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Original Research

Proportion and predictors of FVC decline in patients with interstitial lung disease

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ABSTRACT

Rationale: The proportion of patients who develop progressive pulmonary fibrosis (PPF), along with risk factors for progression remain poorly understood.
Objectives: To examine factors associated with an increased risk of developing PPF among patients at a referral center.
Methods: We identified patients with a diagnosis of interstitial lung disease (ILD) seen within the Cleveland Clinic Health System. Utilizing a retrospective observational approach we estimated the risk of developing progression by diagnosis group and identified key clinical predictors using the FVC component of both the original progressive fibrotic interstitial lung disease (PFILD) and the proposed PPF (ATS) criteria.
Results: We identified 5934 patients with a diagnosis of ILD. The cumulative incidence of progression over the 24 months was similar when assessed with the PFILD and PPF criteria (33.1 % and 37.9 % respectively). Of those who met the ATS criteria, 9.5 % did not meet the PFILD criteria. Conversely, 4.3 % of patients who met PFILD thresholds did not achieve the 5 % absolute FVC decline criteria. Significant differences in the rate of progression were seen based on underlying diagnosis. Steroid therapy (HR 1.46, CI 1.31–1.62) was associated with an increased risk of progressive fibrosis by both PFILD and PPF criteria.
Conclusion: Regardless of the definition used, the cumulative incidence of progressive disease is high in patients with ILD in the 24 months following diagnosis. Some differences are seen in the risk of progression when assessed by PFILD and PPF criteria. Further work is needed to identify modifiable risk factors for the development of progressive fibrosis.

Progressive pulmonary fibrosis (PPF) encompasses a heterogeneous collection of interstitial lung diseases (ILD) characterized by fibrotic destruction of the lung parenchyma [1–4]. Not all patients with interstitial lung disease develop PPF. However, increasing evidence suggests that among patients who do develop this progressive phenotype, mortality is high [5–7]. Idiopathic pulmonary fibrosis (IPF), the most common progressive fibrotic interstitial lung disease, is characterized by a median survival of approximately three years [8]. A similar pattern of mortality is seen in patients who develop fibrotic progression in non-IPF ILD, with a median survival of less than 5 years across the majority of diagnostic groups [9–12]. While the true prevalence of PPF within the United States is unknown, analysis of medical claims data suggest between 15 and 24 % of U.S. patients with non-IPF fibrosing ILD will experience progression [13,14].

The development of PPF is associated with an irreversible loss of lung function. Delays in diagnosis result in greater loss of lung function, increased morbidity, and increased healthcare costs [14]. Previous research has shown that while the majority of patients with PPF will ultimately experience further progression, the timing and pattern of progression exhibit significant variability [15]. Variation in treatment practices, and social and environmental factors may further impact an individual's risk of progression [16]. While several studies have investigated the risk of fibrotic progression for disease subcategories within PPF, risk factors for progression across patients with PPF as a whole

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remain poorly understood. Identifying the diagnoses within PPF associated with the highest risk of progression, along with individual patient factors that may contribute to the overall risk is necessary to guide further research efforts.

The definition of PPF has changed over time. The original description of the phenotype was described in the INBUILD study [17]. Within this cohort patients were defined as meeting criteria for progressive fibrotic interstitial lung disease (PFILD) based on a greater than 10 % relative decline in forced vital capacity (FVC) over a 24-month period. A subsequent statement from the American Thoracic Society proposed a novel definition of progressive pulmonary fibrosis (PPF). Here 2 out of 3 criteria were needed to define progression, with an FVC physiologic criterion defined as a 5 % absolute decline over a 12 month interval [18]. The differences in the performance characteristics of these diagnostic criteria remains unknown. While non-physiologic criteria, including progression of fibrosis on imaging and worsening of respiratory symptoms have also been utilized as markers of progression, in patients with non-IPF fibrotic ILD, physiology progression, specifically FVC decline is most clearly associated with transplant free-survival [19–21].

