ORIGINAL RESEARCH

Associations between Patient-reported Outcomes and Death or Lung Transplant in Idiopathic Pulmonary Fibrosis

Data from the Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry

Amy Hajari Case[1], Anne S. Hellkamp[2,3], Megan L. Neely[2,3], Shaun Bender[4], Daniel F. Dilling[5], Mridu Gulati[6], David L. Hotchkin[7], Tristan J. Huie[8], Lisa Lancaster[9], Laurie D. Snyder[2,3], Craig S. Conoscenti[4], and Scott M. Palmer[2,3]; on behalf of the IPF-PRO Registry Investigators

[1]Piedmont Healthcare, Atlanta, Georgia; [2]Duke Clinical Research Institute, Durham, North Carolina; [3]Duke University Medical Center, Durham, North Carolina; [4]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut; [5]Division of Pulmonary and Critical Care, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois; [6]Yale School of Medicine, New Haven, Connecticut; [7]Division of Pulmonary, Critical Care & Sleep Medicine, The Oregon Clinic, Portland, Oregon; [8]National Jewish Health, Denver, Colorado; and [9]Vanderbilt University Medical Center, Nashville, Tennessee

ORCID IDs: 0000-0001-8663-2022 (A.H.C.); 0000-0002-9723-510X (D.F.D.).

Abstract

Rationale: Progression of idiopathic pulmonary fibrosis (IPF) is accompanied by worsening of symptoms, exercise capacity, and health-related quality of life. However, the utility of patient-reported outcomes as predictors of mortality remains uncertain.

Objectives: To assess whether patient-reported outcomes are independently associated with mortality beyond clinical risk factors in patients with IPF.

Methods: Data from the observational IPF Prospective Outcomes Registry were used to examine associations between patient-reported outcomes at enrollment and the composite outcome of death or lung transplant in the following year. Associations were examined using univariable models and models adjusted for age and clinical variables that have been associated with death or lung transplant in patients with IPF in this cohort (oxygen use, forced vital capacity % predicted, and diffusing capacity of the lungs for carbon monoxide % predicted at enrollment).

Results: Among 662 patients, 45 died and 12 underwent lung transplant over 1 year. In the model adjusted for age and clinical variables that were associated with death or lung transplant, worse scores on the St. George's Respiratory Questionnaire (SGRQ) total score (hazard ratio [HR], 1.22 [95% confidence interval (CI), 1.01–1.48] per 10-point increase), SGRQ activity score (HR, 1.25 [95% CI, 1.02–1.54] per 10-point increase) and SGRQ symptoms score (HR, 1.17 [95% CI, 1.01–1.36] per 10-point increase) were associated with death or lung transplant over 1 year.

Conclusions: Patient-reported outcomes that assess symptoms and physical activity are independently associated with mortality in patients with IPF.

Keywords: interstitial lung diseases; mortality; observational study; registries

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A complete list of the IPF-PRO Registry Investigators may be found before the beginning of the References.

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Correspondence and requests for reprints should be addressed to Amy Hajari Case, M.D., 1968 Peachtree Road Northwest, Atlanta, GA 30309. E-mail: ashajari@gmail.com.

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Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing, interstitial lung disease characterized by worsening lung function and high mortality (1). In the United States, median postdiagnosis survival in patients with IPF before the approval of antifibrotic drugs was estimated to be between 3 and 5 years (2, 3). IPF is associated with substantial impairment in health-related quality of life (HRQL), particularly in domains concerning symptoms, emotional well-being, and physical activity (4). As IPF progresses, patients experience worsening of dyspnea, cough, and exercise capacity, and deterioration in their HRQL (4–7).

