Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Determining the Etiology of Progressive Pulmonary fibrosis in an Indian CohorT of Interstitial Lung Disease Patients-the DEPICT ILD prospective study

Rajesh Venkitakrishnan

rajeshdhanya@rediffmail.com

Rajagiri Hospital

Mariyam Beevi

Baby Memorial Hospital

Melcy Cleetus

Rajagiri Hospital

Ramachandran Divya

Rajagiri Hospital

Anand Vijay

Rajagiri Hospital

Hasha Thankam Somson

Rajagiri Hospital

Susan John

Rajagiri Hospital

Research Article

Keywords: Progressive pulmonary fibrosis, antifibrotic therapy, predictors of poor outcome

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11196512/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Introduction:

Non-Idiopathic Pulmonary Fibrosis (Non-IPF) interstitial lung diseases (ILDs) may develop a progressive pulmonary fibrosis (PPF) phenotype. This study evaluated the causes, outcomes, and predictors of adverse outcomes in non-IPF PPF.

Methods: This single-centre prospective cohort study at Rajagiri Hospital, Kochi, enrolled adults with PPF and followed them for 12 months. Baseline clinical, functional, and etiological assessments were performed, with multidisciplinary evaluation. Outcomes included PPF etiology, lung function, exacerbations, hospitalizations, mortality, and antifibrotic treatment-related adverse events.

Results: A total of 104 patients (mean age 64.8 years, 58.7% females) were included. Connective tissue disease–associated interstitial lung disease (CTD-ILD) was the commonest etiologic subtype. Radiologically, usual interstitial pneumonia (UIP) was identified in 46.2% of patients. The mean forced vital capacity and DLCO changed from 67.7% to 62.4% and 56.3% to 49.8%, respectively, from baseline to 12 months. The 55.8% received antifibrotic therapy, of whom 93.10% received nintedanib. The patients experiencing ≥ 2 exacerbations and requiring ≥ 2 hospitalizations per year decreased from 71.2% to 29.3% and 59.6% to 10.6% after treatment, respectively ($P < 0.001$). During the follow-up, 26.9% of patients died. Low baseline oxygen saturation, 6 MWD < 300 metres as baseline ≥ 2 exacerbations at baseline were predictive of poor outcomes.

Conclusion:

CTD related ILD was the most common cause of PPF in the present study. Most patients with PPF continued to have fall in lung functions during follow up. Antifibrotic therapy decreases exacerbation rates in PPF. Poor baseline lung function and frequent exacerbations are predictors of poor outcomes.

Take home message

Connective tissue disease–associated interstitial lung disease was the leading cause of non-idiopathic pulmonary fibrosis progressive pulmonary fibrosis. Antifibrotics reduced exacerbations, low oxygen saturation, 6-minute walk distance.

Introduction

Interstitial lung diseases (ILDs) comprise a heterogeneous group of more than 200 diffuse parenchymal lung disorders characterized by varying degrees of inflammation and fibrosis,

leading to impaired gas exchange, progressive respiratory failure, and premature mortality [1]. Over time, ILD classification has evolved from purely histopathologic descriptions to an integrated, multidisciplinary approach incorporating clinical, radiologic, and, where feasible,

histopathologic data [2–4]. Landmark statements by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) formalized the classification of idiopathic interstitial pneumonias (IIPs) and emphasized the importance of multidisciplinary team discussion in

establishing diagnostic confidence [4, 5]. High-resolution computed tomography (HRCT) now plays a pivotal role in identifying usual interstitial pneumonia (UIP) patterns and enabling a noninvasive diagnosis of Idiopathic Pulmonary Fibrosis (IPF), the prototype progressive fibrosing ILD. Despite these diagnostic advances, substantial challenges persist in cases having overlapping features, interstitial pneumonia with autoimmune features and unclassifiable ILD [6]. Although IPF has been the most intensively studied ILD and is characterized by self- perpetuating fibrosis and progressive declining lung function, it is increasingly recognized that progression is not unique to IPF. Several non-IPF ILDs, including connective tissue disease associated ILDs (CTD-ILDs), chronic hypersensitivity pneumonitis, sarcoidosis, occupational ILDs, idiopathic nonspecific interstitial pneumonia (NSIP), and unclassifiable ILD may follow a progressive pulmonary fibrosis (PPF) phenotype. According to the Contemporary American Thoracic Society/ European Respiratory Society guidelines definition PPF is defined as at least two of the following three criteria occurring within the past year worsening respiratory symptoms, physiological and radiological evidence of disease progression [7].

Disease progression in fibrosing ILDs is most reliably quantified using serial pulmonary

function testing with measurements of forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) as well as serial imaging with HRCT [8, 9]. Risk factors for progression and mortality include older age, male sex, and the presence of a UIP pattern on imaging.

Therapeutically, management paradigms in ILD are shifting from disease-specific to phenotype-driven approaches. Trials have demonstrated that antifibrotic agents such as nintedanib and pirfenidone initially developed for IPF have benefit in non-IPF ILDs exhibiting progressive fibrosing ILDs [8–11]. Despite these advances, data from India regarding the epidemiology, etiologic distribution, progression rates, and therapeutic responses of PPF remain sparse. The absence of robust region-specific evidence limits contextually appropriate prognostication and management strategies. The present study was undertaken to evaluate the etiology, clinical outcomes, predictors of adverse outcomes PPF arising from non IPF-ILDs.

Methods

Study design

This single-centre, prospective, longitudinal observational cohort study was conducted at the Department of Pulmonary Medicine, Rajagiri Hospital, Aluva, Kochi which is a tertiary care centre in Kerala, South India. The study was conducted over a period of 18 months, from March 2022 to September 2023. This included a recruitment phase of 6 months (March to September 2022), followed by a 12-month follow-up period extending from the enrolment of the final participant. The study setting

encompassed both outpatient and inpatient services, thereby facilitating the inclusion of a broad and representative cohort of patients with progressive fibrosing interstitial lung diseases (ILDs).