Utilizing the electronic medical records from a large interstitial lung disease referral center, we describe the rate of progression to PPF phenotype by ILD diagnosis group and identify risk factors for the development of progressive fibrosis, comparing risk factors for progression by both definitions of progression in fibrotic ILD. Identifying patients at risk for progressive fibrosis prior to the onset of fibrosis has the potential to improve our understanding of disease prognosis and guide early interventions including therapy initiation.

1. Methods

1.1. Study design

We extracted data from the Cleveland Clinic Health System Electronic Medical Record (EMR) to identify a cohort of patients who received care between 2009 and 2019. Adult patients (age $\geq$18 years) were identified as having a diagnosis of ILD utilizing ICD-9 and ICD-10 coding from office visits, hospitalization, or billing encounters. For inclusion, patients were required to have at least two documented ICD 9/10 codes specific for interstitial lung disease across two separate encounters (Supplemental Table 1). To ensure the accuracy of this initial diagnosis, chart audits were performed across a randomly selected subset of 5% of the total cohort by two members of the study team with clinical expertise in ILD care. These audits were utilized to refine EMR data-collection strategies for pulmonary function testing and key demographic information.

Baseline pulmonary function at time of cohort entry was defined as the first documented forced vital capacity (FVC) within the twelve months preceding, or six months following the initial documentation of ILD. This value functioned as the "index" FVC for subsequent analysis. For inclusion in the final cohort patients were required to have at least one additional FVC measurement within three to twenty-eight months of initial FVC documentation.

To minimize biasing the cohort by inclusion of end-stage ILD patients, we excluded those who had lung transplantation or were referred for transplant evaluation within three months of the date of their first documented ILD diagnosis. Because our clinical practice does not routinely refer patients for transplant evaluation until there is evidence of significant progression or resting hypoxemia, this search strategy is unlikely to result in routine exclusion of patients with mild/early disease.

Baseline FEV1/FVC and diffusion capacity for carbon monoxide (DLCO) were obtained where available, and the presence of comorbidities including asthma, lung cancer, pulmonary hypertension, coronary artery disease, congestive heart failure, pulmonary embolism, diabetes, hypertension, cerebrovascular accident, gastroesophageal reflux disease, obstructive sleep apnea and chronic kidney disease were identified utilizing relevant ICD 9/10 codes.

ILD specific ICD9/10 diagnosis codes were grouped based on underlying disease characteristics into eight categories-idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), smoking and drug related lung disease, occupational lung disease, connective tissue disease associated interstitial lung disease (CTD-ILD), sarcoidosis, hypersensitivity pneumonitis, or unspecified, undifferentiated, and other. Diagnosis was defined at two time points. An "index" diagnosis was made based on the first documented ILD specific ICD9/10 code at the time of cohort entry. Patients were subsequently assigned a "specific" diagnosis based on the sub-category of their most documented ICD 9/10 code following the index ILD diagnosis. Recognizing that many patients enter quaternary care with undifferentiated ILD that is subsequently classified into a diagnostic subgroup, this "specific" diagnosis was utilized as a surrogate for the most likely final diagnostic subgroup after patients had completed evaluation and testing.

This study was approved by the Cleveland Clinic IRB (study number 20–1165).

2. Outcome

The primary study outcome was progression of disease, defined as a greater than 10 % relative decline in the percent predicted FVC within the 24-month period from the date of index FVC measurement. Lung transplant and all cause death were considered competing risks if they occurred in the absence of progression and were identified based on EMR data. Risk of progression was analyzed both by diagnosis at time of cohort entry, and by specific diagnosis. In recognition of the recently disseminated PPF diagnostic criteria, the risk of disease progression was also calculated utilizing a greater than 5 % absolute decline in percent predicted FVC within any 12-month period in the first 24 months following index FVC.

