Changes in Lung Function and Mortality Risk in Patients With Idiopathic Pulmonary Fibrosis

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BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease associated with lung function decline and high mortality.

RESEARCH QUESTION: What are the associations between thresholds of lung function decline and the risk of mortality in patients with IPF?

STUDY DESIGN AND METHODS: The Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry enrolled patients with IPF that was diagnosed or confirmed at the enrolling center within the prior 6 months. Associations between time to first decline in FVC or diffusing capacity of the lungs for carbon monoxide (DLCO) of ≥ 2% predicted, ≥ 5% predicted, and ≥ 10% predicted (and ≥ 15% predicted for DLCO) and risk of subsequent death or lung transplantation was assessed using Cox proportional hazards models with a time-dependent covariate. Models were unadjusted or adjusted for FVC and DLCO % predicted, age, sex, smoking status, BMI, antifibrotic treatment (yes or no), and oxygen use at enrollment.

RESULTS: Among 1,001 patients, median follow-up time was 38.4 months. Significant associations were observed between all thresholds of decline in FVC and DLCO % predicted and the risk of death or lung transplantation in unadjusted and adjusted analyses. In adjusted analyses, absolute declines in FVC of ≥ 2% predicted, ≥ 5% predicted, and ≥ 10% predicted were associated with 1.8-fold, 2.3-fold, and 2.7-fold increases in the risk of subsequent death or lung transplantation, whereas absolute declines in DLCO of ≥ 2% predicted, ≥ 5% predicted, ≥ 10% predicted, and ≥ 15% predicted were associated with 2.0-fold, 1.4-fold, 1.5-fold, and 1.9-fold increases in the risk of subsequent death or lung transplantation, respectively. For DLCO, but not FVC, the increase in risk generally was greater for patients meeting a threshold based on a relative rather than an absolute decline.

INTERPRETATION: Our results show that even small declines in FVC and DLCO % predicted inform prognosis in patients with IPF.

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ABBREVIATIONS: DLCO = diffusing capacity of the lungs for carbon monoxide; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IPF-PRO = Idiopathic Pulmonary Fibrosis Prospective Outcomes

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Take-Home Points

Study Question: What are the associations between thresholds of lung function decline and the subsequent risk of mortality in patients with idiopathic pulmonary fibrosis (IPF)?

Results: Among patients in the Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry, significant associations were observed between absolute and relative declines in FVC and diffusing capacity of the lungs for carbon monoxide (DLCO) of ≥ 2% predicted, ≥ 5% predicted, and ≥ 10% predicted (and ≥ 15% predicted for DLCO) and the subsequent risk of death or lung transplantation, both in unadjusted analyses and analyses adjusted for baseline factors including lung function.

Interpretation: Our results show that even small declines in FVC and DLCO % predicted inform prognosis in patients with IPF.

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease (ILD) associated with loss of lung function and high mortality.[1] Decline in FVC or diffusing capacity of the lungs for carbon monoxide (DLCO) % predicted in patients with IPF is indicative of disease progression, and these lung function parameters are used in clinical practice to monitor the course of the disease. Reductions in FVC of > 5% predicted or > 10% predicted or in DLCO of > 15% predicted generally are regarded as clinically meaningful cutoffs to define progression of IPF and worse prognosis, mainly based on data collected in clinical trials.[2-9] However, smaller declines in lung function also have been associated with an increased risk of mortality.[3,9] Debate continues around whether absolute or relative declines in FVC should be used to define progression of ILD.[1,10,11]

To investigate the relationships between changes in FVC and DLCO and mortality in patients with IPF, we used data from the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry to determine associations between absolute and relative changes in these lung function measures over clinically relevant periods and the subsequent risk of mortality. We also examined associations between commonly used cutoffs for decline in lung function and the subsequent risk of mortality.

Study Design and Methods

Patients

Patients with IPF who received a diagnosis or whose diagnosis was confirmed at the enrolling center in the previous 6 months were enrolled into the IPF-PRO Registry at 46 sites between June 2014 and October 2018.[12] At enrollment, retrospective data were obtained from patients' medical records. Patients then were followed up prospectively until death, lung transplantation, or withdrawal from the registry. Data for this analysis were extracted from the database in September 2023. The study was approved by the Duke University institutional review board (Identifier: Pro00046131). The protocol was approved by the relevant institutional review boards, local independent ethics committees, or both before patient enrollment at every site (e-Appendix 1). All patients provided written consent before entering the registry.

