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Original Article

Assessment of Disease Progression in Idiopathic and Collagen Vascular ILDs Using Spirometry, DLCO, and 6 Minute-Walk-Test

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Abstract

Background: Monitoring progression in interstitial lung diseases is essential for timely intervention, with spirometry, DLCO, and 6MWT serving as key functional tests.

Objectives: To evaluate disease progression in idiopathic and collagen vascular interstitial lung diseases (ILD) using pulmonary function parameters, including spirometry, DCLO (Diffusing Capacity of the Lungs for Carbon Monoxide), and the six-minute walk test.

Methods: This prospective observational study was performed from January 2023 to December 2024 at Shadan Institute of Medical Sciences , Hyderabad, India. In this study, the pulmonary function in 51 ILD patients were assessed using spirometry, DLCO, and the six-minute walk test. Patients underwent detailed clinical evaluation, routine investigations, chest X-ray, ABG analysis, and HRCT to confirm ILD. Those suspected of CTD-ILD had RF and ANA testing, with a complete ANA profile if positive. Subjects were categorized into IPF and CTD-ILD groups. Pulmonary parameters were compared, and standard treatments were administered. Six deaths occurred during follow up period. For statistical purposes p value less than 0.05 was taken as statistically significant.

Results: Fifty-one patients with diffuse parenchymal lung disease were included, with idiopathic pulmonary fibrosis (IPF) (46.4%) and connective tissue disease-associated ILD (CTD-ILD) (44.6%) as the main types. The CTD-ILD patients were younger (mean age 48.64 vs. 61.80 years, p=0.0006) and predominantly female. IPF patients had lower six-minute walk distance (239.73 vs. 312.60 meters, p=0.0066) and SpO2. Strong correlations were observed between lung function parameters in both groups. However, 6MWT showed no correlation in CTD-ILD.

Conclusion: In ILD patients, FVC and DLCO were found to be reliable for disease monitoring, while simpler tests like 6MWT and FVC proved to be useful in resource-limited settings. Further research is needed to confirm their role in tracking IPF progression and treatment response.

Keywords: Connective tissue disease-associated interstitial lung disease, Idiopathic pulmonary fibrosis, pulmonary function test, six-minute walk test

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse parenchymal lung disorders characterized by varying degrees of inflammation, fibrosis and impaired gas exchange.[1] These diseases primarily affect the lung parenchyma leading to progressive respiratory failure and reduced quality of life. ILDs encompass several distinct conditions that include conditions such as idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis (HP), sarcoidosis and connective tissue disease-associated ILD (CTD-ILD). The global prevalence of ILDs is difficult to estimate because of variations in diagnostic criteria and registry-based data collection. Some estimates suggest a prevalence of approximately 80–100 cases per 100,000 population globally. In India ILDs have gained increasing recognition with the establishment of Indian Registry of Interstitial Lung Diseases (ILD-India). ILD-India has reported a significant burden of these conditions in Indian population.[2]

ILDs can arise from a variety of etiologies that include environmental, occupational, drug-induced, infectious as well as autoimmune causes. Broadly, they are classified into idiopathic interstitial pneumonias (IIPs) and secondary ILDs associated with known triggers such as connective tissue diseases (CTDs), environmental exposures, or infections. Idiopathic interstitial lung diseases, particularly idiopathic pulmonary fibrosis (IPF) is characterized by progressive fibrosis of unknown origin. IPF is associated with a poor prognosis and limited therapeutic options with a median survival of 3–5 years post-diagnosis.[3] Another crucial category is collagen vascular disease-associated interstitial lung disease which includes ILDs secondary to autoimmune disorders such as rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM), and Sjögren's syndrome. Among these, systemic sclerosis-associated ILD (SSc-ILD) and rheumatoid arthritis-associated ILD (RA-ILD) are among the most common. While idiopathic ILDs such as IPF typically demonstrate a usual interstitial pneumonia (UIP) pattern, CTD-ILDs may exhibit nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) patterns with better prognostic outcomes compared to IPF. Given the progressive and often irreversible nature of these diseases, accurate diagnosis and regular monitoring using pulmonary function parameters are imperative for optimizing clinical management.[4]

HRCT has made it possible to characterize ILD with great precision. As a result, the defining features of nearly all ILDs are well described which has helped to predict outcome and decide on an appropriate management plan.[5] While HRCT is important in initial diagnosis of ILD Pulmonary function testing (PFT) plays an important role in prognostication and monitoring of ILDs. ILDs typically present with restrictive lung physiology, leading to reduced lung volumes and impaired gas exchange. Pulmonary function parameters serve as objective markers to evaluate disease severity, functional impairment, and response to therapy.[6] Among the various PFT parameters, forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), and exercise capacity (assessed via the six-minute walk test [6MWT]) are widely utilized in both clinical and research settings. Serial assessment of these parameters provides critical insights into disease progression and helps guide therapeutic decisions including the initiation of antifibrotic or immunosuppressive therapy.