2.1. Statistical analysis

Univariable and multivariable time–to-event analyses were utilized to identify prognostic factors for FVC decline [22]. For each outcome (10 % relative and 5 % absolute FVC decline) time of follow-up was calculated from index date until the incidence of the outcome unless death, lung transplant, or loss to follow-up occurred first, at which point the patient was censored. A Cox proportional hazards model was used to estimate the effect of covariates on the instantaneous risk of the event of interest. The results of regression models, both unadjusted and adjusted for any identified confounders, are presented as hazard ratios (HR) with 95 % confidence interval (95 % CI). All analyses were performed in R version 4.2.1.

3. Results

A total of 58,771 patients with at least one documented diagnosis of ILD were identified within the EMR. After restricting to patients who met full inclusion criteria, a total of 5934 patients were eligible for inclusion. Mean (SD) age at cohort entry was 62 ($\pm$14) years. The majority (83 %) of the cohort identified as White, with 12 % of the cohort identifying as Black. 2.9 % of the sample identified as Hispanic (Table 1). Gastroesophageal reflux (GERD) was the most reported comorbidity at time of cohort entry, present in 35 %. Co-existing pulmonary comorbidities were also common at time of cohort entry. (Table 1).

Slightly more than one-third (39 %) of the cohort were already receiving immunosuppressive treatment at time of first assessment, defined as prednisone or a steroid sparing agent (Supplemental Table 2). Antifibrotic therapy, was prescribed for nintedanib (3.9 %) or pirfenidone (3.9 %) of the cohort, either at baseline or during the 24 months following index diagnosis. A wide distribution of baseline pulmonary function testing was noted, with a median FVC% of 81 % of predicted

Table 1
Baseline cohort characteristics.

Characteristic (N = 5934)	Distribution
Age, Mean (SD)	62 (14)
Race	
Black N (%)	692 (12 %)
White N (%)	4945 (83 %)
Gender	
Female, N (%)	3101 (52 %)
Smoking status	
Current, N (%)	476 (8.0 %)
Former, N (%)	2622 (44 %)
Never, N (%)	2479 (42 %)
Unknown, N (%)	357 (6 %)
Comorbidities	
Chronic Obstructive Pulmonary Disease N (%)	1577 (27 %)
Gastroesophageal reflux, N (%)	2068 (35 %)
Obstructive sleep apnea, N (%)	1022 (17 %)
Asthma, N (%)	1253 (21 %)
Coronary Artery Disease, N (%)	1395 (24 %)
Heart Failure, N (%)	959 (16 %)
Chronic Kidney Disease, N (%)	590 (9.9 %)
Pulmonary Hypertension, N (%)	401 (6.8 %)
Charlson comorbidity index at cohort entry (IQR), N (%)	1, (0, 4)
Immunosuppression, N (%)	2288 (39 %)
Nintedanib, N (%)	237 (3.9 %)
Pirfenidone, N (%)	229 (3.9 %)
Pulmonary Function on index testing (Median (IQR))	
FEV1/FVC Ratio	83 (74, 97)
Baseline FVC (% predicted)	81 (66, 94)
DLCO (% predicted)[a]	41 (20, 67)

[a] DLCO data missing for 1001 patients.

(IQR 66–94 %), and a median DLCO of 41 % predicted (IQR 20–67 %). Most of the sample (82 %) received primary care within the Cleveland Clinic system during the duration of their cohort inclusion. DLCO data were missing for 1001 patients within the cohort.

Among those who did not have an event, the median duration of follow-up (defined as the duration between baseline FVC and final recorded FVC measurement) from index diagnosis was 39.9 months (IQR 25–68 months). The number of available FVC measurements prior to event or censoring in the post-index period per patient varied, with a median of 3 measurements (IQR 2–6). While DLCO data were not available for 16.8 % of the cohort, baseline FVC was not significantly different in patients without a documented DLCO (Median FVC 80 % predicted (IQR 66–94 %) when compared to those with a documented DLCO measurement (Median FVC 82 % predicted (IQR 66–96 %)).

At time of initial cohort entry, 52 % (3088) of patients had undifferentiated ILD. Of those who entered the cohort with undifferentiated ILD, 54 % (1679) subsequently received a more specific ILD diagnosis, while 29.9 % of the cohort remained or were reclassified as undifferentiated.