Ethical considerations

The study protocol was reviewed and approved by the institutional ethics committee

(Reference No: RAJH/2022/035). The name of the ethical committee is Rajagiri Hospital Ethics Committee and is affiliated to Rajagiri hospital, Aluva, Kochi, Kerala, South India. We did not obtain informed consent to participate from the study participants. Since this is an observational study and there was no deviation from standard of care, as per the geographic regulations, need for informed consent for data collection was waived off by Ethics Committee. Patient data were anonymized, and strict confidentiality was maintained throughout the study in accordance with institutional and ethical guidelines. The study complies with the Declaration of Helsinki with regards to the ethical standards.

Study population

Adult patients aged ≥ 18 years with a diagnosis of PPF in fibrotic ILDs other than IPF, willing to initiate antifibrotic therapy with either pirfenidone or nintedanib, and willing to follow up for a minimum duration of one year at the study center were included. The diagnosis of PPF was established based on the 2022 ATS/ERS/JRS/ALAT clinical practice guideline criteria.

Patients with coexisting chronic respiratory conditions such as chronic obstructive pulmonary disease, post-tuberculosis lung fibrosis, or bronchiectasis of known non-ILD etiology were excluded. Patients unable to perform baseline spirometry or diffusion capacity testing, with significant hepatic impairment, pulmonary hypertension requiring parenteral therapy, known immunodeficiency states, and active malignancy were also excluded.

Sampling strategy

A consecutive sampling approach was adopted, whereby all consecutive patients meeting the eligibility criteria during the study period were included. This strategy was employed to minimize selection bias and enhance the external validity of the study findings.

Data collection

Following approval from the institutional ethics committee, eligible patients were

recruited and assigned unique identification numbers to ensure confidentiality. Baseline data

were systematically recorded using a structured and predesigned proforma. Demographic

details, comorbid conditions, comprehensive clinical history and drug history were recorded.

A thorough clinical examination was performed in all patients, with focused assessment for extrapulmonary manifestations suggestive of connective tissue disease or granulomatous disorders such as sarcoidosis. Relevant laboratory investigations, including autoimmune serological panels, were performed. Patients with suspected autoimmune etiologies were evaluated by a rheumatologist.

Radiological and functional assessments at baseline included chest radiography and HRCT of the thorax. The HRCT scans were analyzed for pattern, distribution, and extent of involvement. Pulmonary function testing consisted of spirometry and measurement of DLCO, performed in accordance with standard guidelines. Functional exercise capacity was assessed using the six-minute walk test (6MWT). Prior clinical records, including earlier imaging and pulmonary function data, were reviewed to substantiate the diagnosis of PPF and document evidence of disease progression. 2-dimensional echocardiography was performed by cardiologist.

A multidisciplinary discussion was conducted by pulmonologists, radiologists, pathologists, thoracic surgeons, and rheumatologists to reach a consensus diagnosis, consistent with current best practices in ILD management.

Follow-up and outcome measures

All enrolled patients were followed prospectively at 3-month intervals on an outpatient basis. Unscheduled and emergency department visits were allowed at any time when the patient felt acute worsening beyond day-to-day fluctuations. Patients who failed to attend scheduled visits were contacted telephonically to ensure continuity of follow-up and completeness of data collection. Serial spirometry was performed at 6-month intervals, while HRCT and DLCO assessments were repeated at 12 months to evaluate disease progression.

Antifibrotic therapy with pirfenidone or nintedanib was initiated at the discretion of the

treating physician following shared decision-making with the patient. Clinical outcomes assessed during follow-up included the annual rate of acute exacerbations, longitudinal decline in lung function parameters, all-cause mortality at one year etc.

Acute exacerbations were defined as episodes of clinical deterioration characterized by worsening respiratory symptoms (beyond day-to-day fluctuations) without an identifiable alternative cause.

Adverse events related to antifibrotic therapy were actively monitored through regular clinical assessments and laboratory investigations, including complete blood counts, liver function tests, renal function tests, and serum electrolytes at 3-month intervals.

Primary objective

The primary objective of this study was to identify various underlying etiologies of progressive pulmonary fibrosis in patients with non-IPF interstitial lung diseases.

Secondary objectives

The study aimed to assess the severity of lung function impairment at the time of diagnosis of PPF based on the measurements of FVC (percentage predicted) and diffusion capacity (DLCO-percentage predicted). The study also described the radiological pattern of lung involvement in patients with PPF based on the HRCT findings and assessed the annual decline of lung function at one year after making a diagnosis of PPF. The mortality rate at one year was determined. Further, the annual exacerbation rate and hospitalisation rate at one year of diagnosing PPF with predictors of adverse outcomes in patients were evaluated.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using the Statistical Package for the

Social Sciences (SPSS) software (version 26; IBM Corp., Armonk, NY, USA). Continuous

variables were expressed as mean (standard deviation), whereas categorical variables were

presented as frequencies and percentages. Associations between categorical variables were

analyzed using the chi-square test. Continuous variables were compared using the unpaired t-

test, and comparisons involving more than two groups were performed using one-way analysis of variance (ANOVA). P-value < 0.05 was considered statistically significant.

Results

A total of 150 patients diagnosed with diffuse parenchymal lung disease were

screened during the study period. Of these, 46 patients were excluded based on predefined

criteria. Reasons for exclusion included the presence of coexisting alternative diagnoses such as chronic obstructive pulmonary disease, post-tuberculous fibrosis, bronchiectasis of known etiology (n = 4), and lung malignancy (n = 2). Additionally, 22 patients were diagnosed with IPF following multidisciplinary discussion and were excluded. A further 18 patients did not fulfil criteria for PPF on retrospective evaluation. After exclusions, 104 patients with non-IPF interstitial lung disease demonstrating a progressive fibrosing phenotype were included in the final analysis. The flow of study patients is illustrated in Fig. 1.

Baseline demographic and clinical characteristics

The mean (SD) age at diagnosis was 64.8 (12.5) years. A majority of patients (64.4%, n = 67) were between 61 and 80 years of age. Females constituted 58.7% (n = 61), of the cohort, while males accounted for 41.3% (n = 43). At baseline, the mean body mass index was 24.4 kg/m^2.