Patient-reported outcomes may provide prognostic information in patients with chronic lung diseases, independent of clinical indicators of disease severity, such as pulmonary function. For example, in patients with chronic obstructive pulmonary disease, the BODE (Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity) index, which includes body mass index, airflow obstruction, dyspnea, and exercise capacity, has been shown to be a better predictor of death than the degree of airflow obstruction alone (8). Several patient-reported outcomes have shown utility as measures of HRQL in patients with IPF (9–12), but the role of these instruments in predicting outcomes, including survival, remains uncertain. An analysis of data from the multicenter Australian IPF Registry suggested that patient-reported outcomes were predictors of mortality in both univariate analyses and in multivariate analyses adjusted for demographic factors and forced vital capacity (FVC) % predicted (13). However, a separate analysis of data from this registry demonstrated a significant association between St. George's Respiratory Questionnaire (SGRQ) total score and mortality in univariable analyses, but not in multivariable analyses adjusted for measures of disease severity and age (5).

The IPF-PRO (IPF Prospective Outcomes) Registry (NCT01915511) is an ongoing observational U.S. registry of patients with IPF who were diagnosed or confirmed at the enrolling center in the past 6 months (14). A recent analysis of data from 662 patients participating in this registry showed that oxygen use at rest, oxygen use with activity, lower FVC % predicted, and lower diffusing capacity of the lungs for carbon monoxide (D_{LCO}) % predicted at enrollment were associated with an increased risk of death or lung transplant over a median follow-up period of 11.4 months (15). These findings are consistent with previous studies of predictors of mortality in patients with IPF, but the association observed between oxygen use at rest and death or lung transplant was particularly striking (hazard ratio [HR], 2.44 in a multivariable model that included patient characteristics as covariates) (15). We used the same cohort of patients from the IPF-PRO Registry to investigate associations between patient-reported outcomes at enrollment and death or lung transplant over the following year, adjusted for the previously identified clinical predictors of this outcome, to determine whether these patient-reported outcomes are independently associated with death or lung transplant. Some of the results presented in this article have been previously reported in the form of an abstract (16).

Methods

Patients enrolled in the IPF-PRO Registry from its inception on June 5, 2014 to October 26, 2017 comprised the analysis cohort. These patients were diagnosed or confirmed with IPF at the enrolling center according to the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society guidelines (17) in the past 6 months. Patients who were listed for lung transplantation were not eligible to enroll in the registry, but patients could be listed for lung transplant after enrollment.

A number of patient-reported outcomes were evaluated at enrollment. The cough symptoms and cough impact domains of the Cough and Sputum Assessment Questionnaire (CASA-Q) assess the frequency and severity of cough and its impact on daily activities (18). Domain scores range from 0 to 100, with lower scores indicating worse cough. The SGRQ is a 50-item questionnaire divided into three domains: symptoms (frequency and severity); activity (effects of breathlessness on physical activities); and impact (psychological impact of the disease and its effect on social functioning) (19). Total and domain scores range from 0 to 100; higher scores indicate worse HRQL. The Short Form-12 questionnaire (SF-12) is a 12-item measure of physical and mental health status with two components: the mental component score and the physical component score. Both component scores range from 0 to 100, with lower scores indicating worse HRQL (20). The EuroQoL score and EuroQoL visual analog scale (VAS) comprise five domains assessing general health status, with a total score ranging from 0 to 1 and a VAS score from 0 to 100; higher scores indicate better HRQL (21).

The primary outcome studied in this analysis was a composite of death or lung transplant in the year after enrollment. Secondary outcomes were death, a composite of respiratory-related death or lung transplant, and respiratory-related death in the year after enrollment. Data on deaths were collected at the enrolling center and, in patients who had not attended a visit, telephone calls every 6 months were used to confirm vital status. The principal investigator at the enrolling site determined whether a death was respiratory related based on the medical records surrounding the death.

