the other until transbronchial cryobiopsy emerged as a promising new approach lately. [7] However, because the ILD patients are already in some form of respiratory compromise and have a higher risk of complications, it is better to opt for a less invasive intervention.

When combined with thorough clinical assessment, lung function testing, blood tests, and imaging, the BAL cellular analysis can offer further diagnostic information that may eliminate the necessity for high-risk interventions like surgical lung biopsy or cryobiopsy. In addition, BAL has the ability to detect other factors that may be causing confusion, including infection and cancer. [8]

Because it is a challenging task to establish a diagnosis of ILD owing to the diversity of the aetiology, this study was conducted with the purpose to analyse the clinical manifestations and radiographic patterns & its association with the cellular composition of the BAL fluid to help in narrowing differential diagnoses of ILD and excluding infectious mimics.

Primary objective: To evaluate the association of clinical features and radiological patterns of interstitial lung disease with BAL cellularity.

Secondary objective:

1. To describe the clinical and radiological profile of patients with ILD.
2. To analyze the cellular composition of BAL fluid across different ILD subtypes.
3. To evaluate BAL in excluding infectious mimics of ILD, particularly tuberculosis.

MATERIALS AND METHODS

Settings And Study Design

This was a cross-sectional analytical study conducted in the Department of Respiratory Medicine from October 2022 to March 2024. All ILD patients following inclusion & exclusion criteria were enrolled and the study was performed in accordance with the declaration of Helsinki.

Inclusion Criteria

- All patients aged >18 years with ILD admitted to the Department of Respiratory Medicine.

Exclusion Criteria

- Patients not willing to give consent.
- Patients <18 years of age.
- Pregnant ladies, HIV positive, HBsAg positive, Anti HCV positive and Post TB patients.
- Patients hemodynamically unstable.
- Patients with coagulopathy.
- Patients with Chronic Kidney Disease and Chronic Liver Disease.

Data collection

Following the selection of patients and obtaining written consent from them, a detailed history was obtained, along with a thorough examination of all systems of the body.

The patients had routine blood tests, including complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), serum electrolytes, random blood sugar (RBS), and inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR). Patients suspected of having CTD underwent anti-nuclear antibody (ANA) Profile,

Rheumatoid Factor, and Anti-CCP (Anti-Cyclic Citrullinated Peptide) antibody tests. The patients then had a series of diagnostic tests, including a Chest X-ray (postero-anterior view), Spirometry, ECG (electrocardiography), 2D-Echocardiogram, and HRCT Thorax.

Patient Preparation
The patients were advised to fast for 6-8 hours prior to the procedure. Following a thorough examination and clearance from the cardiology department, the patients were taken up for bronchoscopy.

Procedure
Bronchoalveolar lavage (BAL) was performed during flexible bronchoscopy following standard techniques as recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS). Sterile normal saline was instilled in aliquots into a subsegment of the affected lung, with gentle aspiration after each instillation. The retrieved fluid was pooled, filtered, and processed immediately for microbiological, cytological, & CBNAAT (Cartridge Based Nucleic Acid Amplification Test) analysis. Differential cell counts were obtained after centrifugation and staining, and BAL cellular patterns were interpreted according to established ATS/ERS criteria. The BAL samples were labelled & then sent to the laboratory promptly analysis.

BAL cytology
The BAL samples that were sent immediately after the collection (within half an hour) were processed in the laboratory as follows:

Slide Preparation
The BAL fluid was centrifuged at a speed of 1500 rpm (revolutions per minute) keeping the sediment. The supernatant was discarded. Multiple smears were prepared by spreading the sediment onto clean glass slides. The slides were allowed to air dry or fixed immediately in 95% ethanol for staining.

Staining and Examination
Diff Quik (DQ) stain, Haematoxylin and Eosin stain, o Papanicolaou stain. The stained slides were then examined under a microscope to evaluate cell types, cellularity, and any abnormal findings.

Statistical Analysis
The responses from the participants were entered into Microsoft Excel 365 and analysed using IBM SPSS statistics for windows version 21.0.0.0 (Armonk, NY; IBM corp.). Categorical variables were represented in terms of frequency and percentage whereas mean & standard deviation (SD) were used to express descriptive statistics & continuous variables. Fisher Freeman Halton exact test was employed to find out the association between categorical variables. The significance level was assessed at 5% level of significance.

