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Prevalence and Characteristics of Progressive Fibrosing Interstitial Lung Disease in a Prospective Registry

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Key words:

interstitial lung disease, disease prevalence, progressive fibrosis

Take home message:

In the setting of fibrotic ILD, disease progression was observed in 50% of prospectively evaluated patients at 24 months. Highest rates were seen in those with IPF (59%) and HP (58%), followed by U-ILD (51%) and CTD-ILD (45%).

Abstract

Rationale

Progressive fibrosing interstitial lung disease (PF-ILD) is characterized by progressive physiologic, symptomatic, and/or radiographic worsening. The real-world prevalence and characteristics of PF-ILD remain uncertain.

Methods

Patients were enrolled from the Canadian Registry for Pulmonary Fibrosis between 2015-2020. PF-ILD was defined as a relative forced vital capacity (FVC) decline ≥10%, death, lung transplantation, or any 2 of: relative FVC decline ≥5 and <10%, worsening respiratory symptoms, or worsening fibrosis on computed tomography of the chest, all within 24 months of diagnosis. Time-to-event analysis compared progression between key diagnostic subgroups. Characteristics associated with progression were determined by multivariable regression.

Results

Of 2,746 patients with fibrotic ILD (mean age 65±12 years, 51% female), 1,376 (50%) met PF-ILD criteria in the first 24 months of follow-up. PF-ILD occurred in 427 (59%) patients with idiopathic pulmonary fibrosis (IPF), 125 (58%) with fibrotic hypersensitivity pneumonitis (HP), 281 (51%) with unclassifiable ILD (U-ILD), and 402 (45%) with connective tissue disease-associated ILD (CTD-ILD). Compared to IPF, time to progression was similar in patients with HP (hazard ratio [HR] 0.96, 95% confidence interval, CI 0.79-1.17), but was delayed in patients with U-ILD (HR 0.82, 95% CI 0.71-0.96) and CTD-ILD (HR 0.65, 95% CI 0.56-0.74). Background treatment varied across diagnostic subtypes with 66% of IPF patients receiving antifibrotic therapy, while immunomodulatory therapy was utilized in 49%, 61%, and 37% of patients with CHP, CTD-ILD, and U-ILD respectively. Increasing age, male sex,

gastroesophageal reflux disease, and lower baseline pulmonary function were independently associated with progression.

Interpretation

Progression is common in patients with fibrotic ILD, and is similarly prevalent in HP and IPF. Routinely collected variables help identify patients at risk for progression and may guide therapeutic strategies.

Introduction

Fibrotic interstitial lung diseases (ILDs) are a spectrum of lung disorders characterized by fibrosis of the lung parenchyma. Fibrosis represents a final common pathway for conditions that can originate through distinct pathophysiological mechanisms, including autoimmunity, granulomatous inflammation, organic and inorganic dust exposure, and other insults.[1] Such triggers precipitate the activation of fibroblasts and myofibroblasts, leading to exuberant extracellular matrix deposition and the subsequent fibrotic remodeling of the lung parenchyma. Amongst other risk factors, genetic predisposition and aging-related biological mechanisms appear to affect the fibrogenic response in the lungs independent of the initial cause.[2,3]

An important subset of patients with fibrotic ILD experience progressive clinical, physiological, and radiographic decline, with an associated reduction in quality of life and survival despite conventional therapies. Idiopathic pulmonary fibrosis (IPF) is often described as the prototypical fibrotic ILD, however, other ILD subtypes can have a similar poor prognosis.[1] Furthermore, the prevalence of the PF-ILD phenotype in a modern IPF cohort, managed with antifibrotic therapy, has not been robustly evaluated to date.

The INBUILD trial demonstrated the efficacy of the tyrosine-kinase inhibitor nintedanib to attenuate the rate of forced vital capacity (FVC) decline in patients with non-IPF PF-ILD.[4] The rate of FVC decline measured in this trial was comparable to that observed in patients with IPF based on a comparative analysis of the placebo arms of INBUILD with INPULSIS (a randomized controlled trial studying the effect of nintedanib in IPF).[5] Given the strength of this collective evidence, nintedanib has been approved by many regulatory bodies for patients with PF-ILD. Outside of the constraints of a clinical trial, however, robust data regarding the epidemiology and natural history of the PF-ILD phenotype are limited, and external validation in prospective cohorts is required. In a recent retrospective, single-centre analysis, Nasser *et al*, reported a PF-ILD prevalence of 27.2% in a non-IPF ILD population.[6] Similarly, survey data from multiple countries estimate that progressive fibrosis may occur in 14-32% of patients with non-IPF ILD.[7,8]

Our study aims to evaluate the prevalence, clinical characteristics, and outcomes of the PF-ILD phenotype, and its individual components, in a national, multi-centre, prospective fibrotic ILD registry. We sought to identify baseline factors associated with the PF-ILD phenotype that will better inform clinical decision making for patients with fibrotic ILD.