Analyses

FVC % predicted was calculated using the equations published by the European Respiratory Society Global Lung Function Initiative.[13] DLCO % predicted was calculated using standard formulas.[14,15] Because lung function measurements were collected as part of clinical care, they varied in their frequency and timing. Therefore, for these analyses, a joint model between each lung function measure (FVC % predicted and DLCO % predicted) and visit frequency was used to generate estimates for each measure for every day of follow-up (e-Appendix 1).[16] In these models, the relationship of the lung function measures to time was allowed to be nonlinear by using restricted cubic splines. Patient-level random effects were included to accommodate patient-to-patient variation in intercept and slope. Changes in each lung function measure from enrollment to each time point of interest (6 months [183 days], 12 months [365 days], and

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18 months (548 days]) were calculated. Absolute change was calculated as the follow-up value minus the enrollment value. Relative change was calculated as 100 × (absolute change / enrollment value). Differences between observed lung function measures and values estimated based on the joint model were calculated to assess how well the model fitted the data (e-Appendix 1).

In landmarked analyses, associations between absolute and relative declines in FVC % predicted and DLCO % predicted at 6, 12, and 18 months and the risk of subsequent death or lung transplantation were assessed using a Cox proportional hazards model. The model was landmarked at the time point at which lung function change was evaluated. Patients who died or underwent a lung transplantation before the landmark were not included in the risk set. The risk of death or lung transplantation was calculated per 1-unit difference in change in FVC % predicted or DLCO % predicted. The Kaplan-Meier method was used to estimate the cumulative incidence of death or lung transplantation, landmarked at 12 months, stratified by change in FVC % predicted and DLCO % predicted at 12 months more than vs less than the median.

In a complementary analysis, associations between time to first absolute or relative decline in FVC or DLCO of ≥ 2% predicted, ≥ 5% predicted, and ≥ 10% predicted (and ≥ 15% predicted for DLCO only) and the risk of subsequent death or lung transplantation was assessed using Cox proportional hazards models with a time-dependent covariate. The time-dependent covariate started at 0 and switched to 1 at the first occurrence of a decline in FVC or DLCO % predicted at or beyond the threshold. To ensure that effect estimates for the smaller pulmonary function test decline thresholds are not being driven by patients with larger declines, a sensitivity analysis was performed using a Cox model with a time-dependent multilevel categorical variable so that each participant fell into only 1 decline group at any given time during follow-up. The following group levels were considered: reference (decline < 2% predicted or increase), decline of ≥ 2% predicted to < 5% predicted, decline of ≥ 5% predicted to < 10% predicted, decline of ≥ 10% predicted (and ≥ 15% predicted for DLCO only). A separate time-dependent Cox model was fit for each combination of FVC and DLCO and of absolute and relative decline.

For both the landmarked and time-dependent analyses, Cox models were unadjusted or adjusted for covariates that may be associated with the outcome in patients with IPF: FVC % predicted, DLCO % predicted, age, sex, smoking status (ever vs never), BMI, antifibrotic treatment (yes or no), and oxygen use (none, with activity, at rest) at enrollment. The adjustment covariates were selected based on the authors' clinical expertise and published literature. Missing data for these covariates were imputed from a single imputed data set using the full conditional specification method. All analyses were performed using SAS software version 9.4 (SAS Institute).

Results

Patients

Of 1,002 patients enrolled in the registry, follow-up data after enrollment were available for 1,001 patients. The characteristics of these patients at enrollment are shown in Table 1. Median age was 71 years (interquartile range, 66-75 years), 74.6% of patients were male, 94.9% of patients were White, and 66.9% of patients had a current or former smoking history. Median FVC was 70.1% predicted (interquartile range, 59.6%-80.8% predicted) and median DLCO was 42.4% predicted (interquartile range, 32.6%-51.6% predicted); 54.0% of patients were taking nintedanib or pirfenidone. Of the 1,001 patients with follow-up data after enrollment, 925 patients (92.4%) had estimated lung function values at the 6-month follow-up time point, 838 patients (83.7%) had estimated lung function values at the 12-month time point, and 733 patients (73.2%) had estimated lung function values at the 18-month time point (e-Table 1). Median follow-up time was 38.4 months.

