Epidemiology and Prognostic Significance of Cough in Fibrotic Interstitial Lung Disease

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At a Glance Commentary (85/200 words)

Scientific Knowledge on the Subject: Cough is a common symptom in patients with fibrotic interstitial lung disease (ILD). Little is known about cough severity and health outcomes in this population.

What This Study Adds to the Field: Cough severity measured using visual analog scale persists and worsens over time in patients with idiopathic pulmonary fibrosis (IPF) and non-IPF fibrotic ILD irrespective of ILD-targeted therapy. Patient-reported cough severity has prognostic implications on health-related quality of life, disease progression, and transplant-free survival in patients with fibrotic ILD.

This article has an online data supplement, which is accessible at the Supplements tab.

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ABSTRACT

Rationale: Cough is a key symptom in patients with fibrotic interstitial lung disease (ILD).

Objective: This study evaluated the prevalence, longitudinal change, associations, and prognostic significance of cough severity in patients with fibrotic ILD.

Methods: We included consecutive patients with idiopathic pulmonary fibrosis (IPF) and non-IPF fibrotic ILD who completed the 100mm-Cough Severity Visual Analog Scale (VAS) from the prospective multi-center Canadian Registry for Pulmonary Fibrosis. Baseline cough severity and associations with patient demographics and clinical factors were determined. Relationships between baseline cough severity and health outcomes were evaluated.

Measurements and Main Results: Patients with IPF (n=1061) had higher median baseline cough severity than those with non-IPF fibrotic ILD (n=2825) [24 vs 20mm, p<0.001], with worse cough associated with gastroesophageal reflux disease for both cohorts. Worse cough severity was independently associated with worse health-related quality of life at baseline, larger annualized decline in DLCO, development of disease progression, and reduced transplant-free survival in both IPF and non-IPF fibrotic ILD cohorts. The IPF cohort (2.2mm, 95% CI 1.6-2.9mm) had larger annualized increments in cough severity compared to the non-IPF fibrotic ILD cohort (1.1mm, 95% CI 0.8-1.4mm; p=0.004). There was no difference in worsening cough over time comparing those receiving and not receiving ILD-targeted therapy or with and without lung function decline.

Conclusion: Cough is common in patients with IPF and non-IPF fibrotic ILD, with increasing cough severity over time irrespective of ILD-targeted therapy. Patient-reported cough severity has prognostic implications on health-related quality of life, disease progression, and survival in fibrotic ILD.

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KEYWORDS: Interstitial lung disease, idiopathic pulmonary fibrosis , cough, chronic cough, health outcomes

INTRODUCTION

Cough is one of the most common symptoms experienced by patients with fibrotic interstitial lung disease (ILD), a heterogeneous group of chronic inflammatory and fibrotic lung conditions. Importantly, cough can result in substantial physical, psychological, and social burden in patients with fibrotic ILD (1). The presence of cough is also independently associated with disease progression in patients with idiopathic pulmonary fibrosis (IPF), the prototypic subtype of fibrotic ILD (2). However, little is known about cough severity and disease outcomes in patients with fibrotic ILD, which is critical to inform clinical practice for cough assessment and patient counseling, as well as trial design for effective non-pharmacological and pharmacological interventions for cough in this population. Of the currently available cough-specific patient-reported outcome assessment tools, the Cough Severity Visual Analog Scale (VAS) is simple and has moderate-to-strong correlations with objective cough frequency in patients with IPF (3) and other chronic lung diseases (4-6).

This study aimed to evaluate cough severity in patients with fibrotic ILD, relationships with baseline clinical parameters, disease progression, and prognosis, as well as its longitudinal changes. We hypothesized that the severity of cough would vary between patients with IPF and non-IPF fibrotic ILD and would be associated with lung function impairment and selected relevant comorbidities, including airway diseases and gastroesophageal reflux disease. We further hypothesized that cough severity would be independently associated with health-related quality of life (HRQoL), disease progression, and transplant-free survival in patients with IPF and non-IPF fibrotic ILD, and that cough severity would worsen over time.

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METHODS

Study design and population

This cohort study was conducted using the prospective multicentre Canadian Registry for Pulmonary Fibrosis (CARE-PF) (7). We included consecutive patients aged ≥ 18 years with a multidisciplinary diagnosis of fibrotic ILD and enrolled between 2015 and 2022 who completed the Cough Severity VAS at least at enrolment. Ethics approval was obtained from the coordinating site: University of British Columbia Research Ethics Board (H19-01368).

Data collection

Extracted data from the registry included patient demographics, smoking status, ILD subtype and diagnosis date, serial lung function including spirometry and diffusing capacity of the lung for carbon monoxide (DLCO), serial cough assessment using the Cough Severity VAS, and dates of death or lung transplantation, with censor date of 10th October 2022. The ILD disease severity was evaluated using the ILD-GAP Index (8). Prospective collection of serial Cough Severity VAS was completed during follow-up clinic reviews, with the intervals typically ranging between 3 and 12 months as clinically indicated.

Additional data included baseline comorbidities of interest and HRQoL measured using the EuroQol 5-Dimension 5-level questionnaire (EQ-5D-5L), European Quality of Life VAS (EQ-VAS), as well as St George's Respiratory Questionnaire (SGRQ) total score in a subgroup of patients with available data given that the SGRQ is no longer collected as part of CARE-PF. Respiratory symptoms, radiological assessments using computed tomography, and use of ILD-targeted pharmacotherapies were collected up to 2 years of follow-up using a standardized protocol-directed medical record review as previously described (9).

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Comorbidities of interest included asthma, chronic obstructive pulmonary disease or emphysema, cardiac disease, gastroesophageal disease, and rhinosinusitis, which were collected based on clinical documentation. Medications evaluated included antifibrotic medications (nintedanib and pirfenidone) and immunosuppressive medications (azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate, rituximab, tacrolimus, tocilizumab, and systemic corticosteroids of prednisone equivalence dose of ≥20 mg/day for ≥30 days).

The EQ-5D-5L is a generic questionnaire consisting of five questions with five response levels for each dimension: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression (10). Scores for each dimension are combined to form a 5-digit score and subsequently converted into an index score based on set values obtained from a reference population ranging from ranged from −0.148 for the worst to 0.949 for the best states (11). The EQ-VAS is a vertical visual analog scale, with patients being asked to rate their general health ranging from 0 (worst possible health) to 100 (best possible health) (10). The SGRQ is a 50-item questionnaire with the total possible score ranging from 0 to 100, with a higher score indicating worse HRQoL (12).

Evaluation of disease progression for both IPF and non-IPF fibrotic ILD was determined with anchoring to the date of baseline assessment according to the definition for progressive pulmonary fibrosis (PPF) proposed in the international clinical practice guideline using a combination of ≥2 of the following criteria over 1 year (13): worsening respiratory symptoms, physiological progression (absolute decline in forced vital capacity (FVC) ≥5% predicted and/or diffusion capacity of the lung for carbon monoxide (DLCO) ≥10%

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predicted), or radiological progression. **Appendix 1** provides detailed information on the evaluation of respiratory symptom and radiological progression, which was based on medical record review at individual sites (9).