With respect to lifestyle factors, 32.7% (n = 34) reported alcohol consumption, whereas 28.0% (n = 29) of patients were current or former smokers. Approximately one-quarter of patients (24%, n = 25) reported both smoking and alcohol use.

More than half of the cohort (52.0%, n = 54) were unemployed. Most patients (88.5%, n = 92) had at least one medical comorbidity. The most common comorbid conditions included systemic hypertension (51.0%, n = 53), diabetes mellitus (47.1%, n = 49), dyslipidemia (29.8%, n = 31), and coronary artery disease (26%, n = 27). Other conditions included hypothyroidism (21.2%, n = 22) and cerebrovascular disease (13.5%, n = 14) (Table 1).

Table 1
Baseline characteristics of study subjects

Characteristics	**Value [N = 104]**
Sex	
Male	43 (41.3)
Female	61 (58.7)
BMI in kg/m² (mean, range)	24.38 (13–37)
Age at diagnosis, years [mean (SD)]	64.84 (12.5)
Age groups	
20–40	5 (4.8)
41–60	22 (21.2)
61–80	67 (64.4)
> 80	10 (9.6)
Smoking and alcohol history	
Never	76 (73.1)
Past	28 (27.0)
Current	1 (1.0)
Alcohol consumer	34 (32.7)
Non-alcohol consumer	70 (67.3)
Both (alcohol+ smoking)	25 (24.0)
Employment	
Unemployed	54 (52.0)
Semi-professionals	22 (21.2)
Professional	19 (18.3)
Unskilled work	9 (8.7)
Comorbidities	
Any comorbidity	**92 (88.5)**
Systemic hypertension	53 (51.0)

Characteristics	Value [N = 104]
Sex	
Diabetes mellitus	49 (47.1)
Dyslipidemia	31 (29.8)
Coronary artery disease	27 (26.0)
Hypothyroidism	22 (21.2)
Dyslipidemia	31 (29.8)
Cerebrovascular accident	14 (13.5)
Obesity (defined as BMI > 30)	5 (4.8)
Chronic kidney disease	5 (4.8)
Pulmonary Function and Clinical Parameters	
FVC	
Mean FVC (% predicted) Mean (SD)	67.69 (19.00)
FVC ≥ 40%	98 (94.2)
FVC ≥ 60%	69 (66.3)
FVC ≥ 80%	31 (29.8)
DLCO	
Mean DLCO (% predicted) Mean (SD)	56.26 (16.9)
DLCO < 40%	13 (12.5)
DLCO ≥ 60%	44 (42.3)
6MWD (m) Mean (SD)	338 (65.0)
6MWT > 300 m (number / %)	78 (75)
SpO_2 > 88% (number of patients / %)	93 (89.4)
GAP Index	
Stage I	63 (60.5)
Stage II	22 (21.1)
Stage III	19 (18.2)
Pulmonary Hypertension (SPAP)	

Characteristics	Value [N = 104]
Sex	
No PAH	57 (54.8)
PAH	47 (45.2)
Radiological Findings	
Non UIP patterns	56 (53.8)
Reticulonodular pattern with volume loss	50 (48.1)
UIP-like fibrotic pattern on HRCT	48 (46.2)
Cystic shadows	10 (9.6)
Pleural effusion / pleural thickening	3 (2.9)
Hilar lymphadenopathy	3 (2.9)
Therapy after diagnosis of ILD	
Prednisolone	73 (70.2)
Immunosuppressants (MMF, MTX)	62 (59.6)
Nintedanib	14 (13.5)
Pirfenidone	4 (42.3)

Data are presented as n (%), unless otherwise specified.

BMI, body mass index; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; GAP, gender-age-physiology; HRC, high-resolution computed tomography; ILD, interstitial lung disease; MMF, mycophenolate mofetil; MTX, methotrexate; 6MWD, 6-minute walk distance; 6MWT, six-minute walk test, PAH, pulmonary arterial hypertension; SD, standard deviation; SPAP, systolic pulmonary artery pressure; SpO_2, peripheral oxygen saturation.

Baseline functional and radiological assessment

At baseline, most patients had moderate impairment of lung function. The mean (SD) FVC was 67.7 (19.00) percentage predicted, and the mean (SD) DLCO was 56.3 (16.9) percent predicted. FVC ≥ 40% predicted was observed in 94.2% (n = 98) of patients, while DLCO ≥ 60% predicted was seen in 42.3% (n = 43) of patients. Approximately 12.5% (n = 13) had severely reduced DLCO (< 40%). The mean (SD) 6 MWD was 338 (65) meters. The majority of patients (75%, n = 78) were able to walk more than 300 meters with the six-minute walk test (6 MWT), and 89.4% (n = 93) maintained oxygen saturation above 88% at rest. Most Patients (60.5%, n = 63) had the Gender-Age-Physiology (GAP) index stage I. Pulmonary arterial hypertension (PAH) was present in 45.2% (n = 47) of patients at baseline. The mean (SD) pulmonary artery pressure at diagnosis of PPF was 35.5 (15.0) mmHg. (Table 1).

Radiological features at baseline

Radiographically, the most common chest X-ray finding was a reticulonodular pattern with volume loss (48.1%). The HRCT demonstrated a UIP pattern in nearly half of the cohort. The UIP pattern was identified in 46.2% (n = 48), followed by fibrotic nonspecific interstitial pneumonia (NSIP) in 37.5% (n = 39) of patients. Bronchiolocentric pattern with expiratory air trapping suggesting hypersensitivity pneumonitis (HP) was seen in 4.8% (n = 5) patients; organizing pneumonia pattern in 2.9% (n = 3); and perilymphatic nodules with lymphadenopathy and superimposed fibrosis was seen in 2.9% (n = 3). Combined pulmonary fibrosis and emphysema feature was found in 1.9% (n = 2) patients despite COPD being an exclusion criterion. Collectively, UIP and fibrotic NSIP accounted for 83.7% (n = 87) of all HRCT patterns observed. Focal ground-glass opacities were identified in 75.0% (n = 78) patients. Features suggestive of established fibrosis were highly prevalent, including traction bronchiectasis in 57.7% (n = 60) patients, and honeycombing in 51.9% (n = 54) patients. Subpleural cystic changes were present in 15.4% (n = 16) patients, whereas consolidation and localized pulmonary nodules were relatively uncommon, occurring in 5.8% (n = 6) and 1.9% (n = 2) patients, respectively.