The cumulative incidence of 10 % relative decline in FVC in the 24 months following cohort entry was 33.1 % (CI 31.8–34.3 %)

(Fig. 1). When progression was defined using a >5 % absolute decline in FVC over any 12-month period within the first 24 months following cohort entry, the cumulative incidence of progression was 37.9 % (CI: 36.6–39.2 %).

Within the cohort 1537 patients (25.9 %) met criteria for progression by both FVC criteria. A total 564 (9.5 %) of patients met criteria for progression based on an 5 % absolute decline within any 12-month interval but did not meet criteria for decline by the original PFILD criteria (10 % relative decline within 24 months). Conversely, 255 (4.3 %) patients met criteria for decline based on a 10 % relative decrease within 24 months but did not meet criteria for decline utilizing the PPF definition (5 % absolute decline within any 12-month interval) (Table 2).

Patients who met criteria for decline based on the PPF definition but did not meet criteria for decline by the PFILD definition had a higher baseline FVC (median 90 % predicted, IQR 77–102 %) compared with

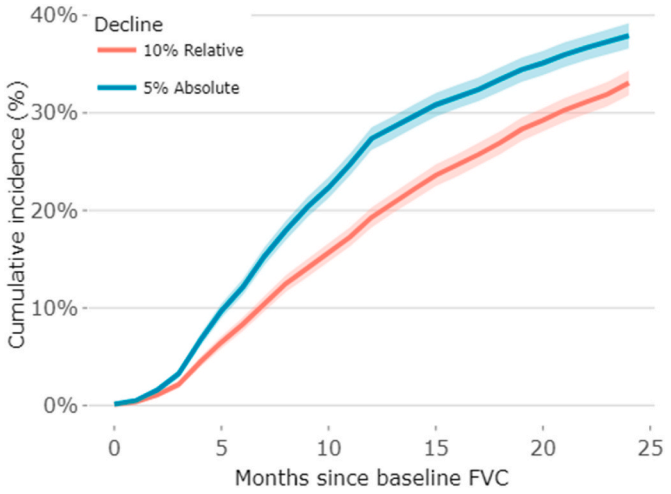

Fig. 1. Cumulative incidence of FVC decline by PFILD and PPF criteria over the first 24 months from index diagnosis date.

Table 2
Patients meeting criteria for progressive by both progressive fibrotic interstitial lung disease (PFILD) and progressive pulmonary fibrosis (PPF) criteria.

	>10 % decline in FVC over 24 months (n)	<10 % decline in FVC over 24 months (n)
> 5 % decline in FVC over 12 months (n)	1537 (25.9 %)	564 (9.5 %)
<5 % decline in FVC over 12 months (n)	255 (4.3 %)	3578 (60.3 %)

those who met both criteria for decline (median 75 % of predicted, IQR 61–88 % of predicted). No significant difference in age or gender was seen. As anticipated, underlying diagnosis significantly impacted the risk of progression. By diagnosis group, the cumulative incidence of progression was highest in patients with a diagnosis of IPF (Fig. 2). A high cumulative incidence of progression was also noted in patients with hypersensitivity pneumonitis, and in smoking related lung disease (Fig. 2). Significant differences in the cumulative incidence of progression in patients with a diagnosis of sarcoidosis was seen based on the definition of progression utilized (Fig. 2).