Methods

Study population

Patients enrolled in the Canadian Registry for Pulmonary Fibrosis (CARE-PF) were studied.[9] CARE-PF is a prospective cohort of patients with fibrotic ILD of any subtype, recruited from eight specialized ILD centres, who are ≥18 years old, and able to provide consent and complete questionnaires in English or French. All patients in the registry were eligible for inclusion, starting from the date of enrollment of the first participant (November 2015) to the date of data extraction (December 2020). Ethics approval was obtained by the research ethics boards at each participating site. Informed consent was obtained from patients at the time of study enrolment.

Data collection and measurements

Baseline characteristics were collected at enrollment into CARE-PF, and included details on demographics, medical history, smoking history, medication use, and family history of ILD, determined by robust clinical chart review and self-reported patient questionnaire. Lung function parameters including FVC (L), forced expiratory volume in 1 second (FEV_1, L) and diffusing capacity for carbon monoxide (DLCO, ml/min/mmHg) were captured serially as clinically indicated. Baseline values nearest to the date of ILD diagnosis were used to calculate the ILD-Gender-Age-Physiology (GAP) score, a validated prognostic risk score for patients with ILD.[10] 6-minute walk distance (6MWD) and right ventricular systolic pressure (RVSP) on echocardiography were also collected nearest to the time of diagnosis. Immunomodulatory and antifibrotic medication use or non-use within 24 months of diagnosis was captured. Date of ILD diagnosis was determined as the date of first evidence of fibrotic ILD on high resolution computed tomography (HRCT), or the date of surgical lung biopsy confirming ILD diagnosis if performed.

ILD diagnoses were established by the treating ILD specialist. In the event of diagnostic uncertainty, multi-disciplinary review was conducted with chest radiologists and, if applicable, lung pathologists. IPF was diagnosed according to guideline criteria available at the time of diagnosis.[11,12] Fibrotic hypersensitivity pneumonitis (HP) was diagnosed based on clinical history, radiographic pattern and, if applicable, pathological confirmation given the absence of available clinical practice guidelines at the time of patient enrolment. Patients without a confident diagnosis (<50% confidence) were considered to have unclassifiable ILD (U-ILD).[13] Patients meeting the proposed research criteria for interstitial pneumonia with autoimmune features (IPAF) were also considered to have U-ILD.[14] Connective tissue disease-associated ILD (CTD-ILD) required the confirmation of an underlying CTD that was thought to be associated with the fibrotic ILD. A diagnosis of idiopathic non-specific interstitial pneumonia (iNSIP) required confirmation by surgical lung biopsy.[15] Patients with fibrotic ILD secondary to other causes (e.g. sarcoidosis, asbestosis) were included in the analysis and grouped into a category labelled “Other” ILD.

Outcome assessment

The primary outcome was time to first event meeting PF-ILD criteria within the 24-month time period following ILD diagnosis.[4] PF-ILD events were defined as: a relative forced vital capacity (FVC) decline ≥10%, death, lung transplantation or any 2 of: relative FVC decline ≥5 and <10%, worsening respiratory symptoms, or worsening fibrosis on HRCT. Symptomatic progression was assessed based on the detailed review of all available clinical notes from the patient’s clinical chart, and required interpretation and judgement on behalf of the site investigators. Key terms that were assessed include: breathlessness, dyspnea, shortness of breath, respiratory symptoms, cough, functional capacity, functional ability, exercise capacity, exercise ability, increased oxygen use, and increase in MRC dyspnea scale to a higher number. A transient episode of clinical worsening < 1 month in duration was not considered sufficient to meet this criterion. Patients could only meet the “radiographic progression” criteria in the event that a repeat CT within 24-months of ILD diagnosis showed worsening fibrosis (allowing observations up to 27 months to account for variable follow-up intervals). This was documented in the clinic letters/notes/referrals or in radiology reports. Direct review of the images was at the discretion of the site investigator. Key terms included worsening fibrosis, honeycombing, interstitial changes, reticulation, architectural distortion, and traction bronchiectasis.

We included all-cause mortality and lung transplantation as a PF-ILD criterion to account for patients who may have had a rapid clinical deterioration that was not captured by serial physiologic/clinical/radiographic assessment. The FVC measurement nearest to the ILD diagnosis date was used as the reference point for determining FVC decline. Meeting the death or transplant criterion only applied to those not previously meeting any other PF-ILD criteria. The remaining patients were classified as non-progressors.

Statistical analysis

Descriptive analyses of patient characteristics were assessed using standard summary statistics. Differences in baseline characteristics between PF-ILD and non-progressors were compared using the $\chi 2$ test for categorical variables, by Student's t-test for normally distributed variables, and by the Mann-Whitney test for non-normally distributed continuous variables. Time-to-event models, to determine time to progression from diagnosis, were constructed using Cox proportional hazards models. Exploratory analyses were conducted to identify factors associated with PF-ILD. Unadjusted analyses followed by multivariable analysis were performed including age, sex, ethnicity, smoking history, family history, comorbidities, history of surgical lung biopsy, and baseline pulmonary function testing as covariates. Thresholds used to categorize physiologic variables were based on guideline recommendations and key values derived from the existing fibrotic ILD literature. The relationship between ILD diagnosis and time to PF-ILD event was evaluated by Kaplan-Meier time-to-event curves. The relative contribution of each component of the PF-ILD definition was also assessed. A sensitivity analysis excluded mortality and lung transplantation in the criteria for PF-ILD. The proportion of patients excluded from the analysis due to missing data was compared across ILD diagnoses to determine if missing data were balanced across these subgroups. Subgroup analyses were performed to identify variables associated with time to progression for individual ILD subtypes. Statistical analyses were performed using STATA version 15 (Stata Corporation, College Station, TX, USA).