Changes in Lung Function

Comparison of observed lung function measurements with values estimated based on the joint model suggested that the model provided reliable estimates (e-Table 2). Median changes in FVC % predicted at 6, 12, and 18 months generally were similar for absolute and relative changes (e-Fig 1, e-Table 3). Median changes in DLCO % predicted at 6, 12, and 18 months were larger for a relative change than for an absolute change (e-Fig 1, e-Table 3). The proportions of patients meeting thresholds of relative changes in FVC % predicted and DLCO % predicted at 6, 12, and 18 months are shown in e-Table 4.

TABLE 1] Baseline Characteristics (n = 1,001)

Characteristic	Data
Age, y	70 (65-75)
Male sex	747 (74.6)
BMI, kg/m^2	28.9 (26.0-32.3)
White race	929 (94.2)
Smoking status	
Former	651 (65.1)
Never	331 (33.1)
Current	18 (1.8)
Definite IPF[a]	654 (65.3)
FVC % predicted	73.4 (62.4-83.2)
Dlco % predicted	43.3 (35.5-50.3)
Oxygen use at rest	199 (20.0)
Oxygen use with activity	346 (34.6)
Antifibrotic drug use	540 (54.0)

Data are presented as No. (%) of patients with available data or median (interquartile range). Dlco = diffusing capacity of the lungs for carbon monoxide; IPF = idiopathic pulmonary fibrosis.
[a]According to 2011 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) diagnostic guidelines.[17]

Changes in Lung Function and Outcomes

The incidence of death or lung transplantation was higher among patients with a change in FVC % predicted or Dlco % predicted at 12 months of more than vs less than the median (e-Fig 2). The associations between absolute or relative changes in each lung function measure at 6, 12, and 18 months and subsequent risk of death or lung transplantation are shown in e-Table 5. At each time point, a greater decline in lung function was associated with an increased risk of death or lung transplantation. All associations were significant in both unadjusted and adjusted analyses, but the effect size was smaller when the association was assessed over a longer interval.

Time to the first occurrence of an absolute or relative decline in FVC or Dlco of ≥ 2% predicted, ≥ 5% predicted, and ≥ 10% predicted (and ≥ 15% predicted for Dlco only) is shown in Figure 1. For each threshold of decline in FVC % predicted, the median time to meeting that threshold was similar for an absolute or relative decline. For each threshold of decline in Dlco % predicted, the median time to a relative decline was shorter than the median time to an absolute decline. The proportions of patients meeting thresholds of decline in FVC % predicted and Dlco % predicted over the entire duration of follow-up are shown in Table 2.

Significant associations were observed between all thresholds of decline in FVC % predicted and subsequent risk of death or lung transplantation in both unadjusted and adjusted analyses (Table 3). In adjusted analyses, an absolute decline in FVC of ≥ 2% predicted, ≥ 5% predicted, and ≥ 10% predicted was associated with a 1.8-fold, 2.3-fold, and 2.7-fold increase in the risk of subsequent death or lung transplantation, respectively. The hazard ratios generally were similar when considering an absolute or relative decline.

Significant associations were observed between all thresholds of decline in Dlco % predicted and subsequent risk of death or lung transplantation in both unadjusted and adjusted analyses (Table 4). An absolute decline in Dlco of ≥ 2% predicted, ≥ 5% predicted, ≥ 10% predicted, and ≥ 15% predicted was associated with a 2.0-fold, 1.4-fold, 1.5-fold, and 1.9-fold increase in the risk of subsequent death or lung transplantation, respectively. The hazard ratios generally were greater for patients meeting a threshold based on a relative vs an absolute decline.

Sensitivity analyses using a time-dependent multilevel group variable for decline thresholds of interest generally supported these conclusions, although the effect estimates for small relative declines in Dlco (ie, ≥ 2% predicted to < 5% predicted) attenuated and were not statistically significant (e-Tables 6, 7).