In univariable analysis, male gender (HR 1.26, 95 % CI 1.15–1.39, P < 0.001) and increased age (HR 1.13 per 10-year increase, CI 1.09–1.17, P < 0.001) were associated with an increased likelihood of developing PFILD, though this effect did not persist after adjustment for baseline diagnosis (Table 3). A similar relationship was noted between male gender, increased age, and the likelihood of PPF. Higher baseline FVC was associated with a lower risk of progression by PFILD (HR 0.95 per 5 % difference, CI 0.94–0.96) criteria. No association was seen between the presence of comorbidities, including obesity, tobacco use, and pulmonary hypertension and the risk of PFILD development (Table 3). An association was seen between prednisone therapy and the development of PFILD (HR 1.51, CI 1.35–1.68, P < 0.001). This effect was not seen in patients with a prescription for non-prednisone immunosuppression when assessed using PFILD criteria (HR 1.06, CI 0.95–1.19, P = 0.289), but was seen when assessed using PPF criteria (HR 1.15, CI 1.04–1.28, P < 0.006). Receiving primary care within our healthcare system was associated with a reduced risk for PFILD (HR 0.83, CI 0.74–0.93, P = 0.002) and PPF (HR 0.88, CI 0.79–0.98, P = 0.024). There was no significant difference in the risk of progression in patients with and without a documented DLCO (HR 0.96).

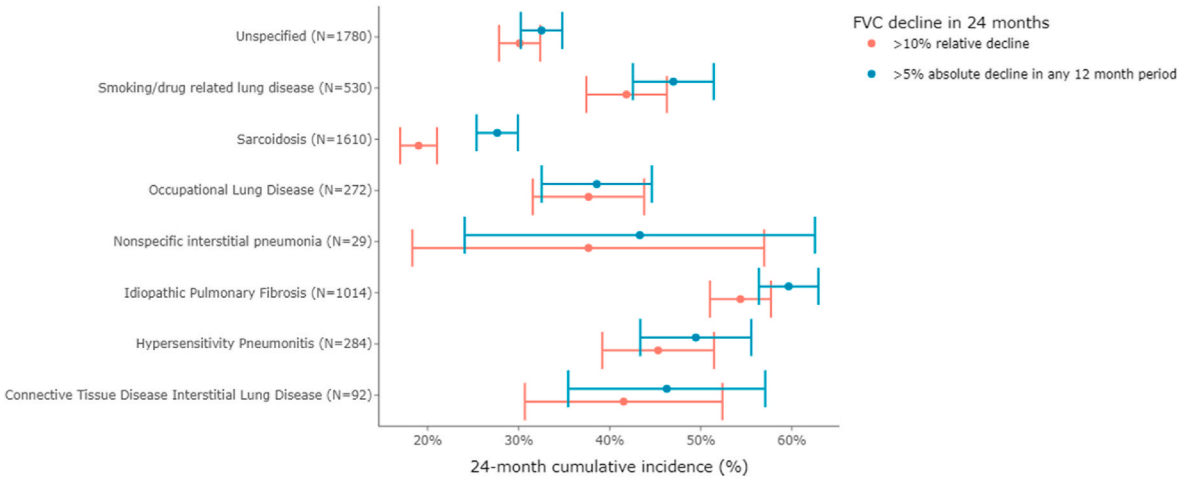

Fig. 2. Percent of cohort with evidence of absolute and relative FVC defined progression within 12 and 24 months by specific diagnosis category.

4. Discussion

In our study, the cumulative incidence of disease progression (defined as a greater than 10 % relative decline in FVC) in the 24 months following diagnosis of ILD was 33.1 %. This proportion varied by underlying ILD diagnosis subtype. Cumulative incidence of progression was highest in patients with idiopathic pulmonary fibrosis. A significant proportion of patients with hypersensitivity pneumonitis and smoking related lung disease experienced disease progression, with a cumulative incidence of 45 % and 42 % respectively in the 24 months following the first documented diagnosis of disease. This is higher than would generally be anticipated and may reflect the clinical characteristics of patients referred to evaluation at our center. The possibility that this decline may represent transient disease exacerbation can also not be excluded.

When progression was defined using a >5 % absolute decline in FVC over the first 12 months following cohort entry, a greater number of patients met criteria for progression. This difference was most pronounced among our sarcoidosis cohort (27 % versus 19 %), though also evident across several other diagnostic categories (Fig. 1). This may reflect differences in underlying disease behavior or treatment. Alternatively, this may be attributable to differences in patterns of testing type or frequency and follow-up by disease category. Which definition most accurately captures true progression remains to be determined.