Results

Baseline characteristics and incidence of PF-ILD

In total, 2,746 patients (mean age 65±12 years, 51% female) had fibrotic ILD with data available for assessment of PF-ILD as defined above. Criteria for PF-ILD were met in 1,376 (50%) within 24 months of diagnosis, including 59% of all patients with IPF, 58% with fibrotic HP, 51% with U-ILD, and 45% with CTD-ILD. Patients with diagnoses other than these major categories were least likely to show progression (39%). **Table 1** displays and compares the baseline characteristics of PF-ILD and non-progressors.

Contribution of individual components of the PF-ILD definition

The PF-ILD phenotype was most commonly established based on the presence of an FVC decline ≥10% over 24 months (675, 49% of PF-ILD patients). Death occurred in 61 patients who did not meet any other PF-ILD criteria prior to their death, accounting for 4% of PF-ILD cases. Contributions of the other criteria are outlined in **Table 2**. There were 85 patients classified as PF-ILD using symptom and radiographic progression criteria who were missing serial FVC data.

Clinical characteristics of PF-ILD

Compared to non-progressors, patients with PF-ILD were slightly older, more often male, had a higher cumulative pack-year smoking history in ever-smokers, were more likely to have a history of coronary artery disease or gastroesophageal reflux disease, and had lower baseline predicted FVC, baseline predicted DLCO and 6MWD. In the 1,140 patients with echocardiographic data, patients with PF-ILD had higher median RVSP. Baseline ILD-GAP scores were higher in patients with PF-ILD (**Table 1**).

Table 3 describes the distribution of PF-ILD by underlying diagnosis. In the CTD-ILD group, criteria for PF-ILD were met in a similar percentage of patients with systemic sclerosis, rheumatoid arthritis, myositis, undifferentiated CTD, and mixed CTD (42-49% of patients progressed). Progression was less common in patients with Sjogren's disease and systemic lupus erythematosus (25-37% of patients progressed). Amongst patients with other types of fibrosing ILD, those with idiopathic NSIP, occupational ILD, and smoking-related ILD had higher rates of progression (41-56%) compared to those with sarcoidosis and drug-induced ILD (31-32%). **Supplementary Appendix Table 1** details the distribution of immunosuppressive and antifibrotic use amongst diagnostic subgroups. As expected in a real-world population, treatment varied across diagnostic subtypes. Antifibrotic therapy was only utilized in the setting of IPF where 66% of patients received therapy with either nintedanib or pirfenidone. Immunomodulatory therapy was utilized in 49%, 61%, and 37% of patients with CHP, CTD-ILD, and U-ILD respectively. Statistical analyses further exploring these findings were not performed given the presence of significant confounding by indication.

Factors associated with progression in PF-ILD

Compared to patients with IPF, time to progression was similar in HP (hazard ratio [HR] 0.96, 95% confidence interval, CI 0.79-1.17), but was delayed in CTD-ILD (HR 0.65, 95% CI 0.56-0.74), and U-ILD (HR 0.82, 95% CI 0.71-0.96) (**Table 4**). Kaplan-Meier curves for risk of progression are shown in **Figure 1**. Progression rates were similar for all ILD subtypes in a sensitivity analysis that excluded death within 24 months as a PF-ILD event (**Supplementary Appendix Table 2**). There were 219 patients excluded from the analysis due to missing data

(**Supplementary Appendix Figure 1**), with missingness balanced across ILD subtypes (**Supplementary Appendix Table 3**).

Variables associated with progression on unadjusted analysis included increasing age, male sex, higher pack-year smoking history, history of GERD, and reduced baseline FVC and DLCO (**Table 5**). The median time from initial lung function measurement to baseline timepoint was 19 days. In a multivariable model, increasing age, male sex, history of GERD, reduced baseline FVC <70% predicted, and DLCO <75% predicted remained associated with progression. When assessing factors associated with progression, there was no detectable difference in the rate of progression comparing patients with HP who had or did not have an identifiable exposure. Similar results were observed across all relevant diagnostic subgroups.

Discussion

This study represents the largest analysis evaluating ILD progression, and the PF-ILD phenotype, across the spectrum of all fibrotic ILDs. Our results show that progression of fibrotic ILD, as defined by clinical, radiographic, and physiologic criteria, occurs in approximately 50% patients at 24 months, with the highest rates in those with IPF and HP, followed by U-ILD and CTD-ILD. Variables associated with progression include increasing age, male sex, a history of GERD, baseline FVC below 70% predicted, and DLCO below 75% predicted.