OBSERVATION & RESULTS
A total of 49 cases were studied according to their demographic, clinical & radiological characteristics & bronchoscopy findings. Among them 19 (38.8%) cases were male and 30 (61.2%) cases were female.

The overall mean age of patients was 46.08 ± 13.75 years with the minimum and maximum age being 18 years and 82 years respectively (table 1). Shortness of breath (93.9%) was the most common pulmonary symptom followed by cough (87.8%). Among the extrapulmonary symptoms, joint pain was the most common symptom seen in 9 patients (18.4%). On general examination, 14 patients (28.6%) had pallor, which was the most common clinical sign followed by clubbing (24.5%). 20.4% of the patients had bony deformities like swan-neck deformity of fingers, deformity of wrist joint and contracted elbow. Cutaneous manifestations were found in 6 patients (12.2%). Majority of the patients (91.8%) had crepitations, which was most commonly fine late inspiratory bi-basal crepitations (table 2).

In our study CTD associated ILD was found to be the most common ILD (table 3) which was seen in 22 patients (44.9%). The next most common was IPF seen in 7 out of 49 (14.3%) patients followed by HP (12.2%). Fourteen others were diagnosed as Sarcoidosis, pneumoconiosis, diffuse alveolar hemorrhage, organizing pneumonia, Respiratory bronchiolitis related ILD and with ILD related to ankylosing spondylitis, bilateral pneumonia & post-infection.

31 (63.3%) out of 49 patients had reticular shadows in chest x-ray (CXR) (fig 1). Reticulonodular CXR was found in 6 patients (12.2%) and a normal CXR was found in 1 patient (2%).

It is evident from the table that the most common HRCT pattern was Usual Interstitial Pneumonia (UIP), accounting for 42.9% (table 4). The BAL cellularity was either normal or inflammatory. 43 out of 49 patients i.e. 87.8% of the patients had an inflammatory type of BAL (fig 2). Mixed cellularity was seen in 19 patients (38.8%), neutrophilic BAL in 12 patients (24.5%) and lymphocyte predominance in 12 patients (24.5%). There was significant association found between the HRCT pattern and the BAL cellularity (p = 0.008) which is shown in table 5. All patients with UIP pattern and OP

(Organising Pneumonia) pattern had an inflammatory BAL. Inflammatory BAL cytology was also found to be a predominant finding in NSIP pattern accounting for 92.3%.

Table 6 depicts the presence of all Inflammatory cells in BAL in CTD ILD, HP and IPF. Other lung disorder exhibits mix distributions of both inflammatory and the normal findings. The observed difference in distribution across these four categories was statistically significant as indicated by P value of 0.001 based on Fisher Freeman Halton exact test.

Table 7 summarizes BAL cellular patterns across ILD diagnoses. CTD-ILD (n = 22) showed exclusively inflammatory BAL, predominantly mixed pattern (45.4%). HP (n = 6) demonstrated mainly lymphocytic BAL (66.7%). IPF (n = 7) was characterized by predominant neutrophilic BAL (57.1%). In the other ILD group (n = 14), BAL findings were heterogeneous, with normal cellularity observed in 42.9% of cases.

TABLES AND FIGURES

Table 1: Sociodemographic and anthropometric profile of study participants (N=49)

Variable	Mean ± SD
Age (years)	46.08 ± 13.75
Gender n (%) Male Female	 19 (38.8) 30 (61.2)
Weight (kg)	51.63 ± 8.77
Height (meter)	1.54 ± 0.08
BMI (Kg/m^2)	21.75 ± 3.89

Table 2: Clinical sign and symptoms of ILD patients (N=49)

Clinical Manifestations		Frequency (%)
Pulmonary	Cough	43 (87.8)
	Shortness of breath	46 (93.9)
	Chest Pain	4 (8.2)
	Haemoptysis	5 (10.2)
Extrapulmonary	Dysphagia	2 (4.1)
	Joint Pain	9 (18.4)
	Rashes	2 (4.1)
Clinical signs	Clubbing	12 (24.5)
	Pallor	14 (28.6)
	Cyanosis	0
	Cutaneous	6 (12.2)
	Bone & joints deformity	10 (20.4)
	Others	2 (4.1)
Respiratory system examination findings	Crepitation	45 (91.8)
	BBS	3 (6)
	Rhonchi	6 (12.2)
	Diminished breath sound	2 (4)
CVS examination findings	Muffled S1 S2	1 (2)
	Loud P2	1 (2)
	Normal	47 (96)

Table 3: Disease wise distribution of ILD (N= 49)

DIAGNOSIS	FREQUENCY	PERCENTAGE
CTD	22	44.9
HP	6	12.2
IPF	7	14.3
Others*	14	28.6

[*Others include Sarcoidosis, Pneumoconiosis, diffuse alveolar hemorrhage, organizing pneumonia, Respiratory bronchiolitis related ILD etc.]