Subgroup analysis demonstrated distinct HRCT phenotypes across CTD-ILD subgroups. In rheumatoid arthritis-associated ILD, UIP was the dominant pattern, occurring in 23 of 36 patients (63.9%), whereas NSIP was observed in 27.8% (n = 10) patients. In systemic sclerosis-associated ILD, NSIP predominated, accounting for 61.5% of cases, while UIP was identified in 38.5%. Patients with mixed connective tissue disease similarly demonstrated a predominance of NSIP (55.6%), whereas polymyositis/dermatomyositis-associated ILD showed a higher frequency of UIP (66.7%). As expected, most patients with sarcoidosis demonstrated characteristic sarcoid HRCT patterns. The overall radiological profile of the cohort was therefore characterized by extensive fibrotic lung disease, with a predominance of UIP and NSIP patterns and a high prevalence of established fibrotic features such as traction bronchiectasis and honeycombing.

Etiology of progressive pulmonary fibrosis

The underlying etiologies of PPF are summarized in Table 2. Autoimmune-related interstitial lung disease (CTD-ILD) was the most common etiology, accounting for 69.2% (n = 72) of cases. Among these 72 cases, rheumatoid arthritis-associated ILD was the predominant subtype (50.0%, n = 36), followed by systemic sclerosis (18.1%, n = 13) and mixed connective tissue disease (13.8%, n = 10). Other autoimmune etiologies included polymyositis/dermatomyositis (8.3%, n = 6), systemic lupus erythematosus (5.5%, n = 4), and Sjögren's syndrome (4.1%, n = 3). The IIP accounted for 14.4% (n = 15) cases, while chronic fibrotic hypersensitivity pneumonitis comprised 9.6% (n = 10). Less common causes included sarcoidosis (2.9%, n = 3) and drug-induced ILD (75%, n = 3).

Table 2
Underlying etiologies in subjects with PPF

Etiologies	Patient (n = 104)
Chronic fibrosing hypersensitivity pneumonitis	**10 (9.6)**
Idiopathic interstitial pneumonia	**15 (14.4)**
Familial idiopathic interstitial pneumonia	2 (13.3)
Non-Familial idiopathic interstitial pneumonia	13 (86.7)
Sarcoidosis	**3 (2.9)**
Autoimmune ILD	**72 (69.2)**
Rheumatoid arthritis-ILD	36 (50.0)
Systemic sclerosis ILD	13 (18.06)
Dermatomyositis/Polymyositis-ILD	6 (8.33)
Mixed connective tissue disease-ILD	10 (13.8)
Systemic lupus erythematosus	4 (5.5)
Sjogren's syndrome	3 (4.1)
Other ILDs	**4 (3.8)**
Drug induced	3 (75)
Silicosis	1 (25)
Data are presented as n (%). ILD, interstitial lung disease.	

A gender-based distribution revealed a predominance of CTD-ILD among females (62.5%); males with CTD-related ILD and PPF tended to present later in life, with 75% diagnosed between 60 and 80 years. Idiopathic NSIP demonstrated male predominance (2:1), while hypersensitivity pneumonitis showed a relatively balanced gender distribution among both sexes.

Lung function at follow-up

At 12 months, follow-up pulmonary function data were available for 72 patients. 28 patients expired during the follow-up visit, and 4 patients could not perform satisfactory spirometry and/or DLCO testing. The mean (SD) FVC changed from 67.69 (19.0%) at baseline to 62.43 (17.82%) at 1 year (mean change: 5.06%). At one year, 88.0% (n = 91) of patients maintained an FVC ≥ 40% predicted, while 59.7% (n = 62) had FVC values ≥ 60% predicted. A clinically significant decline in lung function was observed in a

substantial proportion of patients. An absolute decline in FVC ≥ 10% was noted in 52.8% (n = 38) patients, while 12.5% (n = 9) demonstrated a decline of 5–10%. A smaller proportion (23.6%) exhibited minimal decline (< 5%), whereas 11.1% showed improvement in FVC over the follow-up period. The mean (SD) DLCO at 12 months was 49.76 (18.43%) of predicted. Among the cohort, 31.9% had DLCO ≥ 60% predicted, while 27.8% had values < 40%. A decline in DLCO ≥ 15% was observed in 48.6% (n = 35) of patients, whereas 18.1% (n = 13) had a lesser decline (< 15%). No substantial change was observed in 27.8% (n = 20), and only 5.6% (n = 4) demonstrated improvement in DLCO.

Clinical outcomes at follow-up

Clinical outcomes were assessed using an intention-to-treat approach in all 104 patients.

The majority of patients (71.2%, n = 74) experienced ≥ 2 exacerbations annually, while 28.8% (n = 30) had fewer than two exacerbations per year. Similarly, 59.6% (n = 62) of patients required ≥ 2 hospitalizations per year. 55.8% (n = 58) received antifibrotic therapy, of whom 93.10% (n = 54) received nintedanib, while 44.2% (n = 46) did not receive antifibrotic treatment based on a shared decision-making session.

Among the 58 patients who received antifibrotic therapy, all had a history of ≥ 2 exacerbations in the year before treatment initiation. At one year following initiation of antifibrotic therapy, a significant reduction in disease-related events was observed. The proportion of patients experiencing ≥ 2 exacerbations decreased to 29.3% after treatment, with 70.7% achieving fewer than 2 exacerbations annually (P < 0.001). Likewise, the proportion of patients requiring ≥ 2 hospitalizations per year declined significantly from 59.6% to 10.6%, representing a relative reduction of approximately 73% (P < 0.001). These findings demonstrate a substantial reduction in exacerbation frequency and hospitalization burden (Fig. 2).