9.5 % of patients who met the criteria for progression utilizing the PPF guidelines did not meet criteria based on a 10 % relative decline in 24 months. Similarly, 4.3 % of patients who met criteria for progression based on the PFILD definition did not meet criteria for progression based on a 5 % absolute decline in 12 months, suggesting that for some patients, FVC may fluctuate without steady decline. Further work is needed to identify whether these fluctuations in FVC represent measurement error or predict a poor long-term prognosis and persistent decline beyond the 24-month period included in our study.

Within our cohort several factors were associated with an increased risk of progression, regardless of the definition of progression utilized. Underlying diagnosis was a major predictor of the risk of progression, with the highest risk of progression seen among patients with IPF (HR 2.04, CI 1.78–2.35). Lower, but still significant risk of progression was seen in patients diagnosed with hypersensitivity pneumonitis and CTD-ILD. Age, gender and baseline pulmonary function have previously been associated with an increased risk of disease progression in patients with CTD-ILD and chronic hypersensitivity pneumonitis [23–25]. In patients with CTD-ILD FVC decline is highly associated with increased mortality [21,26]. A similar finding was seen within our cohort, with an increased risk of progression among male patients (HR 1.21, CI 1.06–1.39, P 0.005), and a small change in risk of progression with baseline FVC and age, though this relationship did not persist after adjustment for diagnosis. This likely reflects an increased risk of primarily fibrotic disease associated with age and male gender. Alternatively, this may reflect differences in health seeking behavior and patterns of accessing care.

The impact of treatment choice and timing of treatment initiation on the trajectory of PPF remains poorly understood. Within our cohort, documented prescription of prednisone was associated with a significantly increased risk of progression by both absolute and relative FVC decline criteria. The reasons for this are unclear. Patients who display progressive disease may be more likely to receive a trial of steroids due to their clinical decline. Alternatively, steroids themselves may contribute to morbidity or progression. Among patients with CTD-ILD, treatment with prednisone has been associated with an increased risk of progression [27]. Previous research has shown that in patients with progressive ILD, glucocorticoid therapy is associated with significant morbidity, even when utilized in comparatively short durations [28]. The finding that this extends across diagnosis groups is significant, and has not previously been reported. A risk of progression was not seen with prescription for non-prednisone immunosuppression by PFILD criteria, though was seen when utilizing PPF criteria for progression. This may reflect differences between diagnosis group in progression by each criterion-patients with sarcoidosis were significantly more likely to meet PPF criteria for progression, without meeting PFILD criteria. Sarcoidosis was also associated with a lower risk of progression by FVC criteria-whether this reflects a true decreased likelihood of progression, or the limitations of FVC as a marker of progression in sarcoidosis remains to be determined. Our observations reinforce the notion that clinicians should be cautious about unintended adverse effects of steroids on outcomes in this population.

Rates of anti-fibrotic prescription were low, with less than 10 % of the cohort receiving a prescription for either therapeutic agent. This may reflect the timing of cohort enrollment-anti-fibrotic therapy was not approved by the Federal Drug Administration for use in non-IPF fibrotic lung disease until 2019. Initiation of antifibrotic therapy has been shown to reduce the rate of FVC decline in patients with ILD and may alter the inherent risk and timing of progression [7,29,30].

Unmeasured social determinants of health may play an important and unrecognized role in the risk of fibrotic progression. Within our cohort, patients who received primary care within the Cleveland Clinic system were less likely to experience progression than those who did not (HR 0.83, CI 0.74–0.93, P = 0.002). Patients who already receive care within the system may face reduced barriers to accessing specialist care, resulting in earlier referral and diagnosis. Regardless of diagnosis, early referral has previously been shown to reduce mortality in patients with ILD [31,32]. Similarly, residence in a disadvantaged neighborhood has been shown to increase the likelihood of mortality for patients with a

Table 3
Risk of greater than 10 % relative decline in percent predicted FVC by key patient characteristics.