Table 4: Distribution of different HRCT patterns

HRCT Pattern (N=49)	Frequency	Percentage
UIP	21	42.9
NSIP	13	26.5
OP	2	4.1
Others	13	26.5

Table 5: Association of HRCT pattern with BAL cellularity

HRCT Pattern	BAL Cellularity		P value
	Inflammatory	Normal	
UIP (n=21)	21 (100%)	0	0.008*
NSIP (n=13)	12 (92.3%)	1 (7.7%)	
OP (n=2)	2 (100%)	0	
Others (n=13)	8 (61.5%)	5 (38.5%)	

*P value is calculated using Fisher Freeman Halton exact test

Table 6: Association of Diagnosis of ILD with BAL cellularity

Diagnosis	Inflammatory	Normal	P value
CTD ILD	22(100%)	0	0.001*
HP	6 (100%)	0	
IPF	7 (100%)	0	
Others	8 (57.1%)	6 (42.9%)	

*P value is calculated using Fisher Freeman Halton exact test

Table 7: Correlation of Diagnosis with BAL cellularity

Diagnosis	Inflammatory			Normal
	Neutrophilic	Lymphocytic	Mixed	
CTD (n= 22)	6 (27.3%)	6 (27.3%)	10 (45.4%)	0
HP (n = 6)	0	4 (66.7%)	2 (33.3%)	0
IPF (n = 7)	5 (57.1%)	0	2 (28.6%)	0
Others (n = 14)	1 (7.1%)	2 (14.3%)	5 (35.7%)	6 (42.9%)

Fig 1: Distribution of Chest X-ray findings of ILD patients

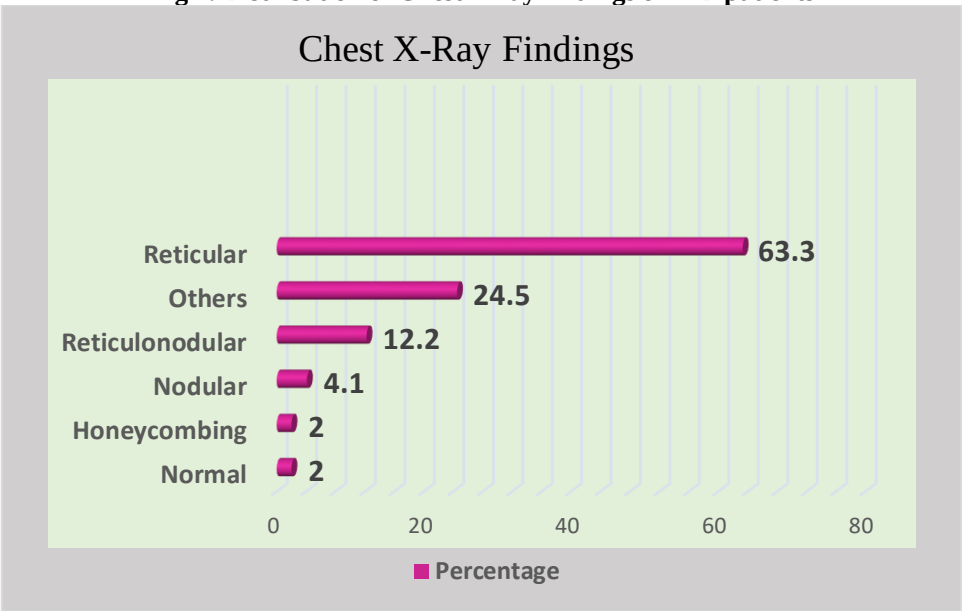
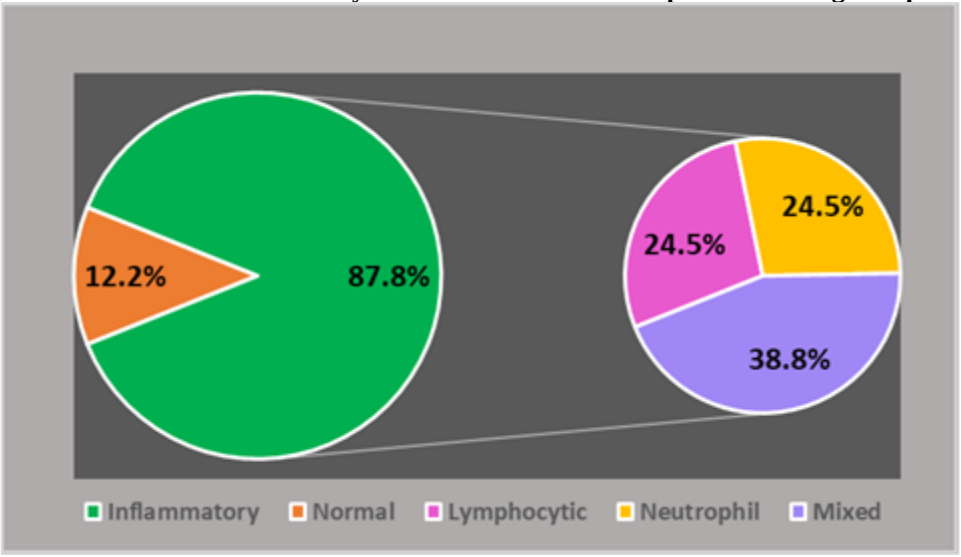