A decline in pulmonary function parameters over time correlates with increased mortality in ILD patients.[7] For instance, a decrease in FVC by ≥10% over six months is a strong predictor of poor prognosis in IPF. Similarly, DLCO reduction is associated with worsening pulmonary vascular involvement and gas exchange impairment. The six-minute walk test, an essential measure of functional status, reflects exercise-induced oxygen desaturation, an early indicator of ILD progression. Given these associations, periodic assessment of pulmonary function tests is critical in the comprehensive management of ILD patients.[8]

While individual pulmonary function parameters such as FVC and DLCO have been extensively studied in IPF, their predictive value in CTD-ILD and other idiopathic forms of ILD remains underexplored. The integration of 6MWT as a functional marker alongside spirometry and DLCO could provide a more holistic assessment of disease trajectory. This study aims to bridge these gaps by systematically evaluating the progression of idiopathic and collagen vascular ILDs using spirometry, DLCO and the six-minute walk test.

Methods

This prospective observational study was conducted in the Department of Pulmonary

Medicine at Shadan Institute of Medical Sciences, Hyderabad, Telangana, India, over a 23-month period from January 2023 to December 2024. The Institutional Ethics Committee approved the study, and informed written consent was obtained from all participants. Ethical guidelines were followed per international standards, including those from the American Thoracic Society (ATS) and the FDA (USA). No invasive procedures or experimental treatments were involved.

A total of 51 subjects with interstitial lung disease (ILD) of idiopathic and collagen vascular etiology were included in the study. The study aimed to assess pulmonary function status using spirometry, diffusing capacity of lung for carbon monoxide (DLCO), and the six-minute walk test (6MWT).

The study included subjects aged 30 years and above with respiratory symptoms such as cough and shortness of breath for more than three months, bilateral abnormalities on chest X-ray or high-resolution computed tomography (HRCT) scan of the thorax consistent with an interstitial pattern, and restrictive or mixed defects on spirometry. ATS/ERS classification was used for categorizing the cases into different ILDs. Patients with a history of smear-positive tuberculosis, infectious diseases, or malignancy were excluded.

All participants underwent a detailed clinical evaluation and routine investigations, including complete blood picture, blood chemistry, chest X-ray, and arterial blood gas (ABG) analysis. High-resolution computed tomography (HRCT) of the chest was performed to confirm ILD. Spirometry, DLCO (using the EASY PRO, Switzerland) and the six-minute walk test (6MWT) were conducted following ATS guidelines.

Patients suspected of having collagen vascular disease (CTD-ILD) underwent rheumatoid factor (RF) and antinuclear antibody (ANA) testing. If either was positive, a complete ANA profile was done. Additional investigations were conducted as required. Subjects were categorized into idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated interstitial lung disease (CTD-ILD) groups. Pulmonary function parameters, including forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, DLCO, carbon monoxide transfer coefficient (KCO), initial and final SpO2, and six-minute walk distance (6MWD) were recorded. These parameters were analyzed and compared between the IPF and CTD-ILD groups.

All subjects received standard treatment, including oxygen therapy, antioxidants and antifibrotic agents (Pirfenidone). Some patients were also prescribed N-acetylcysteine. Patients were followed up every 6 months till the end of study period. They were encouraged to report earlier in case of disease exacerbation or medication side effects. The follow up was mainly for knowing mortality during study period. During the study period 50 patients completed one-year follow-up. Six deaths were recorded—five in the IPF group and one in the CTD-ILD group.

Statistical analysis was performed using Windostat Version 9.2 software. Continuous variables were expressed as mean ± standard deviation (SD). The Fisher's exact test was applied for categorical data, while the Student's t-test was used for continuous variables. Pearson's correlation was applied to examine associations between variables. A p-value of less than 0.05 was considered statistically significant.

Results

In this study, a total of 51 consecutive patients with diffuse parenchymal lung disease were included. Idiopathic pulmonary fibrosis (IPF) was found to be the most common variety (n=26, 46.4%) followed by CTD (n=25, 44.6%). Of the 25 cases of CTD, rheumatoid arthritis (RA) (n=16, 64%) and systemic lupus erythematosus (SLE) (n=5, 20%), were the most common followed by systemic sclerosis (n=4, 16%) .A majority of patents of CTD–DPLD

