Ascertainment of Individual Risk of Mortality for Patients with Idiopathic Pulmonary Fibrosis

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***Rationale*: Several predictors of mortality in patients with idiopathic pulmonary fibrosis have been described; however, there is a need for a practical and accurate method of quantifying the prognosis of individual patients.**

***Objectives*: Develop a practical mortality risk scoring system for patients with idiopathic pulmonary fibrosis.**

***Methods*: We used a Cox proportional hazards model and data from two clinical trials (n = 1,099) to identify independent predictors of 1-year mortality among patients with idiopathic pulmonary fibrosis. From the comprehensive model, an abbreviated clinical model comprised of only those predictors that are readily and reliably ascertained by clinicians was derived. Beta coefficients for each predictor were then used to develop a practical mortality risk scoring system.**

***Measurements and Main Results*: Independent predictors of mortality included age, respiratory hospitalization, percent predicted FVC, 24-week change in FVC, percent predicted carbon monoxide diffusing capacity, 24-week change in percent predicted carbon monoxide diffusing capacity, and 24-week change in health-related quality of life. An abbreviated clinical model comprising only four predictors (age, respiratory hospitalization, percent predicted FVC, and 24-wk change in FVC), and the corresponding risk scoring system produced estimates of 1-year mortality risk consistent with observed data (9.9% vs. 9.7%; C statistic = 0.75; 95% confidence interval, 0.71–0.79).**

***Conclusions*: The prognosis for patients with idiopathic pulmonary fibrosis may be accurately determined using four readily ascertainable predictors. Our simplified scoring system may be a valuable tool for determining prognosis and guiding clinical management. Additional research is needed to validate the applicability and accuracy of the scoring system.**

Keywords: interstitial lung disease; risk factors; vital capacity; mortality

Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening, interstitial lung disease of unknown etiology (1). Respiratory failure resulting from IPF is the most frequent cause of death, and has been reported to account for over 80% of all fatalities (2, 3). Heart failure, bronchogenic carcinoma, ischemic heart disease, infection, and pulmonary embolism are also causes of mortality in IPF (3).

Although median survival among patients with IPF is only 2 to 3 years, some patients live much longer. Several studies have focused on identifying predictors of mortality in patients with IPF, including those based on data obtained at a single point in time (baseline predictors), and those based on data obtained over time (longitudinal predictors) (1, 4–18). Research published to date, however, has been limited in one or more facets of study design or study population, including retrospective data collection, small sample size, or use of a putative predictor that is not commonly assessed in clinical practice. Moreover, presumably because of these limitations, research in this area has failed to yield a scoring system that is routinely used in clinical practice to predict individual risk of mortality (4, 5). Development of such a scoring system is important, because it may serve as a basis for clinical decision making and simplify clinical trial design.

Using data from two large clinical trials in patients with IPF, we undertook a study to identify independent predictors of mortality and, based on these findings, develop a risk scoring system that once validated could be used by clinicians in daily practice without the need for sophisticated measures of disease status that are available only in specialized centers. This work has been presented in part at the 2010 international meeting of the American Thoracic Society (19).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Several studies have identified independent predictors of mortality in patients with idiopathic pulmonary fibrosis. Research published to date, however, has failed to yield a scoring system to predict individual risk of mortality.

What This Study Adds to the Field

Our findings suggest that a practical risk scoring system based on four readily and reliably ascertainable predictors may be used to accurately assess the risk of 1-year mortality in individual patients with idiopathic pulmonary fibrosis and thereby facilitate clinical decision making. Validation of the risk scoring system in other populations of patients with idiopathic pulmonary fibrosis is needed.

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METHODS

Source and Study Populations

The source population consisted of all randomized patients (n = 1,156) in two clinical trials of IFN-γ1b (protocols GIPF-001 [n = 330] and GIPF-007 [n = 826]) irrespective of treatment assignment (placebo [n = 443] or IFN-γ1b [n = 713]). The designs of these trials are described in detail elsewhere (2, 20). Briefly, eligible patients were required to have a high-resolution computed tomography scan showing features consistent with protocol-defined criteria for either a definite or probable diagnosis of IPF. Surgical lung biopsy was required to confirm a diagnosis in all patients with a clinical and radiographic diagnosis of probable IPF, and all patients under the age of 50 years, regardless of the degree of certainty associated with the clinical and radiographic diagnoses.