Fig 2: Distribution of inflammatory and normal BAL cellular patterns among ILD patients



DISCUSSION

The exact burden of ILD in India is unclear owing to its under recognition, lack of awareness, limited availability of diagnostic facilities, wide range of diseases it includes, and relatively less attention it receives due to the high prevalence of more common and infectious diseases such as TB. The present study of clinical features, radiological presentation, and bronchoalveolar lavage cytology of patients with ILD.

A higher proportion of females (61.2%) was observed in our study, which may be attributed to the higher prevalence of CTD-associated ILD, such as scleroderma, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) in our study. This is in line with findings from Singh et al. [2], Dhooria et al. [3], and other studies [9-12]. The mean age in our study was 46.08 ± 13.75 years, which is similar to Kumar R et al. [9] and other studies [13,14,15].

In our study, that shortness of breath was the most common symptom (93.9%) followed by cough which was the second most common (87.8%) symptom. Joint pain was the most common extrapulmonary symptom in our study (18.4%), which is similar to those found in other studies by Jindal et al. [10] and Valappil et al. [16].

Our study revealed that 28.6% of the patients had pallor which may be due to female predominance. Clubbing was the second most common (24.5%) clinical sign possibly due to progressive stage of disease in most patients. However, in the studies done by Kumar K. et al. [17] and others [16,18,19], clubbing was the most common clinical sign. The most common (91.8%) chest auscultation finding was fine crepitations, which was bilateral and basal in most cases. It was a finding in all patients (100%) in the Khanna et al.'s [20] study.

The most common ILD in our study was CTD associated ILD which comprises of 44.9% of the study group. This is in accordance to the other Indian study by Valappil et al. [16] where CTD-ILD was the most common ILD, contributing to 34.9% of the total cohort. Rheumatoid arthritis was the commonest (31.8%) CTD in our study. Singh et al. [2], and other studies [16,17,20] also reported RA as the most common CTD. Hypersensitivity Pneumonitis accounted for 12.2% of the patients included in our study. In their research, Deependra Kumar Rai et al. [12], Kundu et al. [19], and Dhooria et al. [3] all reported a similar conclusion, with HP accounting for 15.6%, 10.9%, and 10.7% of the cases, respectively. In our study, we observed a rather low proportion of cases (14.3%) with IPF. The reason for this could be because of the advanced nature of the disease rendering the patient to be unfit to undergo bronchoscopy and therefore, excluded from the study. Kumar Rai et al. [12], Sen T Udwadia ZF et al. [21], Kumar K. et al. [17] and Kundu et al. [19] had found IPF to be the most common ILD accounting for 24.4%, 43%, 47%, 38%, and 36% of the cases in their studies respectively
In this study, reticular pattern (63.3%) was the most common finding seen on chest radiographs. This is in resemblance to those studies done by Kumar K. et al. [17], and Patel et al. [22]. UIP was the most common HRCT pattern accounting for 49.2% of our study group. UIP was the most common HRCT pattern in Kumar K. et al. [17] (51%), 50.4% in Kumar Rai et al. [12], and others studies [16,18,20,21]. We found that 26.5% of the patients had an NSIP pattern on HRCT which were 36% in Khanna et al. [20], 28% in both Valappil et al. [16] and Kumar K. et al. [17], 27.2 % in Saira Jafri et at. [18] studies. Organising Pneumonia pattern was found in 4.1% of cases in our study. Sen T Udwadia ZF et al. [21] and Valappil et al. [16] also found a closely similar incidence, 2% and 6.2% respectively.