We applied pragmatic criteria to define progression, similar to what was previously used in the INBUILD clinical trial, which demonstrated the efficacy of nintedanib in attenuating the rate of FVC decline in the PF-ILD population.[4] The addition of mortality and lung transplantation as PF-ILD criterions were selected in order to account for patients who may have had a rapid clinical deterioration, that was not captured by serial physiologic/clinical/radiographic assessment, in order to clearly capture our primary intent of describing disease behavior in the setting of fibrotic ILD. The prevalence of PF-ILD in our cohort was 50% at 2 years, greater than that reported in a recent publication from a large European centre that applied comparable criteria to define PF-ILD.[6] In their analysis, Nasser *et al* report that 168 out of 617 patients (27%), assessed over a 7-year period, met PF-ILD criteria. Key differences that distinguish our CARE-PF cohort from this previous analysis include CARE-PF's design as a prospective multi-center study, inclusion of patients with IPF in the analyzed cohort, inclusion of death and lung transplantation within 24-months as a PF-ILD event, and inclusion of patients managed with off-label antifibrotic therapy. Another retrospective study, conducted across 9 specialist centres in the United Kingdom, applied the INBUILD PF-ILD definition to all new incident cases of non-IPF fibrotic ILD assessed over a two-year period starting in 2017. The authors identified 1,749 patients with non-IPF fibrotic ILD, of whom 14.5% met INBUILD PF-ILD criteria. They similarly found progression to be most common in HP, followed by U-ILD and then CTD-ILD.[8] Other reports assessing PF-ILD have used varying definitions and follow-up periods, and have often studied specific diseases rather than the spectrum of all fibrotic ILDs, limiting comparisons across ILD subtypes.[16] International surveys have estimated the real-world prevalence of non-IPF PF-ILD to be in the range of 18-32%.[7]

It is widely accepted that IPF is the prototypical PF-ILD. Rates of progression have been estimated to be as high as 95%, although such estimates use varying criteria and timelines to define progression.[1] Our prospective longitudinal data demonstrate the prevalence of PF-ILD in our IPF population is much lower at only 59% within 24 months of the time of diagnosis. Although somewhat surprising, these data speak to the clinical heterogeneity of real-world populations, most notably our as-treated IPF population, the majority of whom had received antifibrotic therapy at some point in their disease course. These data provide novel insights of the natural history of a contemporary IPF cohort, the relevance of which is heightened as we move past the era of placebo-controlled trials in fibrotic lung disease. Even after excluding patients with IPF, however, we found that progression occurred in 46% of non-IPF patients managed with conventional therapies as outlined in supplementary appendix 1. The rate of PF-ILD was greatest in the patient population with fibrotic HP (58%), followed by U-ILD (51%), CTD-ILD (45%), and other ILDs (31-32%). Within the CTD-ILD group, patients with systemic sclerosis demonstrated the highest rate of progression (49%), similar to previous estimates.[17,18] The comparable nature of these prevalence data to the IPF population emphasizes the critical importance of identifying the PF-ILD phenotype across the spectrum of fibrotic lung disease.

Independent risk factors for progression included increasing age, male sex, history of GERD, baseline percent predicted FVC <70%, and baseline percent predicted DLCO <75%. Highest risk was observed in those patients with the most compromised lung function. One notable difference between the prognostic risk factors assessed in the ILD-GAP index and the risk factors identified in our study, is that HP had similar risk of progression compared to IPF and U-ILD. Prospective validation is required to further delineate the relevance of this finding. Although we have identified clinical factors associated with increased progression, there are likely additional factors that further contribute to this risk. Other factors, including genetic predisposition, molecular signatures, and undocumented environmental exposures are likely of importance, and represent an area of evolving research and understanding. This is particularly relevant as it relates to the development of reliable biomarkers that predict the PF-ILD phenotype.[19,20]

Several criteria have been used to define PF-ILD.[22] Our study incorporated physiologic, symptomatic, and radiographic worsening, comparable to the definition used in the INBUILD trial.[4] Other trials have used different criteria to define PF-ILD. Two recent studies have assessed the role of pirfenidone in reducing disease progression in fibrosing ILD and defined PF-ILD by an absolute FVC decline of ≥5% on at least three measurements over 6-24 months,[23] or defined PF-ILD in patients with U-ILD as an absolute FVC decline of ≥5% or symptomatic worsening within a 6 month period.[24] Strong trends towards reducing FVC progression with pirfenidone were observed in both studies. Such encouraging results, together with the INBUILD study, emphasize the critical importance of identifying the PF-ILD phenotype and the associated therapeutic implications. For the purpose of our study, we used a definition of PF-ILD similar to that described in the INBUILD trial, providing an external and real-world application of this definition. A relative decline in FVC ≥ 10% over 2 years was the primary factor defining progression (49%) in our population, similar to the percentage that was reported in the INBUILD study.[4] Consensus regarding the optimal criteria for PF-ILD remains to be determined.