A preliminary examination using all available follow-up data (~30 mo) indicated that, for most of the patient-reported outcomes, a relationship between the patient-reported outcome and the risk of mortality or lung transplant was evident in the early months, but began to attenuate 10 to 16 months after enrollment. Therefore, we restricted our analyses to the first year after enrollment, during which the proportional hazards assumption of the Cox model was met. The proportional hazards assumption was assessed by testing for interaction between log(time-to-event + 1) and each covariate in an unadjusted Cox model at a significance level of 0.05. Event counts and event-free rates over 1 year were estimated for each outcome using the Kaplan–Meier method, and Cox proportional hazards models were used in association analyses. First, associations between patient-reported outcomes and each outcome were examined in a univariable manner (i.e., with each patient-reported outcome as the only predictor in the model). All patient-reported outcomes were also checked for a nonlinear relationship with each outcome. The linearity assumption was assessed by performing a lack-of-fit test comparing a linear fit of an unadjusted Cox model to a nonlinear fit based on a restricted cubic spline with four knots at a significance level of 0.05. No linearity or proportional hazards

violations were found over the first year after enrollment. Second, we used multivariable models that included a single patient-reported outcome and adjusted for age plus the clinical characteristics previously shown to be associated with death or lung transplant in this cohort (i.e., oxygen use with activity, oxygen use at rest, FVC % predicted, and D_{LCO} % predicted) to determine whether patient-reported outcomes provide important information beyond these clinical predictors. Associations between patient-reported outcomes and each outcome were expressed as HRs with 95% confidence intervals (CIs) and *P* values. For scores that range from 0 to 100, estimates were based on a 10-point difference in the patient-reported outcome to provide a meaningful HR. Chi-square test statistics from the fitted Cox regression models were reported to allow a comparison of the importance of the variables in explaining the outcomes. Variables with missing data from ⩾25% of patients were excluded from these analyses. Multiple imputation was implemented on the model covariates. First, the missing data were filled in five times to generate five complete data sets as per the Full Conditional Specification method. Second, the five complete data sets were analyzed using standard statistical analyses; here, Cox proportional hazards regression. Lastly, the results from the five complete datasets were combined using Rubin's rules to produce the final inferential results.

Results

Patients

A total of 662 patients were included in this analysis, of whom 74.9% were male. At enrollment, median age was 70 years, median FVC was 69.6% predicted, and 19.6% were using supplemental oxygen at rest (Table 1). Median SF-12 mental and physical component scores were 54.1 and 39.2, respectively. Median SGRQ symptoms, activity, impact, and total scores were 43.2, 57.8, 26.1, and 39.5, respectively. Median scores on the CASA-Q cough symptoms and impact domains were 58.3 and 78.1, respectively. Median EuroQoL and VAS scores were 0.8 and 75.5, respectively. For each patient-reported outcome, 15.3–18.1% of patients had missing data at enrollment (Table 1).

Table 1. Characteristics of patients at enrollment into the Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry (*n* = 662)

Characteristics	Summary Measure	Missing Data
Age, yr	70 (65–75)	—
Male	496 (74.9)	—
White	623 (94.1)	—
Body mass index, kg/m^2	29.0 (26.0–32.4)	59 (8.9)
Current or former smoker	446 (68.4)	10 (1.5)
Oxygen use with activity	217 (34.1)	25 (3.8)
Oxygen use at rest	125 (19.6)	24 (3.6)
Receiving nintedanib or pirfenidone	352 (54.0)	10 (1.5)
Prior diagnosis of IPF (which was confirmed at the enrolling center)	301 (45.5)	7 (1.1)
Prior hospitalization (any)	171 (29.3)	79 (11.9)
Respiratory related	106 (18.2)	79 (11.9)
Non-respiratory related	86 (14.8)	79 (11.9)
FVC, % predicted	69.6 (60.1–79.9)	88 (13.3)
D_{LCO}, % predicted	41.7 (32.2–50.1)	98 (14.8)
SF-12 mental component score	54.1 (46.5–58.8)	120 (18.1)
SF-12 physical component score	39.2 (31.4–46.6)	120 (18.1)
CASA-Q cough symptoms domain	58.3 (41.7–75.0)	101 (15.3)
CASA-Q cough impact domain	78.1 (56.3–93.8)	101 (15.3)
SGRQ		
Total score	39.5 (25.8–52.9)	116 (17.5)
Activity domain	57.8 (41.6–72.8)	103 (15.6)
Impact domain	26.1 (14.4–41.9)	105 (15.9)
Symptoms domain	43.2 (30.3–60.2)	107 (16.2)
EuroQoL score	0.8 (0.7–1.0)	104 (15.7)
EuroQoL VAS	75.5 (63.0–85.0)	102 (15.4)

Definition of abbreviations: CASA-Q = Cough and Sputum Assessment Questionnaire; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; SF-12 = Short Form-12 questionnaire; SGRQ = St. George's Respiratory Questionnaire; VAS = visual analog scale.
Data are median (25th, 75th percentile) or *n* (%). Not all patients provided data on all variables.