Table 1 Comparison of Demographics Between Patients with CTD-ILD and IPF

Demographics	CTD-ILD (n=25)	IPF (n=26)	p-value
Mean age (years)	48.64 ± 15.98	61.80 ± 9.01	0.00065
Sex ratio (male: female)	1:4 (5:20)	1:1 (13:13)	0.02492
Smoking, n (%)	2 (8%)	5 (19.2%)	0.45315
Body Mass Index (BMI)	24.74 ± 4.59	25.56 ± 4.59	0.46904

Table 2 Comparison of Physiological Parameters Between CTD-ILD and IPF Groups

Physiological Parameter	CTD-ILD (n=25)	IPF (n=26)	p-value
FVC (% predicted)	58.2 ± 17.39	57.42 ± 18.03	0.8762
FEV1 (% predicted)	55.56 ± 17.67	57.34 ± 16.98	0.7143
FEV1/FVC	96.84 ± 14.7	101.23 ± 15.37	0.3040
DLCO (% predicted)	40.76 ± 18.61	34.57 ± 17.20	0.2235
KCO (% predicted)	73.64 ± 22.84	70.80 ± 29.33	0.7029
Initial SpO_2 (%)	96.5 ± 2.4	94.7±2.9	0.0198
Final SpO_2 (%)	88.2 ± 7.5	85.8±7.1	0.2461
6MWT (meters)	312.60 ± 108.11	239.73 ± 72.60	0.0066

Table 3 Comparison of Various Parameters in CTD-ILD Group

Parameter 1	Parameter 2	Correlation Coefficient (r)	p-value
FVC	FEV1	0.8928	<0.0001*
FVC	DLCO	0.5773	0.002*
DLCO	KCO	0.79676	<0.0001*
KCO	FVC	0.3975	<0.0001*

Notes: 6MWT was an independent parameter showing no correlation with other physiological parameters

belonged to a younger age group than IPF. The mean age for CTD-ILD and IPF was 48.64 ±15.98 years, 61.80 ± 9.01 years respectively, with a significant p value(0.0006). A significant difference was found in the male to female ratio between two groups (p=0.02) (Table 1).

In CTD-ILD group (n=25), spirometry abnormalities were observed in 22(88%) patients, 20(80%) had restrictive defects and 2(8%) had obstructive defects. Mean FVC (% predicted) ,DLCO (% of predicted) was 58.2±17.39, 40.76±18.61 respectively. A DLCO below 25% of predicted was measured in 7 (28%) patients. Mean KCO (% pred) was 73.64±22.84. In IPF group (n=26), spirometry abnormalities were observed in 21 (81%) patients, 19(73%) had restrictive defects and 2 (8%) had obstructive defects. Mean FVC (%pred), DLCO(%pred) in this group was 57.42 ± 18.03, 34.57 ± 17.20 respectively. A DLCO below 25% predicted was observed in 9 (35%) patients. Mean KCO (% predicted) in this group was 70.80 ± 29.33. Baseline 6MWT of CTD-ILD and IPF were 312.60 ± 108.11 meters and 239.73 ± 72.60 meters respectively. Initial spo2 (%) in CTD-ILD group was 96.5 ± 2.4 and in IPF group it was 94.7±2.9 %. Compared to CTD–DPLD,

Table 4 Comparison of Various Parameters in IPF Group Top of Form Bottom of Form

Parameter 1	Parameter 2	Correlation Coefficient (r)	p-value
FVC	DLCO	0.2816	0.163
DLCO	KCO	0.7263	<0.0001*
6MWT	FVC	0.54004	0.004*
6MWT	FEV1	0.41846	0.03*
6MWT	KCO	0.41846	0.03*
6MWT	DLCO	0.45673	0.01*

IPF patients had significantly less baseline six-minute walk distance (p=0.00663). No significant difference was found among other parameters. However, the IPF patients had a significantly lower initial and final SpO2 during the 6MWT compared with the CTD-ILD patients (P=0.0198 and P=0.2461 respectively) (Table 2).

In the CTD-ILD group, FVC and FEV1 exhibited a strong positive correlation (r =0.8928, p<0.0001). FVC and DLCO showed a moderate positive correlation (r = 0.5773, p =0.002). DLCO and KCO demonstrated a strong positive correlation (r=0.79676, p< 0.0001). KCO and FVC had statistically significant positive correlation (r=0.3975, p< 0.0001) suggesting that lung volume and gas exchange efficiency are related to some extent. 6MWT did not show any correlation with other physiological parameters (Table 3).

In the IPF group FVC and DLCO showed a weak positive correlation (r=0.2816, p= 0.163), which was statistically not significant. DLCO and KCO demonstrated a strong positive correlation (r=0.7263, p<0.0001). 6MWT and FVC exhibited a moderate positive correlation (=0.54004, p=0.004), suggesting a relationship between six-minute walk distance and forced vital capacity. 6MWT and FEV1 had a weaker but statistically significant positive correlation (r=0.41846, p=0.03), indicating an association between exercise capacity and forced expiratory volume in the first second. Additionally, 6MWT showed moderate correlations with both KCO (r=0.41846, p=0.03) and DLCO (r=0.45673, p=0.01), as detailed in Table 4.