The results of our study are limited by factors mostly relating to the use of registry data. First, there were 219 patients excluded from our study due to the unavailability of progression data within 2 years of ILD diagnosis. These missing data were balanced across diagnostic subgroups and thus less likely to bias comparisons of risk of progression of any particular ILD diagnosis. As standard practice in Canada involves the routine assessment of patients with fibrotic ILD at 3-6 months intervals, we do not feel that patients with a milder phenotype of disease were preferentially excluded from the analysis.[25] Second, relevant criterion such as acute exacerbation of ILD and respiratory death were not included in the PF-ILD definition. Given Canada's large geographic area, patients travel large distances to access specialty care. As such, capturing data as it relates to cause of death, hospitalization, and acute exacerbation, from sites remote to the study centre, is extremely difficulty to capture reliably and accurately. Third, evidence of progression was only assessed up to 24-months following diagnosis and prolongation of follow-up would lead to increased prevalence of meeting PF-ILD criteria over time. The frequency of this long-term progression is worthy of further evaluation in longer-term cohorts. Third, although we collected information on use of immunosuppression and antifibrotic therapy, we did not pursue cause-effect analyses due to the certainty of confounding by indication and challenges in analyzing such data in a retrospective cohort. Our results should therefore be considered applicable to similar “as-treated” real-world populations. As patients in our registry were recruited from tertiary-care academic referral centers, it is possible that referral bias may have led to an overestimation of the prevalence of PF-ILD. Such bias is commonly encountered in ILD cohorts, given the subspecialty nature of disease management, and has influenced our traditional understanding of the natural history of IPF. The relatively low rates of progression observed in our IPF population, however, suggest that the influence of this inherent bias was minimized.

Conclusion

Progression is common in fibrotic ILD, regardless of the underlying mechanism and trigger for lung injury; however, with a lower frequency of progression in a real-world as-treated population of patients with IPF compared to conventional wisdom. Our results provide real-world context to the previously described pragmatic criteria for assessing progression that are based on serial assessment of FVC decline, worsening symptoms, and radiographic progression; variables that are routinely collected in clinical practice. Future studies identifying additional risk factors for progression such as genetic and molecular profiles are required to better characterize risk in individual patients and further inform management decisions.

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Table 1: Baseline characteristics

	Total cohort	PF-ILD	Non-Progressors	P-value
n	2,746	1,376 (50%)	1,370 (50%)	
Baseline age (years)	65±12	64±12	61±13	<0.0001
Male sex	1,336 (49%)	709 (52%)	627 (46%)	0.003
Ethnicity				
Caucasian	2,196 (80%)	1,110 (81%)	1,086 (80%)	0.64
Asian	279 (10%)	136 (10%)	143 (10%)	
Black	52 (2%)	22 (2%)	30 (2%)	
Other	219 (8%)	108 (8%)	111 (8%)	
Smoking History				
Never-smokers	1,022 (37%)	494 (36%)	528 (39%)	0.14
Ever-smokers	1,712 (63%)	877 (64%)	835 (61%)	
Cumulative smoking history (smokers only, pack-years)	21[8,37]	22[9,38]	20[8,35]	0.04
Comorbidities				
Family history of interstitial lung disease	289 (11%)	138 (11%)	151 (12%)	0.37
COPD	477 (20%)	246 (20%)	231 (19%)	0.50
Coronary artery disease	295 (12%)	168 (14%)	127 (10%)	0.01
GERD	558 (23%)	304 (25%)	254 (21%)	0.02
Lung cancer	42 (2%)	26 (2%)	16 (1%)	0.13
BMI (kg/m^2)	29±6	29±6	29±6	0.95
Baseline PFT's				
FVC % predicted	79±20	77±20	81±19	<0.0001
FEV_1 % predicted	80±20	78±20	82±19	<0.0001
DL_{CO} % predicted	61±21	57±20	64±21	<0.0001
Resting SpO_2	97[95,98]	97[95,98]	97[95,98]	0.05
6MWD (m)	400±124	389±130	414±115	<0.0001
RVSP (mmHg)	31[26,39]	33[26,41]	30[25,37]	0.0001
ILD-GAP score				
0-1	1,220 (44%)	527 (38%)	693 (51%)	<0.0001
2-3	1,003 (37%)	527 (38%)	476 (35%)	
4-5	483 (17%)	292 (21%)	191 (13%)	
>5	40 (2%)	30 (2%)	10 (1%)	

Data are presented as mean ± SD; median [IQR]; or count (column percentage). PF-ILD (progressive fibrosing interstitial lung disease), COPD (chronic obstructive pulmonary disease), GERD (gastroesophageal reflux disease), BMI (body mass index), FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1^{st} second), DLCO (diffusing capacity for carbon monoxide), SpO2 (oxygen saturation on pulse oximeter), 6MWD (6-minute walk distance), RVSP (right ventricular systolic pressure), ILD-GAP (interstitial lung disease – Gender-Age-Physiology score)