Cough assessment

Cough was assessed using a VAS (14). The Cough Severity VAS is a linear scale of 100mm, starting at 0 as no cough with a higher score indicating a more severe cough. Patients were asked to mark their cough severity at the time of assessment, and the distance between the marked point and the starting point was measured as the score.

Statistical analysis

Statistical analyses were conducted using Stata (v17 StataCorp, USA). Separate analyses were performed for patients with IPF and non-IPF ILD. Summary statistics are presented as frequency (%) for categorical data and mean ± standard deviation or median (interquartile range) for continuous data depending on the distribution. Statistical significance was set at $p<0.0033$ to correct for multiplicity for association evaluation, and at $p<0.05$ for other analyses. The Cough Severity VAS was evaluated as a continuous outcome, as well as at a cut-off of 30mm, which is the reported minimal important difference determined by triangulation of multiple anchor-based approaches in individuals with chronic cough (6).

<u>Epidemiology and associations of cough severity at baseline</u>

The score distribution and the prevalence of Cough Severity VAS ≥30mm were determined. One-way ANOVA comparisons were used to examine differences in baseline cough severity for patients with IPF and non-IPF fibrotic ILD according to ILD severity based on the ILD-GAP

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Index. Correlations were performed to evaluate the relationships of baseline cough severity with FVC and DLCO percent-predicted. Unadjusted and multivariable linear regression models were performed to evaluate associations between the baseline cough severity and age, sex, race/ethnicity, smoking history, comorbidities, baseline forced expiratory volume in 1 second (FEV_1) percent-predicted, baseline FVC percent-predicted, baseline DLCO percent-predicted, and current use of ILD-targeted pharmacotherapies, with study site being used as a covariate.

Baseline cough severity and health outcomes

Associations of the baseline cough severity were examined using linear regression for the baseline EQ-5D-5L, EQ-VAS, and SGRQ and annualized changes in %-predicted FVC and DLCO, logistic regression for development of disease progression, and Cox proportional hazards models for transplant-free survival. Separate analyses of the associations with health outcomes were performed for baseline Cough Severity VAS ≥30. Variables included in adjusted analyses were determined a priori and included age, sex, baseline lung function (percent-predicted FVC and DLCO), ILD-targeted pharmacotherapies, and study site.

Longitudinal changes in cough severity

Annualized changes were calculated and compared using linear mixed models for longitudinal changes of the Cough Severity VAS following the baseline assessment (**Appendix 2**). Annualized changes in the scores were further evaluated according to the treatment status for ILD-targeted therapy and the physiological progression status based on FVC and/or DLCO as defined for disease progression over the follow-up period. Variables mentioned above for adjustment were included in these models. Subgroup analyses were

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performed to explore changes in cough severity scores for patients who were initiated on antifibrotic medications (nintedanib or pirfenidone) for IPF and immunosuppressive medications (azathioprine or mycophenolate) for non-IPF fibrotic ILD at 12 months following baseline evaluation, with sensitivity analyses being performed in those with baseline Cough Severity VAS ≥30mm.

RESULTS

Study population

Of the 3886 included patients, 1061 had IPF and 2825 had non-IPF fibrotic ILD (**Figure S1** and **Table 1**). The IPF cohort was older, had higher proportions of males and ever-smokers, and was more likely to have cardiac diseases, compared to the non-IPF fibrotic ILD cohort. At baseline, both cohorts had mild-to-moderate lung function impairment, with 40% of patients with IPF receiving antifibrotic medications and 44% of those with non-IPF fibrotic ILD receiving immunosuppressive medications.

Epidemiology and associations of cough severity at baseline

Baseline cough severity was higher for patients with IPF compared to patients with non-IPF fibrotic ILD (median 24 vs 20mm, $p<0.001$), although there were wide overlapping ranges for both cohorts (**Figure 1**). The prevalence of baseline Cough Severity VAS ≥30mm was higher in the IPF cohort compared to those with non-IPF fibrotic ILD (43% vs 39%; $p=0.03$). Median cough severity was higher with worsening ILD disease severity measured using the ILD-GAP Index for both cohorts ($p<0.001$ for both), but again with substantial variability across the severity groups (**Figure 2**) as well as lung function impairment (**Figure S2**).

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On unadjusted analyses of both the IPF and non-IPF cohorts, worse cough severity was consistently associated with worse lung function impairment as measured by FEV_1, FVC, and DLCO, and the presence of gastroesophageal reflux disease (**Table 2**). On unadjusted analysis in patients with IPF, cough severity was worse in patients who were never-smokers, were of European ancestry, and were treated with antifibrotic medications. On unadjusted analysis in patients with non-IPF fibrotic ILD, the presence of physician-reported asthma was associated with worse cough severity. On multivariable analyses, lower percent-predicted FVC and DLCO, as well as the presence of gastroesophageal reflux disease, remained associated with worse cough severity for both cohorts (**Table 3**). The presence of physician-reported asthma remained associated with worse cough severity in patients with non-IPF fibrotic ILD.

Baseline cough severity and health outcomes

Cough severity both as a continuous variable and at the ≥30mm threshold was independently associated with worse HRQoL and health status at baseline for both IPF and non-IPF fibrotic cohorts. Of the 3886 patients, 2507 had serial lung function tests and 2323 had follow-up clinical and radiological assessments for evaluation of disease progression. In both patients with IPF and non-IPF fibrotic ILD, higher cough severity both as a continuous variable and at the ≥30mm threshold was independently associated with larger annualized decline in DLCO, development of disease progression, and worse transplant-free survival (**Table 4**). There was no association between cough severity and change in FVC.

Longitudinal changes in cough severity

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The Cough Severity VAS increased over time for patients with IPF (annualized change: 2.2mm, 95% CI 1.6 to 2.9mm) and non-IPF fibrotic ILD (annualized change: 1.1mm, 95% CI 0.8 to 1.4mm) (**Figure 3**). The IPF cohort had larger annualized increment in cough severity (p=0.004), compared to the non-IPF fibrotic ILD cohort. Annualized changes in cough severity for both the IPF and non-IPF fibrotic ILD cohorts were comparable between those receiving and not receiving ILD-targeted therapy during the study period (IPF: p=0.60; non-IPF fibrotic ILD: p=0.95; **Figure S3**). There were no significant differences between patients with and without physiological progression based on FVC and DLCO in the IPF (p=0.29) and non-IPF fibrotic ILD cohorts (p=0.19), although the annualized increments were numerically larger in those with progression for both cohorts (**Figure S4**). Subgroup analyses revealed similar persistence or increment in cough severity at 12 months in patients receiving nintedanib (baseline: 27.3mm, 95% CI 23.8 to 30.7mm; 12 months: 38.8mm, 95% CI 33.7 to 43.9mm) or pirfenidone (baseline: 29.5mm, 95% CI 24.7 to 34.4mm; 12 months: 40.6mm, 95% CI 33.1 to 48mm; p=0.92) for IPF, as well as in patients receiving azathioprine (baseline: 28.9 mm, 95% CI 22 to 35.8mm; 12 months: 42.2mm, 95% CI 32.9 to 51.4mm) or mycophenolate (baseline: 26.8mm, 95% CI 24.2 to 29.4mm; 12 months: 34.6mm, 95% CI 31.3 to 38mm; p=0.27) for non-IPF fibrotic ILD, with similar results in those with baseline Cough Severity VAS ≥30mm (**Table S1**).