Discussion

We modeled data from a contemporary cohort of patients with IPF to examine associations between decline in lung function and the risk of death or lung transplantation. We found that even small declines in FVC % predicted or Dlco % predicted (ie, 2% predicted) informed prognosis after adjusting for baseline characteristics known to influence the risk of mortality. Such small declines in lung function may occur within a short period in patients with IPF. In the current analyses, over the first 6 months of follow-up, approximately one-quarter of patients showed a relative decline in FVC % predicted of at least 2%, whereas 18% experienced a relative decline in Dlco % predicted of this magnitude. These data are consistent with a previous analysis of data from the IPF-PRO Registry in which the mean absolute declines in FVC and Dlco were estimated as 2.8% predicted and 2.9% predicted per year, respectively.[18] Declines in FVC of 3.5% predicted and 4.4% predicted per year have been reported in other studies.[19,20]

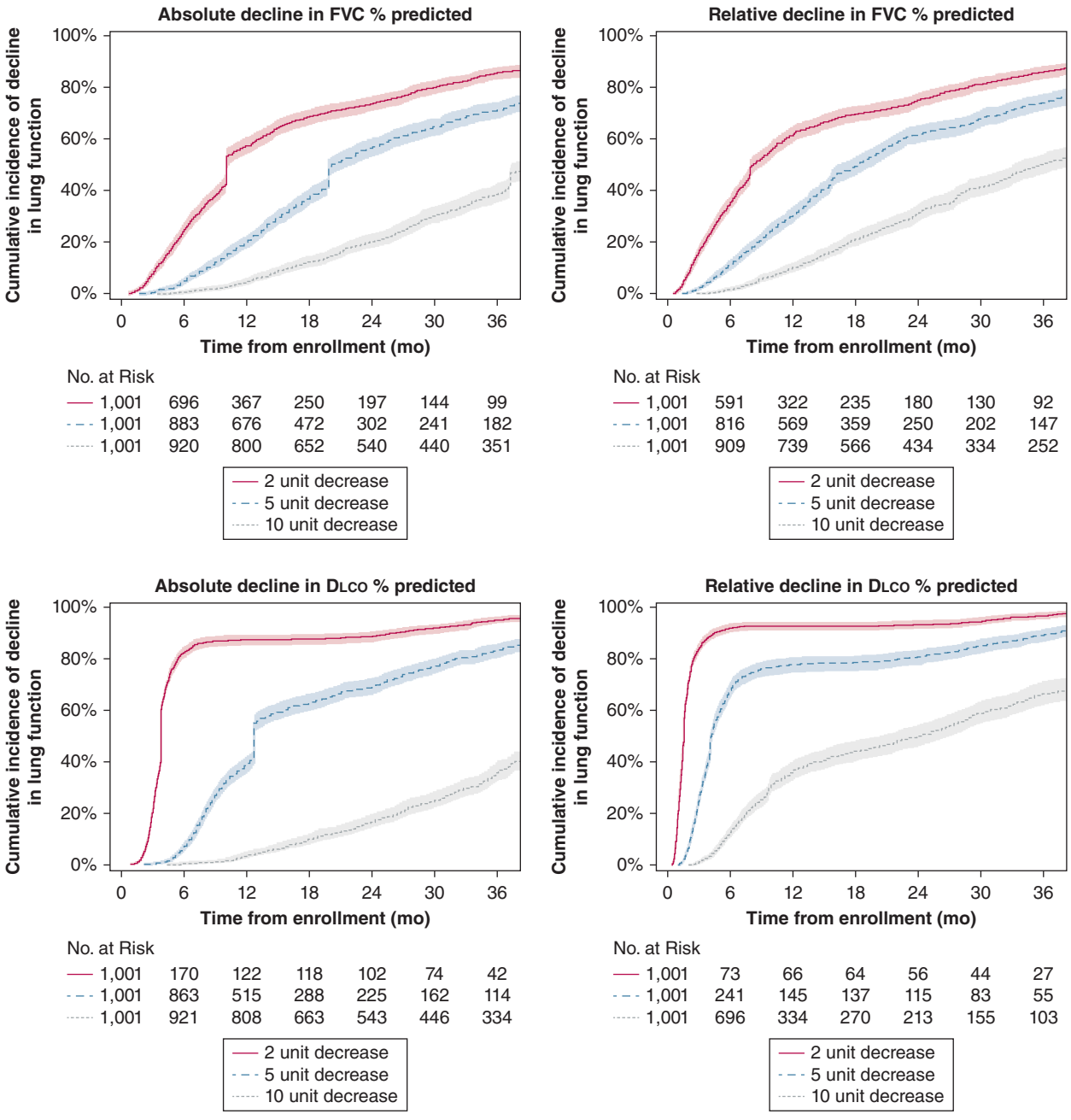

Figure 1 – *A-D, Graphs showing time to absolute and relative declines in FVC % predicted (A, B) and DLCO % predicted (C, D). DLCO = diffusing capacity of the lungs for carbon monoxide.*

Our data add to a body of literature demonstrating that the threshold of decline in FVC % predicted that is associated with an increased risk of mortality in patients with IPF may be much lower than the threshold of 5% or 10% that generally is regarded as indicating progression. Among 1,156 patients with IPF participating in a clinical trial, the minimal clinically important difference for FVC, based on patient referencing using change in general health status and criterion referencing based on hospitalization and death, was estimated to be between 2% predicted and 6% predicted.[3] In an analysis of pooled data from placebo-controlled trials of nintedanib in patients with IPF (n = 1,321), a 1% increase in the absolute annual rate of decline in FVC % predicted increased the risk of mortality over the same period by 14%.[9] Although generated via different methodology, these data lend support to our findings, which showed that a 1% increase in the absolute decline in FVC % predicted at 12 months increased the subsequent risk of death or