Events of Death or Lung Transplant

A total of 45 deaths and 12 lung transplants were observed over the first year of follow-up. The mean age at the time of transplant was 67 years, and the maximum was 71 years. The probability of being free of both events at 1 year was 86.0% (95% CI, 82.1–89.0). Median (25th, 75th percentiles) duration of follow-up among survivors was 8.7 (0.4, 17.7) months, with a maximum of 38.8 months. Event counts and event-free rates for death, respiratory-related death or lung transplant, and respiratory-related death are shown in Figure E1 and Table E1 in the online supplement.

Associations between Patient-reported Outcomes at Enrollment and Death or Lung Transplant in Univariable Models

In the univariable analyses based on data over the first year of follow-up, worse HRQL at enrollment was associated with death or lung transplant (Figure 1). This was the case for HRQL measured using the SF-12 physical component score (HR, 2.04 [95% CI, 1.47–2.81] per 10-point decrease), SGRQ activity score (HR, 1.57 [95% CI, 1.32–1.87] per 10-point increase), SGRQ impact score (HR, 1.34 [95% CI, 1.17–1.54] per 10-point increase), SGRQ symptoms score (HR, 1.34 [95% CI, 1.17–1.55] per 10-point increase), SGRQ total score (HR, 1.52 [95% CI, 1.29–1.79] per 10-point increase), EuroQoL score (HR, 1.21 [95% CI, 1.06–1.38] per 0.1-point decrease), EuroQoL VAS (HR, 1.37 [95% CI, 1.17–1.61] per 10-point decrease), and CASA-Q cough impact domain score (HR, 1.12 [95% CI, 1.00–1.26] per 10-point decrease). Based on chi-square values, the strongest associations were seen for SGRQ total, activity and impact scores, and the SF-12 physical component score (Figure 1). The CASA-Q cough symptoms domain score (HR, 1.10 [95% CI, 0.98–1.23] per 10-point decrease) and SF-12 mental component score (HR, 0.92 [95% CI, 0.65–1.32] per 10-point decrease) were not associated with death or lung transplant. Associations between patient-reported outcomes and death, respiratory-related