BAL analysis in our study predominantly demonstrated an inflammatory cellular profile across major ILD subtypes. Lymphocytic predominance was particularly helpful in patients with HP, supporting earlier observations that BAL lymphocytosis serves as an important adjunctive marker in differentiating HP from other fibrotic ILDs. [23,24] Similarly, the identification of carbon-laden macrophages aided in diagnosing RB-ILD, emphasizing the value of BAL when interpreted in appropriate clinical and radiological contexts. [25]

Although BAL neutrophilia may be indicative of a progressive course of certain ILDs, it could be highly indicative of infectious aetiology or acute lung injury if the differential neutrophil count is ≥50%. In our study, 24.5% had a neutrophilic cellular pattern. Among them, 4 patients were found to have bacterial growth (Pseudomonas spp. & Acinetobacter spp.) in the BAL Culture, out of which 3 patients had a neutrophil count >50%. Given the high incidence of TB in our country, all the BAL fluids were further sent for CBNAAT analysis, which revealed the presence of Mycobacterium tuberculosis (MTB) in one patient.
A statistically significant association was observed between HRCT patterns and BAL cellularity ($p = 0.008$). While UIP is traditionally considered a fibrotic pattern, the presence of inflammatory BAL profiles in our cohort may reflect relatively earlier or active disease stages, as BAL was performed in clinically stable patients. These findings reinforce the concept that BAL findings should be interpreted cautiously and in conjunction with HRCT and clinical features rather than in isolation.

In our study the CTD-associated ILD predominantly demonstrated mixed inflammatory BAL patterns, consistent with immune-mediated alveolar injury involving both lymphocytic and neutrophilic patterns. Hypersensitivity pneumonitis showed a predominance of lymphocytic BAL, supporting its established association with antigen-driven immune responses. In contrast, idiopathic pulmonary fibrosis was characterized by neutrophilic BAL pattern, which has been linked to disease severity and ongoing epithelial injury in fibrotic lung disease. However, overlapping patterns and normal BAL findings in some ILDs highlight that BAL cytology has limited standalone diagnostic value and should be interpreted alongside clinicoradiological features.

The main limitation of our study is the relatively small sample size. Many cases were not included because they either presented in advanced stage of the disease or in severe exacerbation with respiratory failure making themselves unable to perform spirometry and bronchoscopy. Additionally, the study was a single centre study, potentially limiting the generalization of the findings. Secondly, we could not perform BAL fluid CD4, CD8 counts, CD4:CD8 ratio & other biomarker tests because of unavailability of these facilities in our centre. Furthermore, the diagnostic yield might have been increased if a lung biopsy had been performed.

CONCLUSION

Diagnosing interstitial lung disease remains challenging due to its heterogeneous clinical, radiological, and pathological spectrum. In this study, we observed distinct associations between clinical features, HRCT patterns, and BAL cellular profiles among patients with ILD. While BAL analysis alone is insufficient to establish a definitive diagnosis, it provides valuable supportive information when integrated with clinical assessment and imaging findings.

A statistically significant association between HRCT patterns and BAL cellularity was observed, suggesting that BAL can assist in narrowing differential diagnoses, particularly in conditions such as hypersensitivity pneumonitis and sarcoidosis. In tuberculosis-endemic settings, BAL also plays a crucial role in excluding infectious aetiologies that may mimic or complicate ILD.

Therefore, BAL should be considered an adjunctive diagnostic tool in selected ILD patients, especially in resource-limited settings where lung biopsy is not available, to guide clinical decision-making and potentially reduce the need for more invasive diagnostic procedures. However, multidisciplinary discussion remains the gold standard for definitive diagnosis, and further large-scale studies are required to standardize BAL interpretation in ILD.

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