	Univariable Analysis		Multivariable Analysis	
Characteristic	HR (95 % CI)	P-value	HR (95 % CI)	P-value
Age (10-year increase)	1.13 (1.09, 1.17)	<0.001	1.03 (0.98, 1.08)	0.265
Race		<0.001		0.247
Black	–		–	
White	1.19 (1.02, 1.39)		0.98 (0.83, 1.15)	
Other	1.60 (1.26, 2.03)		1.17 (0.91, 1.50)	
Male gender	1.26 (1.15, 1.39)	<0.001	1.1 (0.99, 1.22)	0.064
Primary care provider	0.77 (0.69, 0.86)	<0.001	0.83 (0.74, 0.93)	0.002
Baseline FVC (5 % predicted)	0.92 (0.91, 0.93)	<0.001	0.95 (0.94, 0.96)	<0.001
FEV1/FVC ratio (10-unit increase)	1.02 (0.99, 1.04)	0.268	0.97 (0.94, 1)	0.046
Comorbidities				
Hypertension	1.11 (1.01, 1.22)	0.029	1.02 (0.91, 1.14)	0.757
Cerebrovascular Accident	1.18 (0.95, 1.46)	0.153	1.17 (0.93, 1.46)	0.189
Emphysema	1.05 (0.94, 1.16)	0.382	0.89 (0.79, 1.01)	0.061
Gastroesophageal reflux	0.92 (0.83, 1.02)	0.096	0.87 (0.78, 0.97)	0.01
Obstructive Sleep Apnea	1.07 (0.95, 1.20)	0.295	1.05 (0.92, 1.21)	0.449
Asthma	0.93 (0.83, 1.04)	0.195	1.02 (0.9, 1.16)	0.712
Pulmonary Embolism	0.83 (0.65, 1.06)	0.126	0.82 (0.64, 1.05)	0.098
Heart Failure	1.05 (0.93, 1.19)	0.405	0.95 (0.82, 1.09)	0.455
Coronary Artery Disease	1.19 (1.08, 1.33)	0.001	1.03 (0.91, 1.17)	0.674
Diabetes	1.11 (1.00, 1.24)	0.059	0.98 (0.87, 1.11)	0.805
Chronic Kidney Disease	1.14 (0.98, 1.32)	0.087	1.05 (0.89, 1.23)	0.571
Immunosuppressive	1.06 (0.97, 1.17)	0.196	1.06 (0.95, 1.19)	0.289
Prednisone	1.4 (1.27, 1.53)	<0.001	1.51 (1.35, 1.68)	<0.001
Pulmonary Hypertension	1.03 (0.86, 1.24)	0.739	0.94 (0.78, 1.13)	0.507
Body Mass Index (10-unit increase)	1.01 (0.94, 1.08)	0.766	1 (0.93, 1.09)	0.935
Smoking Description		0.013		0.13
Current	–		–	
Former	1.07 (0.90, 1.27)		0.86 (0.72, 1.03)	
Never	0.9 (0.76, 1.08)		0.8 (0.66, 0.96)	
Unknown	0.93 (0.72, 1.20)		0.85 (0.63, 1.13)	
Diagnosis group		<0.001		<0.001
Unspecified	–		–	
Smoking/drug related lung disease	1.6 (1.36, 1.88)		1.28 (1.08, 1.52)	
Sarcoidosis	0.58 (0.5, 0.68)		0.57 (0.48, 0.67)	
Occupational Lung Disease	1.3 (1.04, 1.63)		1.28 (1.02, 1.6)	
Nonspecific interstitial pneumonia	1.32 (0.7, 2.46)		1.27 (0.68, 2.38)	
Idiopathic pulmonary fibrosis	2.11 (1.86, 2.39)		2.04 (1.78, 2.35)	
Hypersensitivity Pneumonitis	1.73 (1.41, 2.11)		1.37 (1.11, 1.7)	
Connective tissue disease associated interstitial lung disease	1.48 (1.05, 2.09)		1.2 (0.84, 1.7)	
(Missing)	0.76 (0.60, 0.97)		0.84 (0.65, 1.08)	

diagnosis of fibrotic ILD [16].