DISCUSSION

We used a large multicentre cohort of patients with IPF and non-IPF fibrotic ILD to provide a comprehensive evaluation of both baseline and longitudinal change in cough severity. We show that patients with IPF had worse cough severity compared to those with non-IPF fibrotic ILD at baseline assessment. Although cough severity was associated with lung

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function impairment, there was substantial variability across IPF and non-IPF fibrotic ILD cohorts across different stages of disease severity. Cough severity at baseline was independently associated with HRQoL and subsequent disease progression and transplant-free survival. There was worsening cough severity of small magnitude during follow-up for both the IPF and non-IPF fibrotic ILD cohorts, which was similar between those treated and untreated with ILD-targeted therapy and those with and without lung function decline.

Cough is a multi-dimensional symptom with different aspects, including its severity related to frequency and intensity, as well as its impact on physical, emotional, and social well-being. Previous research on cough in fibrotic ILD has focused on its presence or absence, as well as its impact as measured by cough-related quality of life, with most studies being conducted in relatively small numbers of patients (2, 15-19). Our study adds substantial data to the existing literature and extends beyond patients with IPF, confirming the major burden of cough in fibrotic ILD. Furthermore, despite the associations of cough severity with lung function impairment and disease severity in patients with fibrotic ILD, we showed that cough severity varied widely for individual patients. There were patients with mild ILD reporting severe cough. This emphasizes the importance of incorporating cough assessment into patient care across the fibrotic ILD population, irrespective of disease severity. The Cough Severity VAS can be easily administered in clinical settings beyond research purposes with low patient response burden, which is desirable for practical considerations (20).

To date, there are limited data on the longitudinal symptom trajectory of cough in patients with fibrotic ILD, which focused on those with IPF. A recent study of over 600 patients with IPF reported that cough-related quality of life measured using the Leicester Cough

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Questionnaire remained stable during the disease course of individual patients over one year, but only one-third had serial cough assessments (19). Our IPF and non-IPF fibrotic ILD populations had worsening Cough Severity VAS during follow-up, although the mean changes on a population level were small and clinical significance of the magnitude of changes is uncertain. Nevertheless, this suggests cough symptom generally is persistent during the disease course of patients with fibrotic ILD. Of note, baseline Cough Severity VAS was prognostically significant for the development of disease progression and transplant-free survival for both IPF and non-IPF fibrotic cohorts. Previous studies showed the prognostic value for the presence of cough in patients with fibrotic ILD (2), with conflicting findings for the degree of cough-related quality of life impairment (18, 19). These differences may be attributed to evaluation of different aspects of cough, the definition of disease progression, and characteristics of included patients. Our study included the largest cohort of patients with a variety of fibrotic ILD subtypes and used the contemporary definition of PPF for evaluation of disease progression (13, 21), supporting the relevance and generalizability of study findings.

Importantly, cough severity was independently associated with HRQoL and health status using different validated patient-reported outcome measures at baseline in both IPF and non-IPF fibrotic ILD. Our findings strengthen previous findings of the association between cough severity and HRQoL measured using the St George's Respiratory Questionnaire (15) and the King’s Brief ILD Questionnaire (22) in patients with fibrotic ILD. This is also consistent with patients’ perspective of the substantial impact of cough on different aspects of their health and daily living (1, 23-25). While dyspnoea may be a more commonly reported symptom than cough in patients with fibrotic ILD (26), the physical, psychological,

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and social impacts of cough are also of major consequence for both patients and their caregivers (1, 23-25). For example, a previous study of patients with IPF showed that increased cough severity was independently associated with anxiety and depression, in addition to the dyspnoea level (27).

Our findings that cough severity was associated with HRQoL, disease progression, and transplant-free survival in patients with fibrotic ILD highlight the potential benefits of effective interventions for cough. In both patients with IPF and non-IPF fibrotic ILD, those with lung function decline had numerically, although not statistically, worsened cough severity during follow-up than those without lung function decline. Persistent cough in patients with fibrotic ILD may perpetuate lung fibrosis and mediate disease progression through mechanostimulation. Mechanical strain is known to be a stimulus for myofibroblast differentiation, and contributes to activation of the profibrotic transforming growth factor-β (28, 29). Tension from stretch and deformation of alveolar epithelial cells can result in tissue injury and remodeling (30-32). Inhibition of fibroblast mechanotransduction pathways has been shown to modulate lung inflammation and fibrosis in animal models and in vivo human studies (33). There is a need to study the potential mechanistic association of cough and disease mechanisms in fibrotic ILD, which may uncover novel therapeutic targets and the resultant treatment effects.

Of note, there were no significant differences in annualized changes in the cough severity between patients who were treated and untreated with targeted therapy for both IPF and non-IPF fibrotic ILD. Contrary to the recent report (34), our cohorts of newly treated patients for IPF and non-IPF fibrotic ILD showed increasing cough severity at 12 months

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following medication initiation. These findings suggest it is important to continue monitoring cough symptom in patients with fibrotic ILD irrespective of their treatment status. There is no high-level evidence of effective therapeutic interventions for cough in fibrotic ILD. Pirfenidone reduced objective cough frequency and patient-reported cough severity and impact in a small uncontrolled observational study of patients with IPF (35), while nintedanib did not alter cough-related quality of life in post-hoc analyses of randomized controlled trials for IPF (36). In the Scleroderma Lung Study II, post-hoc analyses showed that mycophenolate and cyclophosphamide reduced frequent cough and improved cough-related quality of life (37). The effects of antifibrotic medications on cough in patients with non-fibrotic ILD could not be assessed as their indication for non-IPF fibrotic ILD has only been recently approved.

Some comorbidities may contribute to cough in patients with fibrotic ILD, which may serve as potential treatment targets. Gastroesophageal reflux disease was independently associated with cough for both our IPF and non-IPF fibrotic ILD cohorts, although data on the use of antacid medications are lacking, which warrants prospective evaluation given previous studies reporting conflicting results (16, 18). Ever-smokers with IPF reported reduced cough severity. This is consistent with decreased cough reflex sensitivity and cognition of urge-to-cough observed in healthy smokers (38, 39), which may be facilitated by enhanced descending central inhibitory control for cough (40) There are emerging findings on nicotinic acetylcholine receptor allosteric modulators as novel therapeutic agents for cough suppression (41). Associations of cough severity and airway diseases were inconsistent with evaluation of physician-reported asthma, COPD, and percent-predicted FEV_1, with the need for further evaluation in future studies.