During the follow-up period, 26.9% (n = 28) of patients died. Complete pulmonary function data at 12 months were available in 69.2% of patients (n = 72).

Predictors of adverse outcomes

We defined a composite adverse outcome of mortality, >/= 2 exacerbations or one hospitalisation (at least one out of 3). On multivariable analysis, baseline oxygen saturation < 88% (OR 132.16; 95% CI: 13.15-1328.64; P < 0.001), 6MWD < 300 m with exertional desaturation (OR 37.96; 95% CI: 3.98-361.72; P = 0.002), increasing age (P = 0.033), a relative decline in DLCO > 15% (OR 0.24; 95% CI: 0.08–0.77; P = 0.016), exacerbations in the previous year (≥ 2 per year) (OR 168.96; 95% CI: 1.21-23614.83; P = 0.042), and higher HRCT fibrosis scores (OR 7.00; 95% CI: 1.09–45.11; P = 0.041) were associated with poor outcomes (Table 3, Fig. 3).

Table 3
Predictors of progressive pulmonary fibrosis: univariate logistic regression analysis

Parameter	Odds Ratio (95% CI)	P-value
Age	0.097 (1.007–1.196)	0.033
Sex	0.956 (0.127-7.200)	0.965
Occupation	0.392 (0.084–1.829)	0.233
Smoking	0.534 (0.070–4.084)	0.545
Alcohol	0.693 (0.074–6.475)	0.748
No of exacerbations	168.963 (1.209-23614.832)	0.042
No of hospitalization	0.089 (0.003–2.829)	0.170
SpO_2 at baseline (< 88%)	132.164(13.147-1328.644)	< 0.001
6MWD	37.963 (3.984-361.719)	0.002
Pulmonary hypertension	0.279 (.069-1.122)	0.072
GAP Index	3.505 (0.924–13.297)	0.065
HRCT score	7.000 (1.086–45.113)	0.041
Baseline FVC	0.958 (0.905–1.015)	0.144
DLCO_baseline	1.042 (0.948–1.147)	0.392
Progression in CT chest	0.000 (0.000- 1.249×10^{180})	0.951

CI, confidence interval; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; GAP, gender-age-physiology, HRCT, high-resolution computed tomography; ILD, interstitial lung disease; PF, progressive fibrosing; SPO_2, peripheral oxygen saturation

Relation between etiology and mortality

Among the etiological subgroups, patients with RA-ILD constituted the largest group (n = 36), with 12 deaths, corresponding to a mortality rate of 33.3%. In the IIP subgroup (n = 15), 6 deaths were recorded, yielding the highest mortality rate of 40%. In contrast, patients with chronic fibrotic hypersensitivity pneumonitis (n = 10) demonstrated the lowest mortality, with only one death (10%). Mortality comparisons for other ILD subtypes were not performed due to limited sample size. Survival analysis using the Kaplan-Meier method demonstrated a median survival

duration of 19.57 months for the overall cohort. Despite numerical differences in mortality rates

across subgroups, there was no statistically significant difference in survival between etiologies

(log-rank test, P = 0.874). However, a trend toward improved survival was observed in patients

with chronic fibrotic hypersensitivity pneumonitis compared to other subgroups (Fig. 4). Furthermore, no significant differences were identified in exacerbation rates or hospitalization frequency across the various etiological categories.

Discussion

This prospective cohort study evaluated 104 patients with non-IPF ILD exhibiting a PPF

phenotype over a one-year follow-up period. The findings provide important insights into the

demographic profile, etiological spectrum, disease behavior, and predictors of adverse

outcomes in a real-world Indian setting, while also allowing comparison with existing

international data.

The mean age of the patients in this study was 64.8 years, with the majority of patients

belonging to the 61–80 year age group. This is comparable to previously reported cohorts, including the INBUILD trial (mean age 65.8 years) and other observational studies from Korea and Europe, where the mean or median age ranged between 58 and 63 years [9, 12]. The

relatively older age distribution reflects the chronic and slowly progressive nature of fibrosing

ILDs. A female predominance (58.7%) was observed, which contrasts with some studies reporting a more balanced or male-predominant distribution. This difference is likely

attributable to the higher proportion of CTD-ILD in our study, as autoimmune disorders are more prevalent among females.

A high burden of comorbidities was noted, with 88.5% of patients having at least one

associated medical condition. Systemic hypertension and diabetes mellitus were the most

common, consistent with other Indian papers [13]. The relatively higher prevalence of coronary artery disease in this study may be explained by the older population. The most striking observation was the predominance of CTD-ILD as the etiology of PPF, accounting for 69.2% of cases. This proportion is much higher than that reported in earlier PROGRESS study (46.7%) [14]. This finding may be a direct result of the fact that this study employed a comprehensive autoantibody testing panel which facilitates identification of underlying CTD in patients otherwise classified as idiopathic NSIP. There may be a degree of referral bias associated with a well-established rheumatology service, which would have contributed to a high proportion of CTD-ILD cases. Regular and meticulous longitudinal follow-up of CTD patients employing annual HRCT and lung function measurement would have enabled earlier recognition

and documentation of progressive fibrosing disease. The detection of sarcoidosis cases at an early stage followed by prompt immunomodulation in deserving cases would have led to stability in lung fibrosis and prevented PPF, thus explaining a very small percentage of sarcoidosis patients in the current study.

During the follow-up period, 28 patients (26.9%) died, and 4 patients (3.8%) were lost to follow-up. Complete pulmonary function data at 12 months were available for 72 patients (69.2%). The observed mortality and attrition rates highlight the progressive nature and substantial mortality associated with progressive fibrosing ILD in routine clinical practice.

Within CTD-ILD, rheumatoid arthritis–associated ILD (RA-ILD) was the most common subtype (34.6%), followed by systemic sclerosis and mixed connective tissue disease. This pattern is consistent with other studies [13, 15, 16], where RA-ILD frequently represents the leading autoimmune ILD subtype. These differences likely reflect geographic, environmental, and genetic variability. The IIPs (14.4%) and chronic fibrotic HP (9.6%) were the next most common etiologies in this study. Etiology did not significantly influence survival outcomes, supporting the concept that disease behavior (progressive fibrosis phenotype) may be more prognostically relevant than underlying etiology.