Discussion

This study compared demographic and physiological parameters between IPF and CTD-ILD groups. Fifty-one DPLD cases were studied over a period of two years in the present study. Twenty-six patients were IPF and twenty-five were CTD-ILD. This study showed that, IPF was the more common entity (46.4%) among DPLD cases followed by CTD–DPLD (44.6%). The mean age of IPF cases in the present study was 61.80± 9.01 years. Koo *et al.* conducted a national survey to evaluate whether age affects the survival of patients with idiopathic pulmonary fibrosis (IPF). For this purpose, the authors undertook a study comprising 1,663 patients with IPF. The mean age of cases with IPF in this study was found to be 67.9 years (range, 30–94 years).[9] Similar mean age of cases of IPF was also seen in this study.

The preponderance of males and smokers in the IPF group in this study was similar to the Indian and western literature.[10] Significant difference in age and sex ratio was found between the two groups in this study whereas mean BMI values were found to be comparable in both the groups. CTD-ILD patients were more likely to be young (mean age 48.64 ±15.98 years), female (80%) and non-smokers (8%) compared with IPF group in the present study. similar demographic parameters were found in studies done by Jeganathan *et al.*[11] and Leuschner *et al.*[12] The mean age of CTD-ILD was 57.24 ± 1.55 years which was significantly less than patients with IPF (p<0.05). The percentage of male patients was 31.7% in the CTD-ILD group which was significantly lower than IPF group (69.3%). Percentage of smokers was significantly lower in CTD-ILD group than in the IPF group which indicates that young female ILD patients were more prone to be CTD-ILD patients while older male ILD patients with smoking history were more prone to develop IPF. The present study was supported by a similar study conducted by Margaritopoulos.[13]

In the present study, pulmonary function abnormalities mostly restrictive were observed in 80% patients of CTD-ILD group and 73% patients in IPF group. It is important to note that no significant difference was found in FVC, DLCO and KCO between IPF and CTD-ILD groups of the present study. The observations of authors such as 14. Ciancio *et al.*[14] were similar. In the present study, a positive correlation between FVC and DLCO (r=0.5773, p=0.005) was found in CTD-ILD group which means both the above variables move in same direction in this group of subjects. No positive correlation was found between FVC and DLCO(r=0.2816) in IPF group. A disproportionate reduction in DLCO in IPF group may probably signify coexistent CPFE or pulmonary hypertension in this group.

In IPF group, 6MWT was correlated with FVC, FEV1, KCO and DLCO. Strong positive correlation was found between FVC and 6MWT. These findings suggest that the 6-minute-walk test is a valid, and responsive measure of exercise tolerance in patients with idiopathic pulmonary fibrosis. Hu *et al*.[15] conducted a study to explore the correlation between 6MWT and traditional measures such as pulmonary function and chest computed tomography (CT) and to find out factors that influence the 6-minute walk distance (6MWD).

For this purpose, the authors undertook a study of 73 patients with ILD. All patients underwent 6MWT, pulmonary CT, and pulmonary function tests and their correlations were analyzed. The study found that 6MWD was correlated with forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), diffusing capacity for carbon monoxide (DLCO) and DLCO % pred. The decrease in oxygen saturation (SpO_2) after the test was correlated with FEV1%pred, FVC%pred, TLC, TLC% pred, DLCO, DLCO% pred and the percentage of normal lung calculated by quantitative CT. On the basis of these findings the authors concluded that The 6MWT results were closely correlated with pulmonary function and quantitative CT in patients with ILD.[15]

However, despite its usefulness in global evaluation of exercise capacity in ILD patients 6 MWT does not provide diagnostic information regarding specific causes for dyspnea or exercise limitation, which can only be obtained through more formal cardiopulmonary exercise testing (CPET).

One of the limitations of this study was a small sample size. Larger prospective epidemiological studies are necessary for a better understanding of the spectrum of diffuse parenchymal lung disorders and role of pulmonary function tests in evaluation of disease progression. Additionally, selection bias also cannot be excluded as cases with milder symptoms may not have undergone further investigations for diagnosis of ILD.

In conclusion, this study demonstrated significant demographic differences between IPF and CTD-ILD patients. The 6-minute walk test (6MWT) emerged as an independent functional marker though its prognostic value remains uncertain due to a lack of standardization. FVC and DLCO were found to be most reliable measures for disease monitoring. Simpler tests like 6MWT and FVC were found to be useful in resource-limited settings. However further research is needed to confirm their role in tracking IPF progression and treatment response.

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