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This study has limitations. Serial patient assessments, including measurements of the Cough Severity VAS, were not performed during regular clinical visits but without a prespecified schedule. Nevertheless, the assessment intervals typically ranged between 3 and 12 months, which reflects real-world clinical practice. Objective cough evaluation was not performed in this study, which was not feasible to conduct in a large population. There may be variations in individual clinicians' thresholds for evaluating symptom and radiological progression across different sites. However, this approach represents real-world clinical evaluation supporting wide application of our study findings. While we evaluated common comorbidities that could influence cough severity, there may be other comorbidities and concomitant medications that were not assessed. Treatments with cough-specific medications such as opioid medications and comorbidities of interest such as gastroesophageal reflux disease and airway diseases were not evaluated in this study, and thus their therapeutic effects on cough in patients with fibrotic ILD could not be investigated.

Cough was assessed using the Cough Severity VAS, which allowed completion of serial measurements in a large cohort given its ease of use. Our findings support its clinical value for prognostication in patients with fibrotic ILD. One drawback of the Cough Severity VAS is that it provides a composite measure without evaluating the different aspects of cough severity such as frequency, intensity, and impact on daily living. However, the Cough Severity VAS has good validity with moderate-to-strong correlation of 0.71 to 0.8 against objective cough counts in patients with IPF (3). In recent clinical trials of cough interventions of patients with IPF, the Cough Severity VAS also correlated with changes in objective cough

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counts and cough-specific HRQoL questionnaires (42, 43). Nevertheless, there remain gaps in our understanding of the measurement properties of the Cough Severity VAS.

CONCLUSION

Cough is a significant symptom of high burden and substantial health impacts in patients with fibrotic ILD. Patients with IPF have worse cough severity at baseline than those with non-IPF fibrotic ILD. Patients with fibrotic ILD have persistent cough with small magnitude of worsening over time, which is worse in those with IPF. Patient-reported cough severity is prognostically relevant for health-related quality of life, disease progression, and survival in patients with fibrotic ILD. Cough severity persists and worsens over time in patients with IPF and non-IPF fibrotic ILD, irrespective of the use of ILD-targeted therapy. The Cough Severity VAS is promising for cough evaluation in patients with fibrotic ILD in both clinical and research settings, although further validation of its measurement properties is warranted. Our findings add to the understanding of the trajectories and significance of cough in fibrotic ILD, supporting the urgent need for the development of drug discovery and intervention strategies for effective cough management in this population.

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Figure Legends

Figure 1. Score distribution of the Cough Severity Visual Analog Scale at baseline for patients with (a) IPF and (b) non-IPF fibrotic ILD.

Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

Figure 2. Score distribution of the Cough Severity Visual Analog Scale at baseline for patients with (a) IPF and (b) non-IPF fibrotic ILD based on the ILD-GAP Index.

Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; VAS, visual analog scale

Figure 3. Annualized changes in cough severity stratified by ILD diagnosis

Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

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Table 1. Characteristics for IPF and non-IPF fibrotic ILD cohorts.

	IPF (n = 1061)		Non-IPF fibrotic ILD (n = 2825)	
Age at baseline, years	71 ± 8		62 ± 12	
Male sex	796 (75)		1209 (43)	
Race / ethnicity				
• **African/African American**	6 (0.5)		62 (2.2)	
• **Asian (Including Indian/Southeast Asian)**	65 (6)		343 (12.1)	
• **European**	942 (89)		2265 (80)	
• **First Nation**	26 (2.5)		81 (3)	
• **Hispanic or Latino**	4 (0.5)		12 (0.5)	
• **Métis**	0 (0)		5 (0.2)	
• **Pacific Islander**	4 (0.5)		23 (0.8)	
• **Not specified**	14 (1)		34 (1.2)	
BMI at baseline, kg/m²	28 (26-32)		28 (25-33)	
Smoking history at baseline				
• **Ever-smoker**	811 (76)		1619 (57)	
• **Pack-years among smokers**	26 (12-40)		18 (6-33)	
Pulmonary function at baseline				
• **FEV_1/FVC**	0.81 ± 0.08		0.79 ± 0.09	
• **FEV_1, % predicted**	81 ± 19		77 ± 21	
• **FVC, % predicted**	76 ± 19		76 ± 21	
• **DLCO, % predicted**	52 ± 17		59 ± 21	
Non-IPF ILD subtypes				
• **CTD-ILD**	-		1210 (43)	
• **Fibrotic HP**	-		305 (11)	
• **Idiopathic interstitial pneumonia**	-		152 (5)	
• **Sarcoidosis**	-		150 (5)	
• **Unclassifiable ILD**	-		871 (31)	
• **Other***	-		137 (5)	
Comorbidities at baseline†				
• **Asthma**	27 (3)		176 (6)	
• **COPD or emphysema**	82 (8)		142 (5)	
• **Cardiac diseases‡**	258 (24)		331 (12)	
• **Gastroesophageal reflux disease**	294 (28)		650 (23)	
• **Rhinosinusitis**	66 (6)		142 (5)	
ILD-targeted therapy used	**At baseline**	**1-year follow-up**	**At baseline**	**1-year follow-up**
• **Antifibrotic medications**	423 (40)	724 (68)	53 (3)	109 (4)
– **Nintedanib**	268 (25)	470 (44)	37 (1)	79 (3)
– **Pirfenidone**	157 (15)	297 (28)	16 (0.5)	34 (1)
• **Immunosuppressive medications**	37 (3)	70 (7)	1242 (44)	1583 (56)
– **Azathioprine**	5 (0.5)	11 (1)	228 (8)	293 (10)
– **Cyclophosphamide**	0 (0)	1 (0.1)	23 (1)	40 (1)
– **Cyclosporine**	2 (0.2)	2 (0.2)	6 (0.2)	9 (0.3)
– **Methotrexate**	1 (0.1)	2 (0.2)	127 (4)	153 (5)
– **Mycophenolate**	10 (1)	16 (2)	753 (27)	1067 (38)
– **Prednisone**	17 (2)	46 (4)	164 (6)	285 (10)
– **Rituximab**	1 (0.1)	1 (0.1)	116 (4)	196 (7)
– **Tacrolimus**	1 (0.1)	1 (0.1)	11 (0.4)	16 (0.6)
– **Tocilizumab**	0 (0)	0 (0)	6 (0.2)	8 (0.3)

Data are expressed as mean ± standard deviation, median (interquartile range), or n (%).