The mean baseline FVC was 67.7% predicted and DLCO was 56.3% predicted, indicating moderate functional impairment. These values are comparable to those reported in the INBUILD trial [9]. The PAH was present in 45.2% of patients, highlighting the advanced disease stage in a significant subset. Similar observations have been made in other studies, where PAH is associated with worse prognosis and increased mortality [15].

The mean FVC declined by approximately 5% over one year, indicating substantial disease progression even within a relatively short duration. It also underscores the fact that progressive fibrosis continues in the follow up years also despite antifibrotic therapy. The exacerbation and hospitalization burden were high, with over 70% of patients experiencing two or more exacerbations annually. Mortality at one year was 26.9%, which is consistent with previously reported PPF cohorts [12]. Importantly, as previously mentioned, survival analysis did not reveal significant differences across etiological subgroups, reinforcing the paradigm that progressive fibrosis, rather than underlying disease category, determines outcomes.

A significant proportion of patients received antifibrotic therapy (pirfenidone or

nintedanib), often in combination with immunosuppressants. Notably, patients receiving

antifibrotics demonstrated a reduction in exacerbation and hospitalization rates. These findings

are consistent with evidence from the INBUILD trial [9], which demonstrated that nintedanib

significantly reduces the rate of FVC decline across a broad spectrum of progressive fibrosing

ILDs. No significant differences were identified in exacerbation rates or hospitalization frequency across the various etiological categories. These findings suggest that, while baseline etiology may influence crude mortality rates, disease progression and outcomes in progressive fibrosing ILD are largely independent of the underlying diagnosis.

Limitations of the study

This study has several limitations. This was a single-center study conducted over a

relatively short duration, resulting in a modest sample size, which limits its generalizability.

Second, the follow-up period of one year may not adequately capture long-term disease

behavior or the sustained effects of antifibrotic therapy. The absence of a predefined sample size calculation further limits the statistical robustness of the findings. Therapeutic heterogeneity was present, as initiation and choice of antifibrotic agents were individualized based on clinician judgment and patient preference. Finally, histopathological confirmation was obtained only in a minority, and diagnoses relied on a robust multidisciplinary discussion involving clinical, laboratory, and radiological assessment.

Conclusion

The commonest etiology of PPF noted in the present study was CTD-ILD and RA-ILD was the leading subtype. Baseline lung function indicated significant functional impairment at presentation itself and progressive fibrosis perpetuated in the follow up year too. UIP-like pattern was observed radiologically in many patients. Antifibrotic therapy was associated with a reduction in exacerbation and hospitalization rates. Baseline hypoxemia, reduced exercise capacity, DLCO decline, exacerbations, and higher HRCT fibrosis scores predicted adverse outcomes. Early identification of the PPF phenotype, high-risk subgroups, and timely initiation of antifibrotic therapy may improve outcomes. Future multicentric studies and ILD registries are essential to better define regional disease patterns and optimize management strategies.

Abbreviations

ILD
interstitial lung disease
IPF
Idiopathic pulmonary fibrosis
PPF
progressive pulmonary fibrosis
CTD
connective tissue disease

RA
rheumatoid arthritis
HRCT
high resolution computed tomography
UIP
usual interstitial pneumonia
NSIP
Non specific interstitial pneumonia
FVC
Forced vital capacity
DLCO
Diffusion capacity for carbon monoxide

Declarations

Ethics approval – approved by the Rajagiri Hospital Ethical Committee – letter number RAJH/2022/035. The study complies with the Declaration of Helsinki with regards to the ethical standards.

Consent to participate – We did not obtain informed consent to participate from the study participants. Since this is an observational study and there was no deviation from standard of care, as per the geographic regulations, need for informed consent for data collection was waived off by Ethics Committee.
Consent for publication – Since the study presents no identifying images or other personal / clinical details of participants that compromise anonymity, the need for publication consent was waived off by ethical committee
Availability of data and materials – The dataset supporting the conclusions of this article is available with Rajagiri Hospital Medical Records Department. The obtaining the raw data analysed in this study, Dr Rajesh Venkitakrishnan, the corresponding author may be contacted.

Email id – rajeshdhanya@rediffmail.com

Contact number – 91-9745501976
Competing Interests – Nil
Funding – Nil
Authors' contributions

Rajesh Venkitakrishnan: Conceptualization, study design, clinical supervision, and critical revision of the manuscript. Mariyam Beevi: Data collection, clinical evaluation, and critical revision of the manuscript. Melcy Cleetus: Data collection, clinical evaluation, data analysis, and manuscript drafting. Divya R: Data collection, clinical evaluation, and manuscript drafting/revision. Anand Vijay: Clinical evaluation, data interpretation, and critical revision of the manuscript. Hasha Thankam Somson: Data collection, clinical

evaluation, and critical revision of the manuscript. Susan John: Study design, statistical analysis, data interpretation, and critical revision of the manuscript. All authors contributed to the final approval of the manuscript and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of the work were appropriately investigated and resolved.

Acknowledgement: None to mention

References

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68.
2. Yagihashi K, Huckleberry J, Colby TV, et al. Radiologic–pathologic discordance in biopsy-proven usual interstitial pneumonia. Eur Respir J. 2016;47(4):1189–97.
3. Hutchinson JP, Fogarty AW, McKeever TM, et al. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. Am J Respir Crit Care Med. 2016;193(10):1161–7.
4. Ryerson CJ, Adegunsoye A, Piciucchi S, et al. Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement. Eur Respir J. 2025;66(6):250015.
5. Fischer A, Antoniou KM, Brown KK, et al. ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976–87.
6. Wells AU, Brown KK, Flaherty KR, et al. Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J. 2018;51(5):1800692.
7. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18–47.
8. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718–27.
9. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, Moua T, Crestani B, Wuyts WA, Stowasser S, Quaresma M, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020;8(5):453–60.
10. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021;9(5):476–86.
11. Distler O, Highland KB, Gahlemann M, Azuma A, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019;380(26):2518–28.