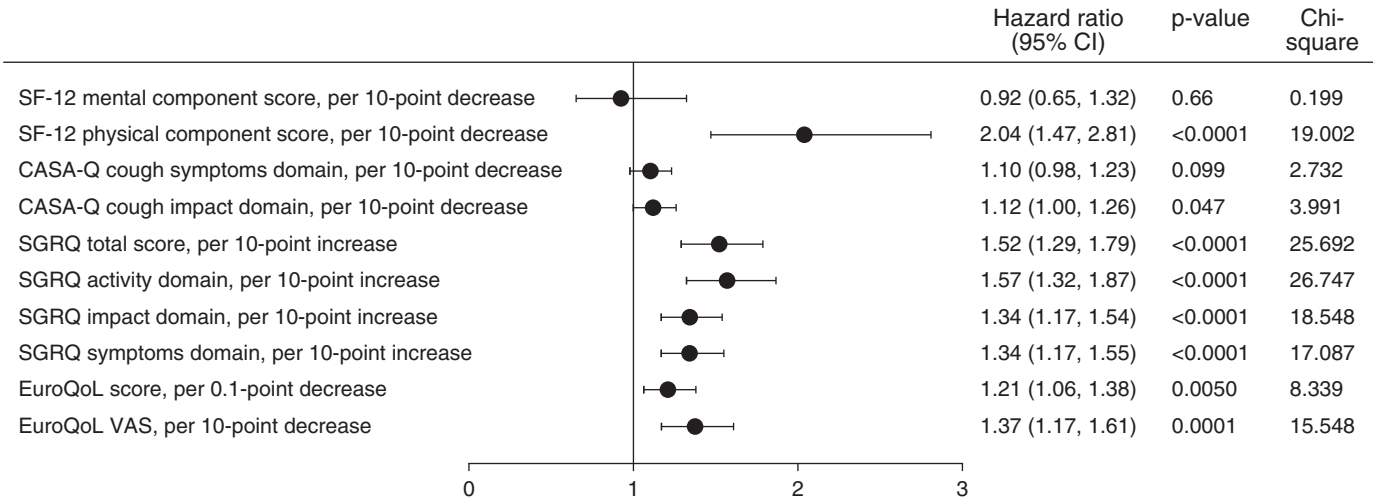

Figure 1. Associations between patient-reported outcomes at enrollment and death or lung transplant in the following year in univariable models. Hazard ratios reflect the risk of death or lung transplant associated with a worse score on the patient-reported outcome. Chi-square statistics were derived from the corresponding Cox proportional hazards regression models. CASA-Q = Cough and Sputum Assessment Questionnaire; CI = confidence interval; SF-12 = Short Form-12 questionnaire; SGRQ = St. George's Respiratory Questionnaire; VAS = visual analog scale.

death or lung transplant, and respiratory death over 1 year were generally consistent with those for death or lung transplant (Tables E2–E4).

Associations between Patient-reported Outcomes at Enrollment and Death or Lung Transplant in Model Adjusted for Clinical Characteristics

In the model adjusted for age and the clinical characteristics previously shown to be associated with death or lung transplant in this cohort, and based on data over the first year of follow-up, worse scores on the SGRQ total score (HR, 1.22 [95% CI, 1.01–1.48] per 10-point increase), SGRQ activity score (HR, 1.25 [95% CI, 1.02–1.54] per 10-point increase) and SGRQ symptoms score (HR, 1.17 [95% CI, 1.01–1.36] per 10-point increase) were associated with death or lung transplant over 1 year (Figure 2). Associations between the other patient-reported outcome measures and death or lung transplant were in the same direction, except for the SF-12 mental component score. Based on chi-square values, the strongest associations were seen for SGRQ total, activity, and symptoms scores (Figure 2). Associations between patient-reported outcomes and death, respiratory-related death or lung transplant, and respiratory death over 1 year were generally consistent with the data on death or lung transplant (Tables E2–E4). Chi-square values for the associations between clinical characteristics and outcomes in the following year in models that did not include patient-reported outcomes are summarized in Table E5.

Discussion

These data, from a large cohort of patients in the IPF-PRO Registry, show that worse scores on certain patient-reported outcomes at enrollment were associated with an increased risk of death or lung transplant over 1 year, both in univariable analyses and after adjustment for age and clinical variables shown to be associated with an increased risk of death or lung transplant in this cohort. This suggests that patient-reported outcomes provide important information beyond physiological measures of disease severity, such as lung function.

Patients with IPF report limitations to their mobility, low levels of energy, and difficulty with basic tasks requiring exertion (22, 23). In our analysis, the SGRQ activity score was associated with death or lung transplant over the following year. Based on chi-square values, in the adjusted model, the SGRQ activity score had the strongest association with death or lung transplant over 1 year of all the patient-reported outcomes. This association was stronger than the association observed for FVC % predicted over the same period, but weaker than that observed for oxygen at rest. Previous studies have shown that a reduced capacity for exercise based on 6-minute walk test distance (24–26) or self-reported daily activity (27, 28) are associated with increased mortality in patients with IPF. In a recent study of 92 patients in the prospective Finnish IPF registry, patients experienced a considerable deterioration in HRQL in the 2 years before death, particularly related to limitations in physical health and functioning (29).