TABLE 2] Proportions of Patients Meeting Thresholds for Decline in FVC % Predicted and D_{LCO} % Predicted

Variable	Absolute Decline	Relative Decline
Decline in FVC, % predicted		
≥ 2	777 (77.6)	814 (81.3)
≥ 5	617 (61.6)	700 (69.9)
≥ 10	385 (38.5)	510 (50.9)
Decline in D_{LCO}, % predicted		
≥ 2	935 (93.4)	971 (97.0)
≥ 5	741 (74.0)	927 (92.6)
≥ 10	404 (40.4)	819 (81.8)
≥ 15	130 (13.0)	666 (66.5)

Data are presented as No. (%) of patients. D_{LCO} = diffusing capacity of the lungs for carbon monoxide.

lung transplantation by 13%, after adjusting for demographic and clinical factors. Although previous work has focused on FVC % predicted, in our analyses, we also looked at changes in D_{LCO} % predicted, for which a larger threshold (15%) is used commonly to define progression.[2,4,6] Our finding that much smaller declines in D_{LCO} confer independent prognostic information may have implications for treatment guidelines and the thresholds used to prompt evaluation for lung transplantation. The association between decline in lung function and the risk of death or lung transplantation was weaker when the decline in lung function was assessed over a longer period. This suggests that the rate of decline in lung function is relevant, as well as the total decline, that is, the loss of a given amount of lung function over 6 months has worse implications for prognosis than the loss of the same amount of lung function over 12 months. The importance of the rate of decline in FVC % predicted as a predictor of mortality also has been demonstrated in other studies in patients with IPF and other ILDs.[6,9,21]

TABLE 3] Associations Between Absolute and Relative Changes in FVC % Predicted and Risk of Subsequent Death or Lung Transplantation

FVC Decline, % Predicted	Unadjusted Analysis	Adjusted Analysis[a]
Absolute		
≥ 2	2.18 (1.73-2.74)	1.80 (1.42-2.28)
≥ 5	2.58 (2.09-3.19)	2.28 (1.84-2.83)
≥ 10	2.79 (2.28-3.41)	2.72 (2.21-3.34)
Relative		
≥ 2	2.53 (1.98-3.23)	1.90 (1.49-2.44)
≥ 5	2.83 (2.27-3.53)	2.13 (1.71-2.67)
≥ 10	3.12 (2.56-3.82)	2.42 (1.97-2.98)

Data are presented as hazard ratio (95% CI). Estimates obtained from a time-dependent Cox model.
[a]Adjusted for FVC % predicted, age, sex, smoking status, BMI, antifibrotic treatment (yes or no), and oxygen use at enrollment. $P < .05$ for all.