Table 2: Individual PF-ILD criteria met within 24 months of ILD diagnosis

First PF-ILD criteria met within 24 months of ILD diagnosis	**Number (%)**
Relative FVC decline ≥10%	675 (49%)
Relative FVC decline 5-9% with worsening respiratory symptoms	166 (12%)
Relative FVC decline 5-9% with worsening fibrosis on HRCT	113 (8%)
Relative FVC decline <5% with both symptom and radiographic progression	352 (26%)
Lung transplantation	9 (1%)
Death†	61 (4%)
Total	1,367

† These patients died without meeting any of the other criteria

Table 3: PF-ILD by diagnosis

Diagnosis	Total number of patients†	Proportion meeting PF-ILD criteria‡
IPF	718 (26%)	427 (59%)
Hypersensitivity pneumonitis	216 (8%)	125 (58%)
CTD-ILD	902 (33%)	402 (45%)
Systemic sclerosis	334	163 (49%)
Rheumatoid arthritis	189	87 (46%)
Myositis*	166	69 (42%)
Mixed CTD	65	28 (43%)
Sjogren's	54	20 (37%)
SLE	28	7 (25%)
Undifferentiated	64	26 (41%)
Unclassifiable ILD	550 (20%)	281 (51%)
IPAF	92	51 (55%)
Other fibrotic ILD	360 (13%)	141 (39%)
Sarcoidosis	92	29 (32%)
Idiopathic NSIP	22	9 (41%)
Occupational ILD	21	9 (43%)
Drug-induced ILD	16	5 (31%)
Smoking-related ILD	27	15 (56%)
Cryptogenic organizing pneumonia	28	10 (36%)
Vasculitis	29	10 (34%)
Other°	125	53 (43%)

†Data presented as column percentage
‡Data presented as row percentage
*Myositis includes dermatomyositis/polymyositis and anti-synthetase syndrome.
°Other detailed in supplementary appendix
IPF (idiopathic pulmonary fibrosis), CTD (connective tissue disease), SLE (systemic lupus erythematosus), IPAF (interstitial pneumonia with autoimmune features), NSIP (nonspecific interstitial pneumonia)

Table 4: Hazard ratios for progression to PF-ILD by diagnosis

ILD diagnosis	**Hazard ratio with 95% confidence intervals**
IPF	*Reference*
HP	0.96 (0.79-1.17)
CTD-ILD	0.65 (0.56-0.74)
Unclassifiable	0.82 (0.71-0.96)

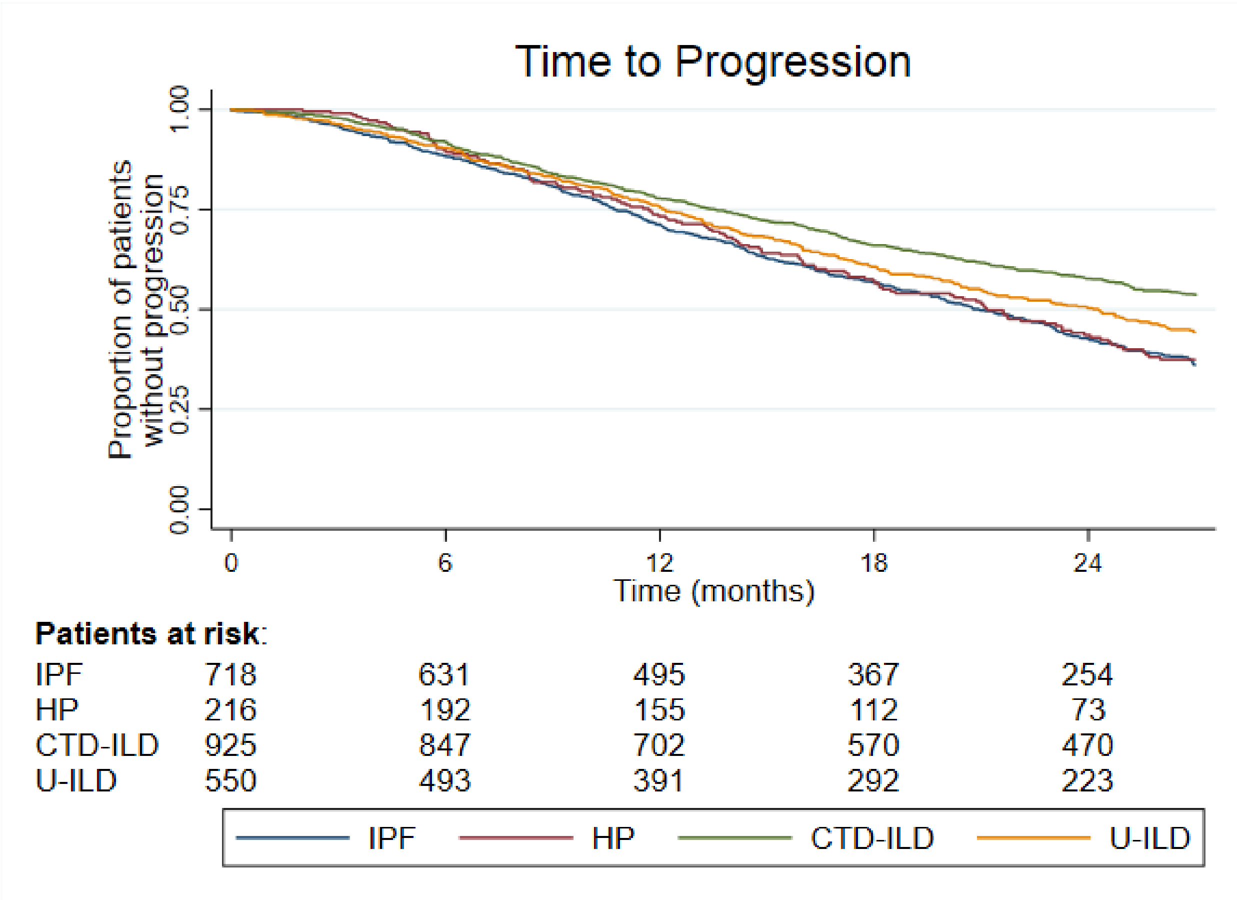
Table 5: Unadjusted and multivariable analyses evaluating risk factors for PF-ILD