In our analyses, the SGRQ symptoms score at enrollment was associated with death or lung transplant in multivariable models. Based on chi-square values, the SGRQ symptoms score had a stronger association with death or lung transplant over 1 year in the adjusted model than that observed for FVC % predicted over the same period. Cough and dyspnea are known to be major determinants of HRQL in patients with IPF (5, 6, 22), and there is some evidence that they are predictors of mortality. Among 1,099 patients with IPF participating in clinical trials, the University of California San Diego Shortness of Breath Questionnaire score was associated with mortality in a univariable model (30). Among 242 patients with IPF in the University of California San Francisco interstitial lung disease database, cough was an independent predictor of disease progression (defined as a decline in FVC $\geq$10% predicted, decline in D_{LCO} $\geq$15%

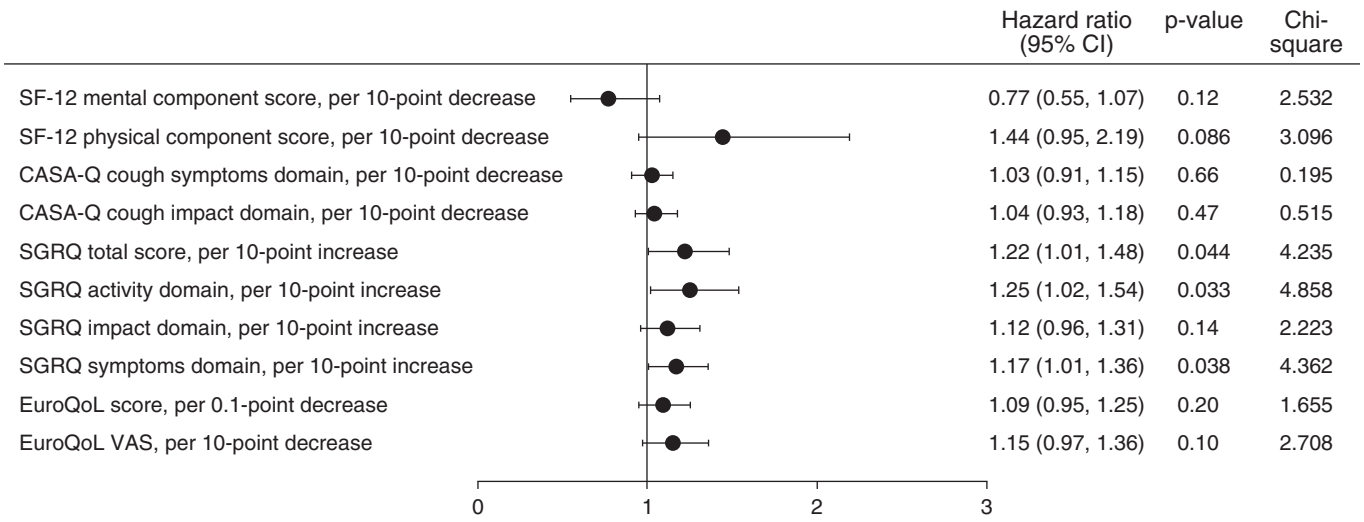

Figure 2. Associations between patient-reported outcomes at enrollment and death or lung transplant in the following year in a model adjusted for clinical characteristics (each model includes the individual patient-reported outcome listed plus age and the following adjustment covariates that were shown in previous analyses of this cohort to be associated with death or lung transplant: oxygen use with activity; oxygen use at rest; forced vital capacity % predicted; and diffusing capacity of the lung for carbon monoxide % predicted). Hazard ratios reflect the risk of death or lung transplant associated with a worse score on the patient-reported outcome. Chi-square statistics were derived from the corresponding Cox proportional hazards regression models. CASA-Q = Cough and Sputum Assessment Questionnaire; CI = confidence interval; SF-12 = Short Form-12 questionnaire; SGRQ = St. George's Respiratory Questionnaire; VAS = visual analog scale.

predicted, lung transplant, or death) in the following 6 months, when adjusting for oxygen use and total lung capacity (31). In a single-center study of 93 Japanese patients with IPF, dyspnea at baseline, measured using the modified Medical Research Council scale, was associated with mortality in a stepwise multivariate Cox proportional analysis that included FVC % predicted, D_{LCO} % predicted, partial pressure of oxygen, 6-minute walk test distance, arterial oxygen saturation, and Borg score in the model (32).