12. Kwon BS, Choe J, Chae EJ, et al. Progressive fibrosing interstitial lung disease: prevalence and clinical outcome. Respir Res. 2021;22(1):282.
13. Khanna A, Jose AP, Deshmukh K, et al. Clinico-Radiological Profile of Patients with Connective Tissue Disease (CTD) Associated Interstitial Lung Disease (ILD) At a Tertiary Care Center in India. J Pulmonol Res Rep. 2023;5(2):1–4.
14. Nasser M, Larrieu S, Si-Mohamed S, et al. Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study). Eur Respir J. 2021;57(2):2002718.
15. Chen X, Guo J, Yu D et al. Predictors of Mortality in Progressive Fibrosing Interstitial Lung Diseases. Front Pharmacol. 2021;12:754851. 10.3389/fphar.2021.754851. PMID: 34712141; PMCID: PMC8546258.
16. Kim K, Lee J, Jo YS. Factors for progressive pulmonary fibrosis in connective tissue disease-related interstitial lung disease. Ther Adv Respir Dis. 2023;17:17534666231212301.

Figures

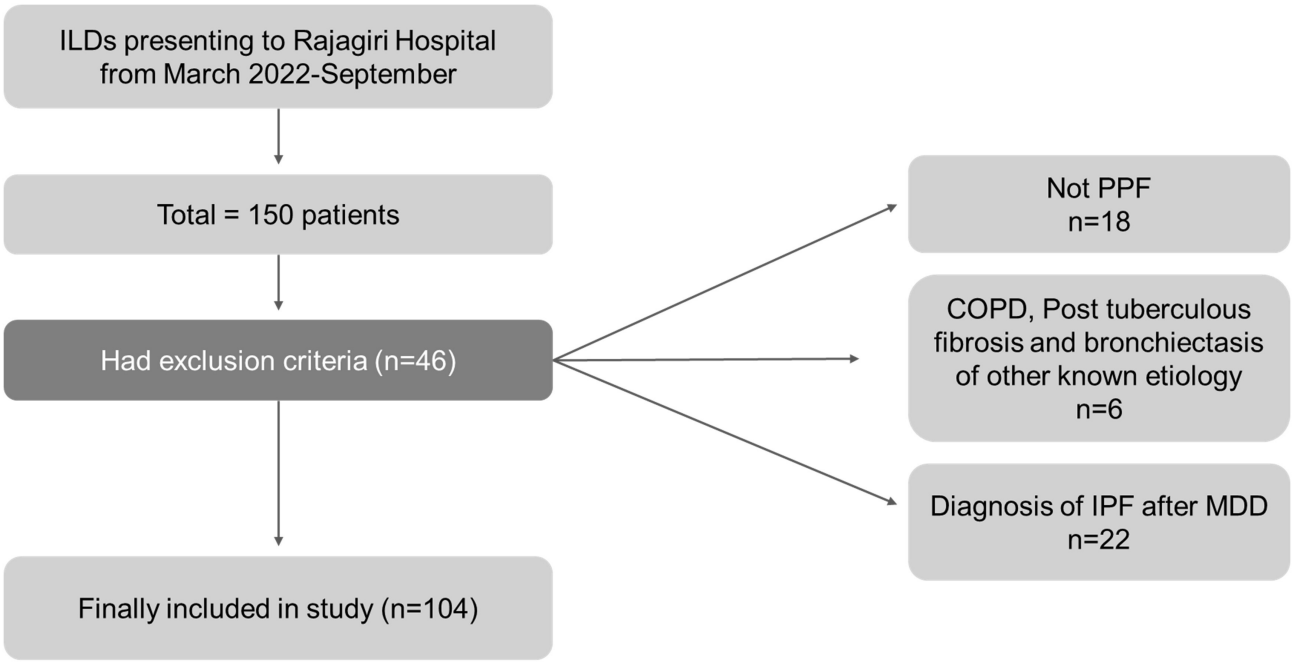


FIGURE 1. Flow of patient recruitment

Figure 1

Flow chart of patient recruitment

COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; MDD, major depressive disorder; PPF, progressive pulmonary fibrosis.

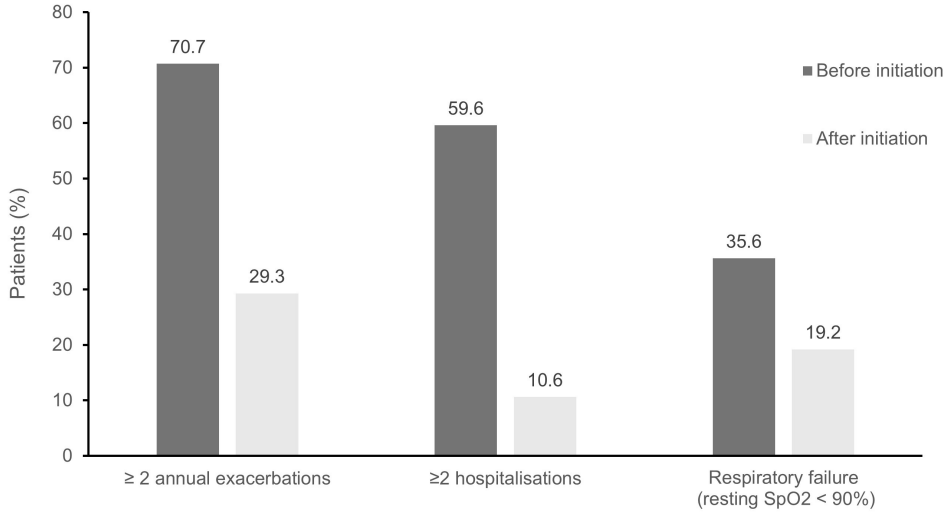


Figure 2

Effect of antifibrotic therapy on A. Exacerbations B. Hospitalizations, and C. Respiratory failure in progressive pulmonary fibrosis.