Variable	Number (%)	Unadjusted HR	Adjusted HR
Age at diagnosis			
Under 50	403 (15%)	Reference	Reference
50-59	578 (21%)	1.25 (1.04-1.52)*	1.25 (1.02-1.55)*
60-69	910 (33%)	1.28 (1.07-1.52)*	1.29 (1.06-1.57)*
70-79	716 (26%)	1.38 (1.15-1.65)*	1.33 (1.08-1.64)*
Over 80	139 (5%)	1.64 (1.27-2.14)*	1.53 (1.12-2.08)*
Male sex	1,336 (49%)	1.17 (1.06-1.30)*	1.20 (1.06-1.36)*
Ethnicity			
Caucasian	2,196 (80%)	Reference	Reference
Asian	279 (10%)	0.91 (0.76-1.09)	0.91 (0.74-1.12)
Black	52 (2%)	0.81 (0.53-1.23)	0.82 (0.50-1.33)
Other	219 (8%)	0.93 (0.76-1.13)	0.96 (0.74-1.24)
Per-10 pack-year smoking increase	-	1.03 (1.01-1.05)*	1.02 (0.97-1.05)
Family history of pulmonary fibrosis	289 (11%)	0.90 (0.76-1.08)	0.94 (0.78-1.14)
History of COPD	477 (20%)	1.04 (0.90-1.19)	0.93 (0.80-1.08)
History of GERD	558 (23%)	1.20 (1.05-1.36)*	1.22 (1.06-1.40)*
History of surgical lung biopsy	579 (21%)	1.10 (0.97-1.25)	1.12 (0.97-1.29)
Baseline FVC % predicted			
≥90	759 (30%)	Reference	Reference
70-89	938 (37%)	1.30 (1.13-1.50)*	1.13 (0.97-1.31)
<70	818 (33%)	1.51 (1.31-1.74)*	1.23 (1.03-1.43)*
Baseline % predicted DLCO			
≥75	611 (24%)	Reference	Reference
60-75	632 (25%)	1.50 (1.26-1.77)*	1.44 (1.21-1.73)*
40-60	897 (36%)	1.55 (1.32-1.82)*	1.42 (1.20-1.69)*
<40	378 (15%)	2.24 (1.87-2.68)*	(1.71-2.56)*