Data from the Australian IPF Registry showed that worse scores on the SGRQ and the University of California San Diego Shortness of Breath Questionnaire, and patient-reported severity of cough (measured on a VAS), were predictive of mortality in univariable analyses and in multivariable analyses adjusted for demographic factors and FVC % predicted (13, 33). A worse score on the SGRQ was also predictive of mortality in univariable and multivariable analyses of 182 patients with IPF in a single-center Japanese cohort (34). A separate analysis of data from the Australian IPF Registry confirmed the association between SGRQ total score and mortality in a univariable analysis, but no association was observed in a multivariable analysis (5). The reasons for different findings being observed in our analysis and in this analysis of data from the Australian IPF Registry may include differences in the study populations, in the statistical models used to assess the associations, or in the death rates and follow-up periods.

Of all the patient-reported outcomes studied, only the SF-12 mental component score was not associated with death or lung transplant. It is possible that this tool, which assesses the emotional impact of disease, may capture information on the impact of IPF that is less closely linked to physiological disease progression than that collected using other instruments.

Lung transplant was included in the primary outcome, as it serves as a marker of disease progression that would otherwise be expected to result in death. Guidelines issued by the International Society for Heart and Lung Transplantation recommend that patients with IPF be listed for lung transplant in the event of disease progression, including FVC decline $\geq$10% predicted over 6 months, decline in D_{LCO} $\geq$15% predicted over 6 months, or hospitalization due to respiratory decline, pneumothorax, or acute exacerbation due to the high risk of death in these patients (35). We observed consistent associations between patient-reported outcomes and death and between patient-reported outcomes and death or lung transplant, supporting the use of this composite outcome in this patient population. Given that lung transplantation is generally associated with an improvement in HRQL in patients with advanced lung disease (36), it might also be speculated that worse HRQL may increase the risk of the primary outcome, because impaired HRQL may play a role in some patients deciding to have a lung transplant.

Our analyses have many strengths and extend previous work regarding the clinical importance of patient-reported outcomes in the prediction of clinically meaningful outcomes in IPF. The IPF-PRO Registry comprises a large population of patients, enrolled at over 40 centers using broad inclusion criteria, making the cohort broadly reflective of U.S. patients with IPF. Also notable is our approach to multivariable adjustment, which included clinical variables known to be associated with an increased risk of death or lung transplant in patients with IPF in general and within the same cohort. This was a comprehensive assessment that enabled comparison of the associations between several pulmonary-specific and generic instruments measuring HRQL and the risk of death or lung transplant. A novelty of our approach was the use of a composite endpoint of death or lung transplant, which

provided a broad definition of disease progression. Similar results were observed for outcomes of death, respiratory-related death or lung transplant, and respiratory death, suggesting that our results were not confounded by the inclusion of patients who had a lung transplant. Our analyses also have limitations. As expected in a registry setting, not all patients completed all the instruments; however, the methodology used for the imputation of missing data was a reasonable approach to address this point. We were unable to assess the associations between patient-reported outcomes and lung transplant specifically, on account of the low number of patients who had a transplant. To date, we have not assessed how patient-reported outcomes change over time, or whether these changes are predictive of mortality; this will be examined once sufficient data have been collected.

In conclusion, data from the IPF-PRO Registry indicated that patient-reported outcomes assessing symptoms and capacity for physical activity represent independent predictors of death or lung transplant in patients with IPF. These results suggest that a multifaceted approach, including assessment of patient-perceived HRQL, may help to identify patients at greatest risk of disease progression. Further analysis of long-term data from the IPF-PRO Registry will investigate the extent to which changes in patient-reported outcomes over time are associated with mortality in patients with IPF.

A visual abstract summarizing our findings has been provided to accompany this artcle. ■

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