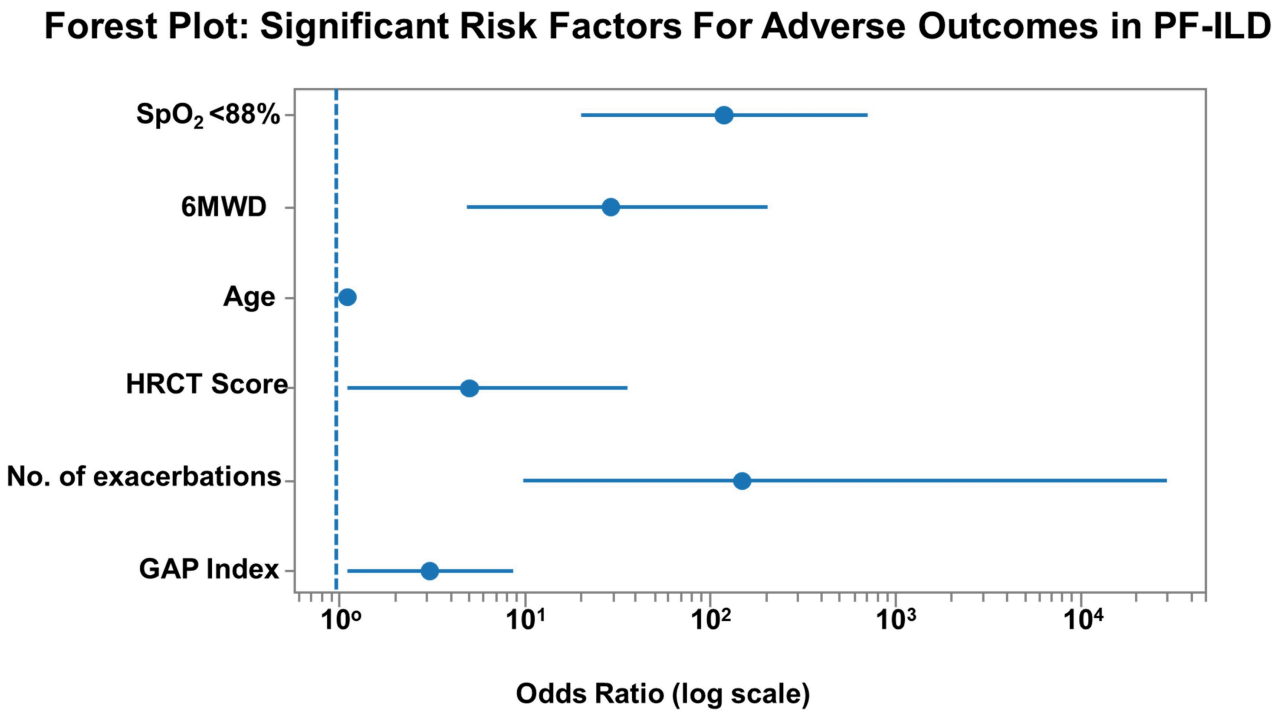


Figure 3

Forest plot: Significant risk factors for adverse outcomes in PF-ILD.

GAP, gender-age-physiology; HRCT, high-resolution computed tomography; PF-ILD, pulmonary fibrosis interstitial lung diseases; 6MWD, 6-minute walk distance; $SPO_{2,}$ peripheral oxygen saturation

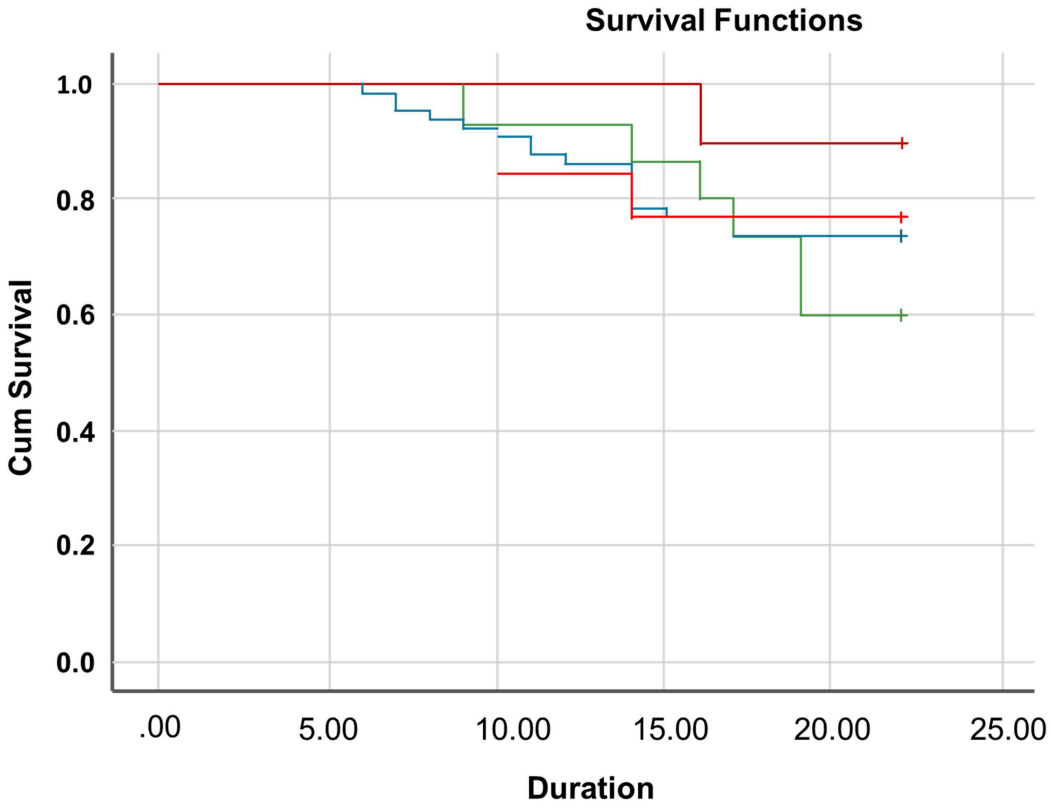


Figure 4

Kaplan-Meier survival curves stratified by ILD etiology.

ILD, interstitial lung diseases.