In keeping with the patient population seeking care at a referral center, a large proportion of patients within our cohort entered the study as "undifferentiated" before receiving a specific diagnosis. The risk of progression based on index diagnosis versus specific diagnosis varied significantly. This may be attributable to differences in referral timing and treatment initiation for those with atypical or progressive disease. Further work is needed to investigate the impact of patient and care provider location on diagnostic timing, treatment initiation and long-term outcomes within this cohort.

Most of our cohort met the criteria for severe DLCO impairment at time of baseline testing, with a median percent predicted DLCO of 41 % (IQR 20–67). However, DLCO values were not available for a large number of patients (n = 1001). This may reflect utilization of outside test sites not captured by our EMR, or a subset of the cohort that was not seen in the ILD clinic.

While the large cohort size and detailed EMR records available for our cohort are a strength, due to the retrospective, observational nature the study our analysis has several limitations. CT confirmation of fibrosis was not required for study inclusion. Progression by FVC criteria may not represent progression of fibrosis, but rather progression of inflammation. We utilized a single physiologic marker of progression within our cohort, FVC decline. The number of patients who experienced decline through other metrics (such as imaging defined worsening of fibrosis, clinical worsening of symptoms or DLCO decline) is unclear. The American Thoracic Society consensus statement requires evidence of decline by at least 2 measures (worsening respiratory symptoms, physiologic evidence of decline and radiologic evidence of disease progression). Given this, we have underestimated the full risk of progression within our cohort. However, across multiple cohorts, FVC

decline has been identified as the strongest predictor of transplant free survival in patients with non-IPF ILD [19,20].

While attempts were made to increase the validity of cohort development through physician led chart review audits, because of our reliance on documented diagnosis codes to identify patients with interstitial lung disease, it is likely that not all patients within our cohort have confirmed ILD. Similarly, it is likely that some patients with ILD were not included. Previous research has shown that EMR based diagnostic classification is specific, but has limited sensitivity [33]. Rates of CTD-ILD within our cohort are likely significantly under-estimated as a result of the nuances of ICD 9/10 coding for ILD associated with an autoimmune condition. While ICD 10 has expanded the option for "combined" diagnoses, we anticipate that a large proportion of our physicians continue to utilize less specific "ILD" diagnosis codes for these conditions.

Our study identifies novel risk factors for the development of PPF. However, most of the risk for PPF remains unexplained. Access to appropriate ILD care, and timing of care initiation may be significant drivers of PPF, independent of underlying diagnosis group. More work is needed to explore the complicated relationship between environment, care access and health.

5. Conclusion

The risk of PPF is significant for all patients with a diagnosis of ILD. While most patients who experience decline will meet both PFILD and PPF criteria for decline, a small subset may not be captured with the use of a single definition. The relationship between primary care provider location and treatment with immunosuppressive therapy and risk of progression suggests that other factors, including care access and timing of therapy initiation, may contribute to the overall risk of fibrotic progression, and highlights the need for early identification and close monitoring of patients with ILD at risk for PPF.

CRediT authorship contribution statement

Maeve Macmurdo: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Xinge Ji:** Formal analysis, Data curation. **Pratik Pimple:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Amy L. Olson:** Writing – review & editing, Methodology, Conceptualization. **Alex Milinovich:** Methodology, Formal analysis, Data curation. **Blaine Martyn-Dow:** Writing – review & editing, Methodology, Formal analysis. **Aman Pande:** Writing – review & editing. **Alex Zajichek:** Writing – review & editing, Formal analysis, Data curation. **Janine Bauman:** Writing – review & editing, Project administration. **Shaun Bender:** Writing – review & editing, Methodology, Conceptualization. **Craig Conoscenti:** Writing – review & editing, Methodology, Conceptualization. **David Sugano:** Writing – review & editing, Methodology, Conceptualization. **Michael W. Kattan:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Daniel A. Culver:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107656.

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