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease-associated interstitial lung disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

* Other non-IPF ILD subtypes included chronic eosinophilic pneumonia (n=7), drug-induced ILD (n=43), pneumoconiosis (n=31), smoking-related ILD (n=7), and vasculitis (n=49)

† Defined as documented comorbidities from chart review

‡ Included ischemic heart disease and heart failure

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Table 2. Unadjusted analyses for associations of cough severity with clinical parameters

Parameters	IPF			Non-IPF fibrotic ILD		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Age (per 10 years)	-2.26	-4.27, -0.26	0.03	0.80	-0.01, 1.61	0.05
Male sex	-0.01	-0.04, 0.02	0.53	-0.02	-0.08, 0.03	0.41
European ancestry	7.74	2.59, 12.89	0.003	0.81	-1.77, 3.38	0.54
Smoking history						
• Ever-smoker	-7.22	-11, -3.46	<0.001	0.40	-1.63, 2.43	0.70
• Pack-years	-0.10	-0.17, -0.03	0.005	-0.01	-0.05, 0.05	0.90
Pulmonary function						
• FEV_1, % predicted (per 10%)	-3.62	-4.45, -2.79	<0.001	-2.17	-2.65, -1.68	<0.001
• FVC, % predicted (per 10%)	-4.26	-5.07, -3.45	<0.001	-2.65	-3.13, -2.18	<0.001
• DLCO, % predicted (per 10%)	-3.54	-4.42, -2.65	<0.001	-2.48	-2.97, -1.98	<0.001
Comorbidities						
• Asthma	6.65	-3.52, 16.82	0.20	9.68	5.43, 13.72	<0.001
• COPD/emphysema	-1.66	-7.67, 4.35	0.59	0.65	-3.94, 5.24	0.78
• Cardiac disease	-0.31	-4.05. 3.42	0.87	2.69	-4.24, 5.81	0.09
• GORD	5.76	2.15, 9.36	0.002	4.18	1.74, 6.62	0.001
• Rhinosinusitis	5.89	-0.79, 12.57	0.08	2.30	-2.30, 6.89	0.98
ILD-targeted therapy used						
• Antifibrotic medications	6.92	3.61, 10.23	<0.001	8.30	0.88, 15.72	0.03
• Immunosuppressive medications	11.56	2.87, 20.24	0.009	1.78	-0.26, 3.81	0.09

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GORD, gastroesophageal reflux disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

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Table 3. Multivariable analyses for associations of cough severity with clinical parameters

Parameters	IPF			Non-IPF fibrotic ILD		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Age (per 10 years)	-2.09	-4.33, 0.25	0.05	0.83	-0.09, 1.74	0.08
Male sex	-0.03	-0.06, 0.01	0.09	-0.03	-0.08, 0.02	0.25
European ancestry	3.53	-1.56, 8.62	0.17	0.36	-2.29, 3.01	0.79
Smoking history						
• Ever-smoker	-4.08	-8.33, 0.18	0.06	1.27	-1.19, 3.73	0.31
• Pack-years	-0.04	-0.12, 0.04	0.30	-0.05	-0.11, 0.01	0.13
Pulmonary function						
• FEV_1, % predicted (per 10%)	1.81	-0.34, 3.96	0.10	0.76	-0.43, 1.95	0.21
• FVC, % predicted (per 10%)	-4.22	-6.39, -2.06	<0.001	-2.58	-3.80, -1.36	<0.001
• DLCO, % predicted (per 10%)	-2.62	-3.59, -1.64	<0.001	-1.53	-2.13, -0.93	<0.001
Comorbidities						
• Asthma	9.68	-0.36, 19.72	0.06	9.21	5.00, 13.41	<0.001
• COPD/emphysema	2.15	-3.90, 8.20	0.70	0.12	-4.84, 5.09	0.06
• Cardiac disease	0.83	-2.78, 4.44	0.65	0.21	-3.05, 3.47	0.90
• GORD	4.85	1.49, 7.40	0.001	4.15	1.76, 6.55	0.001
• Rhinosinusitis	6.85	0.51, 13.19	0.03	2.55	-2.09, 7.20	0.28
ILD-targeted therapy used						
• Antifibrotic medications	3.29	0.05, 6.52	0.05	4.68	-3.01, 12.16	0.24
• Immunosuppressive medications	3.51	-4.97, 12.00	0.42	-0.23	-2.34, 1.88	0.83

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GORD, gastroesophageal reflux disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

* All variables listed in the table were included for multivariable analyses

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Table 4. Associations of baseline cough severity and health outcomes in IPF and non-IPF fibrotic ILD

Parameters	IPF				Non-IPF			
	Unadjusted analyses*		Adjusted analyses†		Unadjusted analyses*		Adjusted analyses†	
Baseline EQ-5D-5L‡	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Cough Severity VAS	-0.002 (-0.003, -0.001)	<0.001	-0.002 (-0.002, -0.001)	<0.001	-0.003 (-0.003, -0.002)	<0.001	-0.002 (-0.002, -0.001)	<0.001
Cough Severity VAS ≥ 30mm	-0.10 (-0.12, 0.08)	<0.001	-0.07 (-0.09, -0.05)	<0.001	-0.12 (-0.14, -0.11)	<0.001	-0.10 (-0.11, -0.08)	<0.001
Baseline EQ-VAS‡	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Cough Severity VAS	-0.24 (-0.28, -0.20)	<0.001	-0.18 (-0.23, -0.14)	<0.001	-0.23 (-0.25, -0.20)	<0.001	-0.18 (-0.21, -0.16)	<0.001
Cough Severity VAS ≥ 30mm	-11.27 (-13.50, -9.04)	<0.001	-8.14 (-10.40, -5.87)	<0.001	-11.35 (-12.82, -9.89)	<0.001	-8.85 (-10.32, -7.37)	<0.001
Baseline SGRQ total score‡§	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Cough Severity VAS	0.48 (0.43, 0.53)	<0.001	0.40 (0.35, 0.45)	<0.001	0.42 (0.39, 0.45)	<0.001	0.36 (0.32, 0.39)	<0.001
Cough Severity VAS ≥ 30mm	21.55 (18.87, 24.23)	<0.001	17.00 (14.29, 19.63)	<0.001	21.00 (19.10, 22.90)	<0.001	17.37 (15.54, 19.20)	<0.001
Annualized change in FVC %-predicted	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Cough Severity VAS	-0.04 (-0.07, -0.01)	0.03	-0.03 (-0.06, 0.01)	0.07	-0.02 (-0.03, 0.01)	0.07	-0.02 (-0.04, -0.01)	0.04
Cough Severity VAS ≥ 30mm	-1.47 (-3.15, 0.21)	0.09	-1.34 (-3.09, 0.40)	0.13	-0.71 (-1.65, 0.23)	0.14	-0.85 (-1.81, 0.11)	0.08
Annualized change in DLCO %-predicted	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Cough Severity VAS	-0.07 (-0.11, -0.03)	0.001	-0.08 (-0.11, -0.04)	<0.001	-0.02 (-0.04, 0.01)	0.08	-0.03 (-0.06, -0.01)	0.005
Cough Severity VAS ≥ 30mm	-2.80 (-4.80, -0.82)	0.006	-3.30 (-5.27. -1.34)	0.001	-0.92 (-2.19, 0.35)	0.15	-1.61 (-2.86, -0.36)	0.01
Development of disease progression‖	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Cough Severity VAS	0.01 (0.01, 0.02)	<0.001	0.01 (0.01, 0.015)	0.016	0.01 (0.00, 0.01)	<0.001	0.01 (0.00, 0.01)	0.01

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Cough Severity VAS ≥ 30mm	0.64 (0.33, 0.95)	<0.001	0.43 (0.09, 0.77)	0.01	0.37 (0.19, 0.56)	<0.001	0.24 (0.05, 0.44)	0.01
Transplant-free survival	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Cough Severity VAS	1.01 (1.01, 1.02)	< 0.001	1.01 (1.00, 1.01)	< 0.001	1.01 (1.00, 1.01)	< 0.001	1.01 (1.00, 1.01)	< 0.001
Cough Severity VAS ≥ 30mm	2.02 (1.68, 2.42)	< 0.001	1.40 (1.15, 1.70)	0.001	1.72 (1.49, 1.99)	< 0.001	1.36 (1.17, 1.58)	< 0.001

Abbreviations: CI, confidence interval; DLCO, diffusing capacity for carbon monoxide; EQ-5D-5L, EuroQol 5-Dimension 5-level questionnaire; FVC, forced vital capacity; ILD, interstitial lung disease; HRQoL, health-related quality of life; IPF, idiopathic pulmonary fibrosis; SGRQ, St George's Respiratory Questionnaire; VAS, visual analog scale

[*] Unadjusted analyses included study site as a covariate.