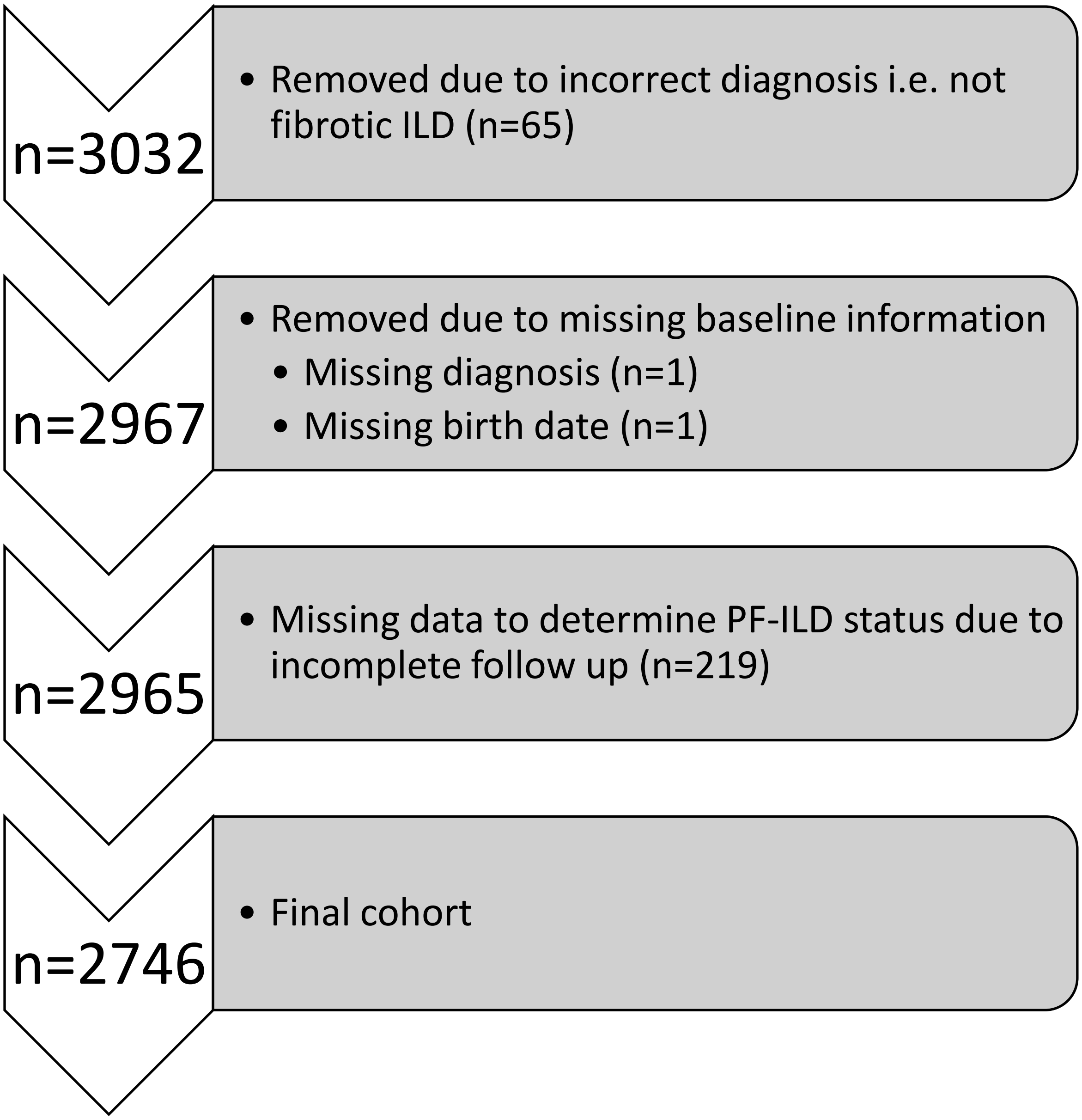
Unadjusted and adjusted hazard ratios with 95% confidence intervals. COPD (chronic obstructive pulmonary disease), GERD (gastroesophageal reflux disease), FVC (forced vital capacity), DLCO (diffusing capacity for carbon monoxide)

* $p < 0.05$

Figure 1: Kaplan-Meier curves for risk of progression



Supplementary Figure 1: Flow diagram of patient enrollment



Supplementary Table 1: Distribution of medication use within 24 months of diagnosis

	PF-ILD	**Non-progressors**	**Total**
HP†	**125 (58%)**	**91 (42%)**	**216 (100%)**
Immunomodulatory	75 (60%)	31 (34%)	106 (49%)
No treatment	50 (40%)	60 (65%)	110 (51%)
CTD-ILD†	**402 (45%)**	**500 (55%)**	**902 (100%)**
Immunomodulatory	270 (67%)	279 (56%)	549 (61%)
No treatment	132 (33%)	221 (44%)	353 (39%)
U-ILD†	**281 (51%)**	**269 (49%)**	**550 (100%)**
Immunomodulatory	128 (46%)	77 (29%)	205 (37%)
No treatment	153 (54%)	192 (71%)	345 (63%)
IPF†	**427 (59%)**	**291 (41%)**	**718 (100%)**
Antifibrotic	291 (68%)	182 (63%)	473 (66%)
No treatment	136 (32%)	109 (37%)	245 (34%)

†denotes row percentages; all other percentages are column percentages

Supplementary Table 2: Sensitivity analysis excluding death and lung transplant as a PF-ILD event

ILD diagnosis	**Hazard ratio with 95% confidence intervals**
IPF	*Reference*
HP	0.96 (0.78-1.18)
CTD-ILD	0.66 (0.57-0.75)
Unclassifiable	0.80 (0.68-0.93)

Supplementary Table 3: Proportion of patients missing data to classify as PF-ILD by diagnosis

ILD diagnosis	Proportion with complete data	Proportion with missing data
IPF	718 (26%)	59 (27%)
HP	216 (8%)	10 (5%)
CTD-ILD	902 (33%)	59 (27%)
U-ILD	550 (20%)	50 (23%)
Other ILD	360 (13%)	41 (18%)

Percentages denote column percentages

Supplementary Table 4: Fibrotic ILD falling in the "Other" category

Diagnosis	Proportion of patients
Post ARDS	10 (8%)
Aspiration-related	7 (6%)
Chronic eosinophilic pneumonia	5 (4%)
Idiopathic interstitial pneumonia	10 (8%)
Idiopathic PPFE	6 (5%)
Diagnosis not classified	87 (70%)
Total	125

ARDS (acute respiratory distress syndrome), PPFE (pleuro-parenchymal fibroelastosis)