The question of whether declines in lung function should be considered as absolute or relative values remains open to debate. A guideline issued for the definition of progressive pulmonary fibrosis in patients with ILDs other than IPF[1] and the inclusion criteria for some clinical trials[22,23] use absolute declines in lung function, but other criteria proposed for the identification of progressive pulmonary fibrosis[24-26] and the criteria for referral for lung transplantation evaluation[7] use relative declines. In a prospective study of 142 patients, a ≥ 5% decline in FVC % predicted over 1 year was significantly associated with death or transplantation over 2 years in an adjusted analysis when based on an absolute decline, but not when based on a relative decline.[5] In our study, for FVC % predicted, the risk of death or lung transplantation associated with a given decline generally was similar when considering an absolute or relative decline, but for D_{LCO} % predicted, the risk of death or lung transplantation was higher if the threshold was based on a relative rather than an absolute decline. To our knowledge, this is the first study to assess the prognostic value of absolute vs relative declines in D_{LCO} % predicted. Our finding that a relative decline in D_{LCO} % predicted provides more prognostic information than an absolute decline adds to the evidence base that will inform future trial design and clinical practice guidelines.

Interestingly, although IPF is, by definition, a progressive disease[1] and the disease ultimately progresses in all patients, some patients with IPF show stability or even improvement in lung function over time. In our study, 22.8% of patients showed an increase in FVC % predicted and 8.7% showed an increase in D_{LCO} % predicted over 18 months of follow-up. Almost one-half of patients showed an increase or a decline in FVC of < 5% predicted, which generally is regarded as indicating stability in lung function, over this time frame. This phenomenon also has been observed in other real-world studies,[6,27,28] as well as in the INPULSIS trials, in which 9.0% of patients in the placebo group and 24.8% of patients in the nintedanib

TABLE 4] Associations Between Absolute and Relative Changes in DLCO % Predicted and Risk of Subsequent Death or Lung Transplantation

DLCO decline, % predicted	Unadjusted Analysis	Adjusted Analysis[a]
Absolute		
≥ 2	3.08 (2.07-4.61)	2.04 (1.34-3.10)
≥ 5	1.96 (1.56-2.48)	1.40 (1.10-1.79)
≥ 10	1.48 (1.19-1.84)	1.46 (1.17-1.83)
≥ 15	1.80 (1.35-2.40)	1.92 (1.43-2.57)
Relative		
≥ 2	4.41 (2.33-8.34)	2.07 (1.10-3.90)
≥ 5	3.92 (2.65-5.80)	1.73 (1.18-2.53)
≥ 10	4.24 (3.20-5.63)	1.88 (1.42-2.50)
≥ 15	3.13 (2.53-3.88)	1.39 (1.11-1.74)

Data are presented as hazard ratio (95% CI). Estimates obtained from a time-dependent Cox model. DLCO = diffusing capacity of the lungs for carbon monoxide.

[a]Adjusted for DLCO % predicted, age, sex, smoking status, BMI, antifibrotic treatment (yes or no), and oxygen use at enrollment. $P < .05$ for all.

group showed an improvement or no decline in FVC (in milliliters) over 12 months.[29]

Strengths of our analyses include the large real-world cohort of patients with IPF and the use of a joint model to estimate patient-specific changes in FVC and DLCO % predicted over time. Our data were collected in a contemporary cohort of patients with IPF with high exposure to antifibrotic therapy.[30] We acknowledge that measurement variability makes individual small changes in FVC and DLCO difficult to interpret. In clinical practice, the interpretation of small changes in lung function may be aided by integrating information on respiratory symptoms or radiologic changes.[1]

Interpretation

These analyses of data from the IPF-PRO Registry suggest that even small declines in FVC and DLCO % predicted inform prognosis in patients with IPF. Our findings add to the evidence base to inform guidelines for the management of patients with IPF.

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Financial/Nonfinancial Disclosures

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Additional information: The e-Appendix, e-Figures, and e-Tables are available online under "Supplementary Data."

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