[†] Adjusted analyses were adjusted for age, sex, FVC % predicted, DLCO % predicted, ILD-targeted therapy use, and study site

[‡] EQ-5D-5L: higher score indicates better HRQoL; EQ-VAS: higher score indicates better health status; SGRQ: higher score indicates worse HRQoL

[§] SGRQ was collected in a subgroup of patients: N = 636 for IPF, N=1614 for non-IPF fibrotic ILD

[ll] Disease progression was defined as a combination of ≥2 of the following criteria over 1 year: worsening respiratory symptoms, physiological progression (absolute decline in FVC ≥5% predicted and/or DLCO ≥10% predicted), or radiological progression

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Epidemiology and Prognostic Significance of Cough in Fibrotic Interstitial Lung Disease

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ONLINE DATA SUPPLEMENT

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Appendix 1. Medical record review for evaluation of respiratory symptom and radiological progression

Standardized protocol-directed detailed review of medical records was conducted at all study sites of CARE-PF for respiratory symptom and radiological progression within 24 months of the ILD diagnosis (observations up to 27 months being allowed to account for variable follow-up intervals), as follows:

- Respiratory symptom progression: Based on available clinical notes from the patient's medical records with interpretation and judgment by the site investigators. Key terms for evaluation of respiratory symptom progression included breathlessness, dyspnoea, shortness of breath, respiratory symptoms, cough, functional capacity, functional ability, exercise capacity, exercise ability, increased oxygen use, and increase in Medical Research Council dyspnoea scale to a higher number. Transient clinical worsening of less than 1 month in duration was not considered sufficient to meet this criterion.
- Radiological progression: Based on available documentation of repeat computed tomography of chest in the clinic letters/notes/referrals or in radiology reports. Key terms for evaluation of radiological progression included worsening fibrosis, honeycombing, interstitial changes, reticulation, architectural distortion, and traction bronchiectasis. Direct image reviews were not mandatory at the discretion of the site investigator.

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Appendix 2. Linear mixed model for longitudinal cough severity

Linear mixed models were used to assess change in the Cough Severity Visual Analog Scale scores over the 24 months of follow-up. This approach allows subjects to have different numbers of observations that are measured at unequal time intervals. Time from baseline was treated as a continuous variable. Random intercept and random slope were used for the subjects to account for between-subject variability and within-subject correlation, respectively. Fixed effects included were time from baseline, comparison groups (idiopathic pulmonary fibrosis (IPF) versus non-IPF fibrotic interstitial lung disease (ILD), treatment status for ILD-targeted therapy and physiological progression status in the IPF and non-IPF fibrotic ILD cohorts), and their interaction. Covariates were selected a priori and included as fixed effects with an independent covariance structure: age, sex, baseline forced vital capacity, baseline diffusing capacity of the lung for carbon monoxide, and study sites.

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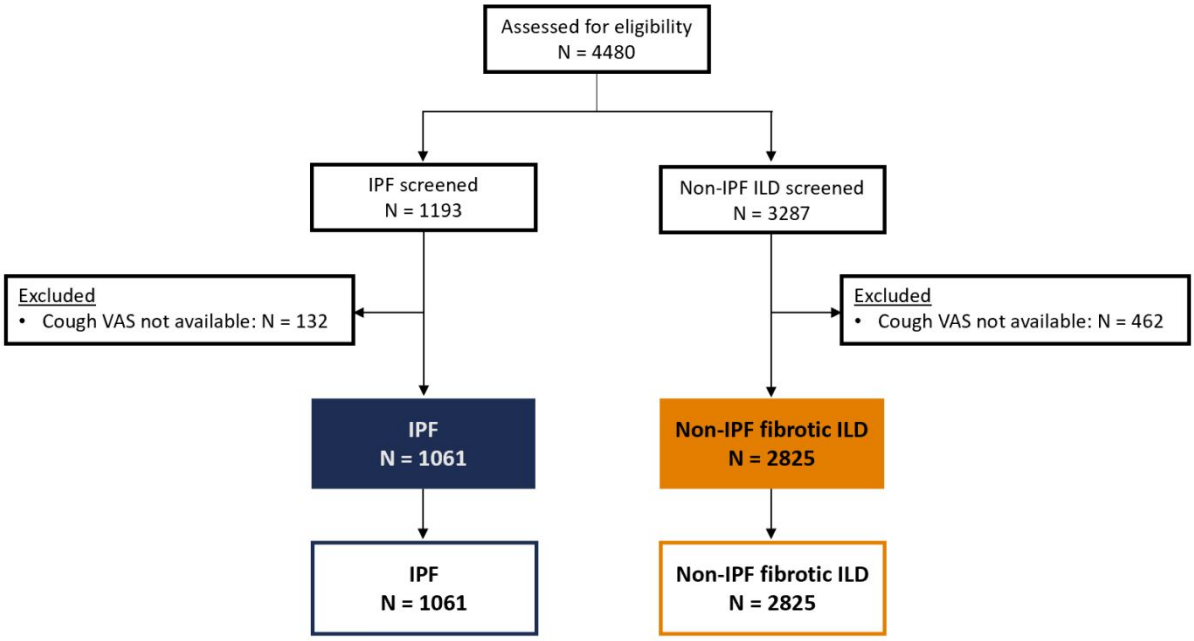
Figure S1. Study flow diagram



Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; VAS, visual analog scale

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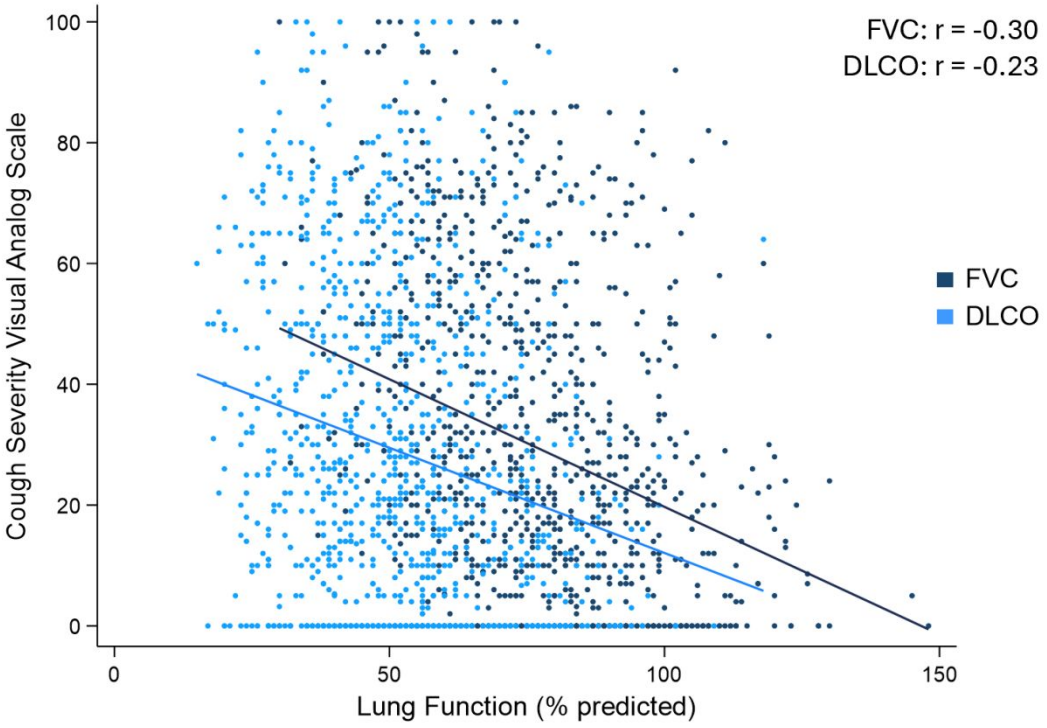
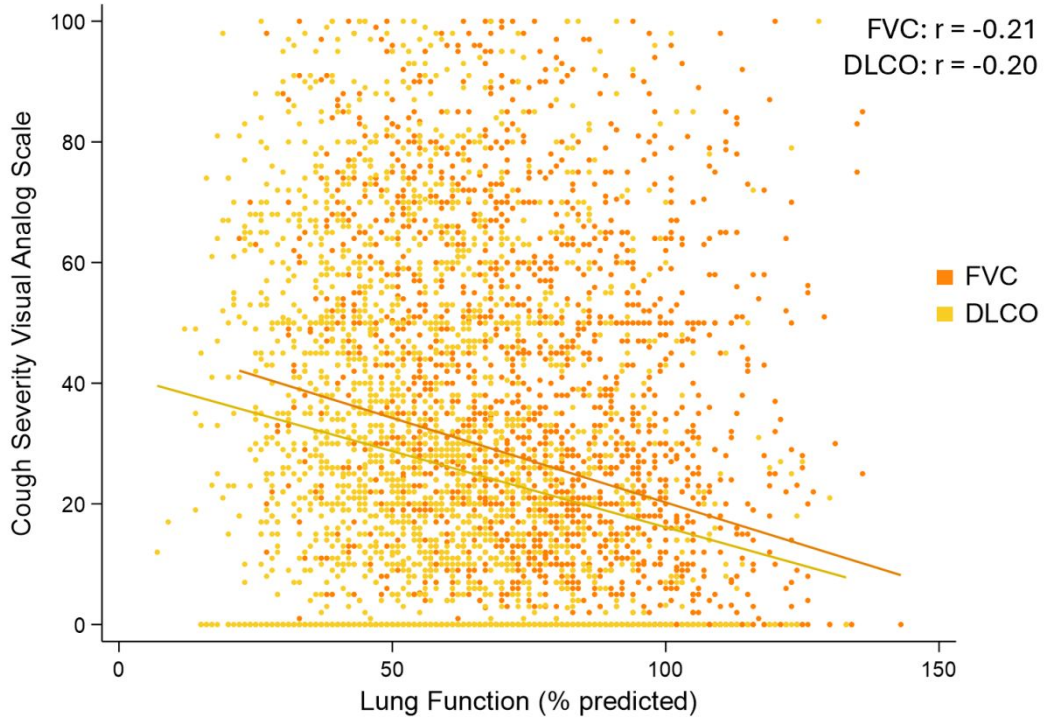
Figure S2. Scatter plots of cough severity and lung function measurements at baseline for IPF and non-IPF fibrotic cohorts

(a) IPF



(b) Non-IPF fibrotic ILD



Abbreviations: DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

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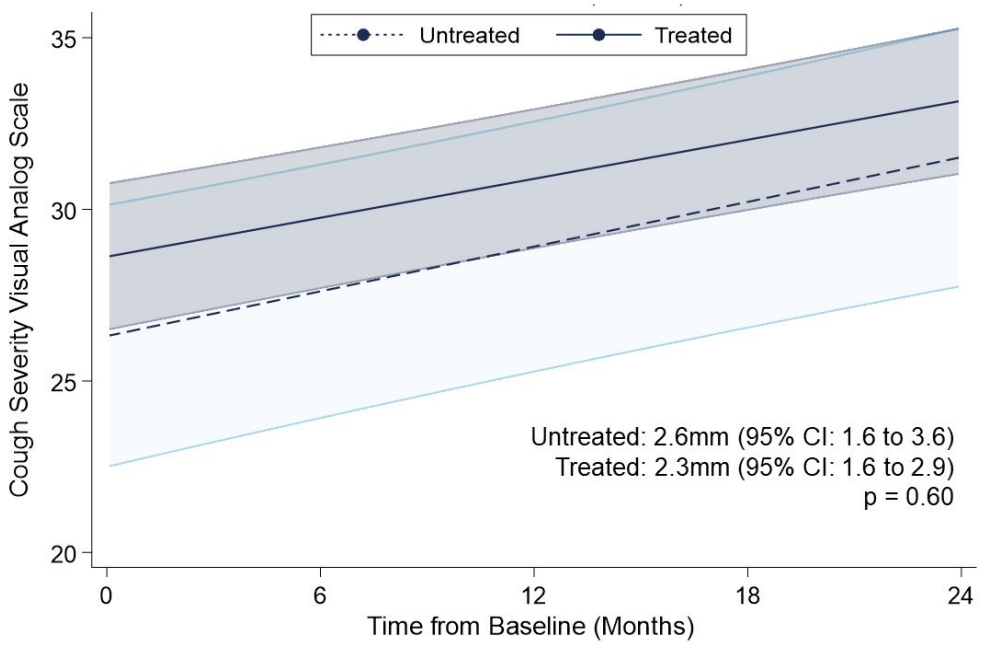
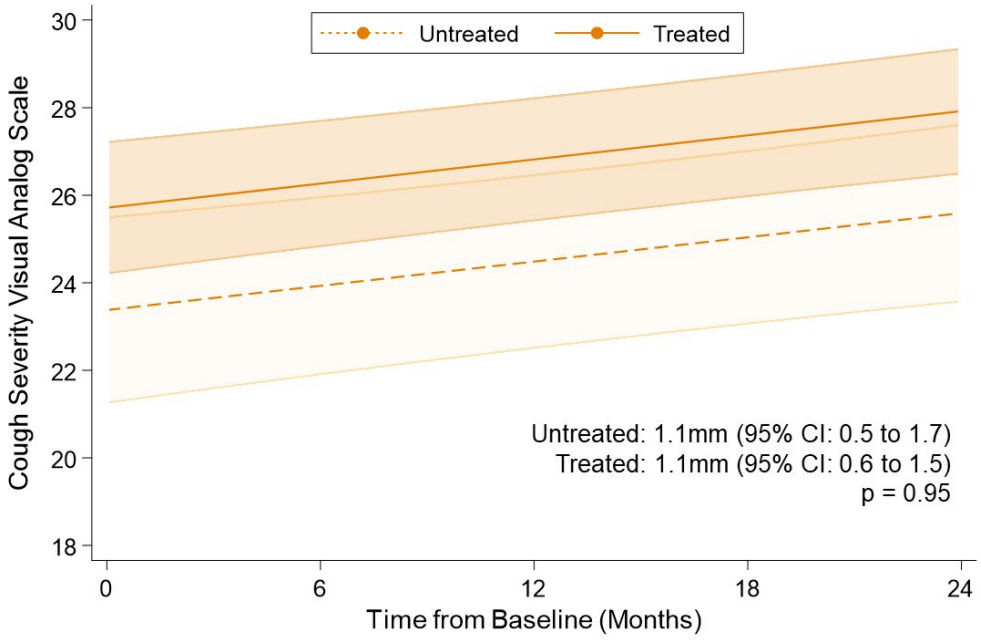
Figure S3. Annualized changes in cough severity for IPF and non-IPF fibrotic cohorts stratified by treatment status for ILD-targeted therapy

(a) IPF



(b) Non-IPF fibrotic ILD



Abbreviations: CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

* Shaded areas represent 95% confidence intervals

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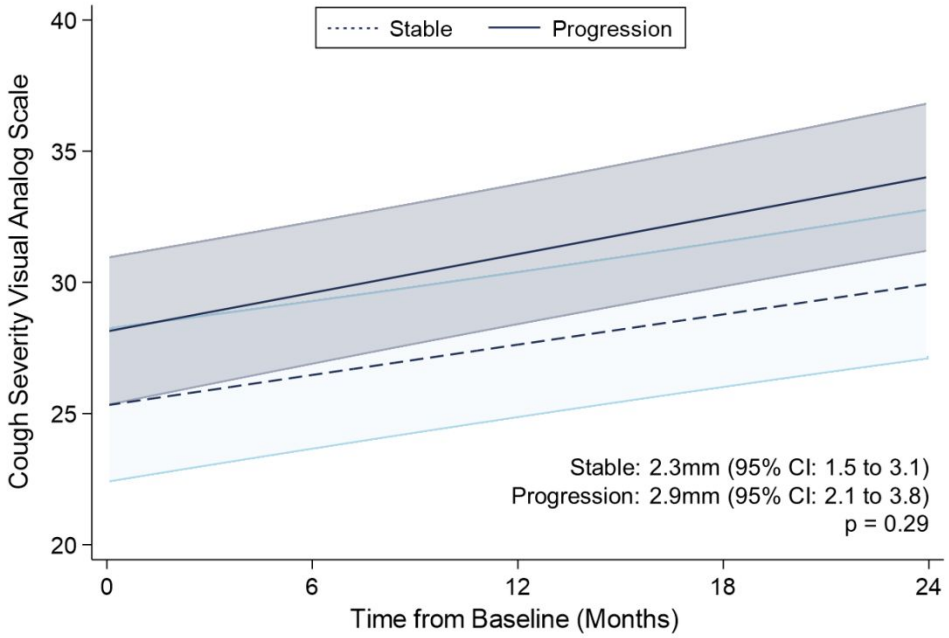
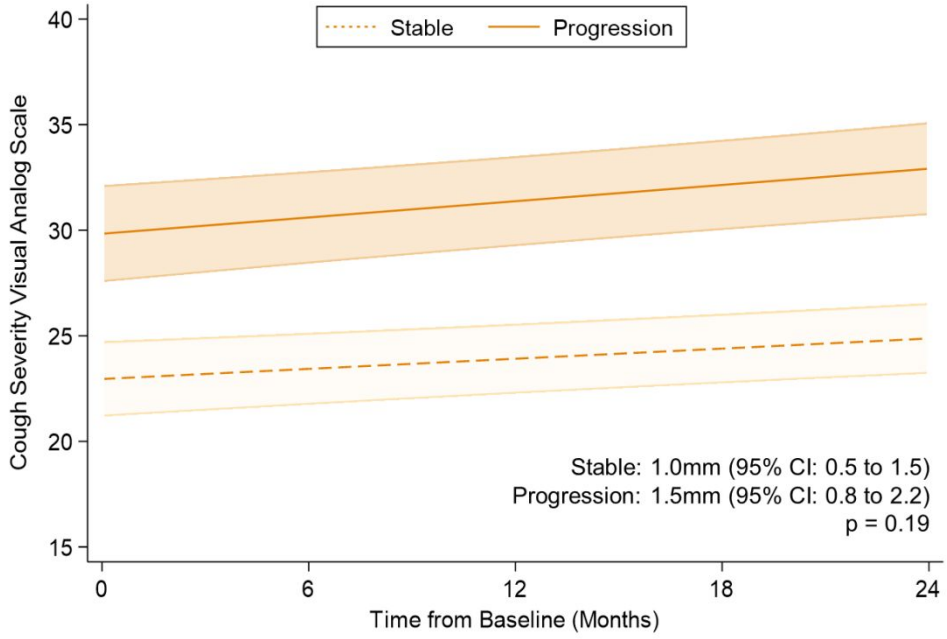
Figure S4. Annualized changes in cough severity for IPF and non-IPF fibrotic cohorts stratified by the physiological progression status

(a) IPF



(b) Non-IPF fibrotic ILD



Abbreviations: CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

* Shaded areas represent 95% confidence intervals

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Table S1. Changes in cough severity at 12 months following treatment initiation in patients with IPF and non-IPF fibrotic ILD

Parameters	Baseline		12 months		p-value*
	Measurement	95% CI	Measurement	95% CI	
Patients with treatment initiation following baseline evaluation					
IPF					
Nintedanib (n=206)	27.3	23.8, 30.7	38.8	33.7, 43.9	0.92
Pirfenidone (n=110)	29.5	24.7, 34.4	40.6	33.1, 48.0	
Non-IPF fibrotic ILD					
Azathiopine (n=61)	28.9	22.0, 35.8	42.2	32.9, 51.4	0.27
Mycophenolate (n=414)	26.8	24.2, 29.4	34.6	31.3, 38.0	
Patients with treatment initiation following baseline evaluation and baseline Cough Severity VAS ≥30mm					
IPF					
Nintedanib (n=77)	53.6	50.3, 57.0	54.2	49.5, 58.9	0.99
Pirfenidone (n=48)	53.8	45.5, 62.2	54.5	40.2, 68.7	
Non-IPF fibrotic ILD					
Azathiopine (n=27)	52.4	46.4, 58.4	50.4	39.2, 61.5	0.54
Mycophenolate (n=162)	55.6	51.1, 60.2	58.6	50.5, 66.7	

Abbreviations: CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

* Comparison between nintedanib and pirfenidone for IPF and between azathioprine and mycophenolate for non-IPF fibrotic ILD

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