From the source population, we selected for inclusion all patients (n = 1,099) who participated in the week-24 trial visit (data from the week-24 visit were required to characterize changes from baseline in longitudinal predictors) (Figure 1). Patients who died or had a lung transplant between baseline and the week-24 visit (n = 39), or who were lost to follow-up during this period (n = 18), were therefore excluded from the analyses.

Predictors of Mortality

Potential predictors of mortality were assessed during the period from the trial baseline to the week-24 trial visit, and during the period from the week-48 to the week-72 trial visits, respectively, and all deaths occurring over the 48-week periods after these periods were identified. Specifically, a record was created for each patient consisting of data on predictors from the baseline and week-24 visits and, if observed, the week-48 and week-72 trial visits, respectively, and patients who died during the subsequent 48 weeks were flagged accordingly. All such records were pooled into a single dataset for analysis; therefore, patients may have contributed up to two unique observations to the study database.

Potential predictors were identified *a priori* based on biologic plausibility and clinical rationale. Patient sex, race, smoking status, history of cardiovascular disease, presence of honeycombing on high-resolution computed tomography scans, use of supplemental oxygen, and history of surgical lung biopsy were evaluated based on information collected at the baseline visit. Age, body mass index, use of concomitant medications, percent predicted FVC, percent predicted carbon monoxide diffusing capacity (D_{LCO}), the University of California at San Diego Shortness of Breath Questionnaire (UCSD SOBQ), and the St. George's Respiratory Questionnaire (SGRQ) were evaluated at the baseline and week-48 trial visits (for baseline data corresponding to the week-24 and week-72 trial visits, respectively). Longitudinal changes in measures of physiologic status, dyspnea (assessed by the UCSD SOBQ), and health-related quality of life (HRQL, assessed by the SGRQ), and the occurrence of respiratory hospitalization, were evaluated over the 24-week periods immediately preceding the week-24 and week-72 trial visits. Trial treatment assignment (IFN-γ1b vs. placebo), trial enrollment (GIPF-001 vs. GIPF-007), and country of residence were included as possible confounders.

Statistical Analyses

Crude (unadjusted) risks of all-cause mortality (per person-year) were estimated for patients stratified by each potential predictor separately, as were corresponding (unadjusted) hazard ratios using Cox proportional hazards models. To optimize model fit and aid in interpretation of study results, potential predictors that are continuous in nature were characterized using categorical variables, because such variables exhibited in formal and informal tests a nonlinear relationship with mortality. Thresholds separating categories for a given predictor were defined initially based on the quintiles of their distributions; some thresholds were subsequently modified based on distributional properties of the empirical data and thresholds previously used in published clinical research (*see* Table E1 in the online supplement).

A multivariate Cox proportional hazards model was estimated to identify independent predictors of all-cause mortality. All dichotomous measures with *P* values less than 0.10 in unadjusted analyses were initially included in the model; grouped dichotomous variables were included if any of the grouped variables had a *P* value less than 0.10. We subsequently excluded from this model all variables that were no longer important predictors in a multivariate context. The robustness of the final specification to alternative approaches for eliminating variables from the model was evaluated.

From the fully specified model, an abbreviated clinical model comprised only of predictors that are readily and reliably evaluable by clinicians and that might be used to assess patient risk in clinical practice was also estimated. The importance of interactions between all levels of selected predictors, along with the selected predictors, was evaluated by the stepAIC method using backward and forward selection.

Only observed data were used (i.e., missing values were not imputed); therefore, the size of the study population may be slightly different across analyses, as noted. Subjects who underwent lung transplant (n = 28) during follow-up were censored on the corresponding date. The presence of multicollinearity, hazards assumptions, and model discrimination were evaluated using published methods (21, 22). Model discrimination was quantified based on the C statistic, which is the probability that among two randomly selected patients the patient with the higher predicted risk of an event will be the first to experience the event. The C statistic ranges from 0.5 (model discrimination is no better than chance) to 1 (model discrimination is perfect). A C statistic between 0.70 and 0.80 is typically considered "acceptable," whereas a value exceeding 0.80 is typically considered "excellent."

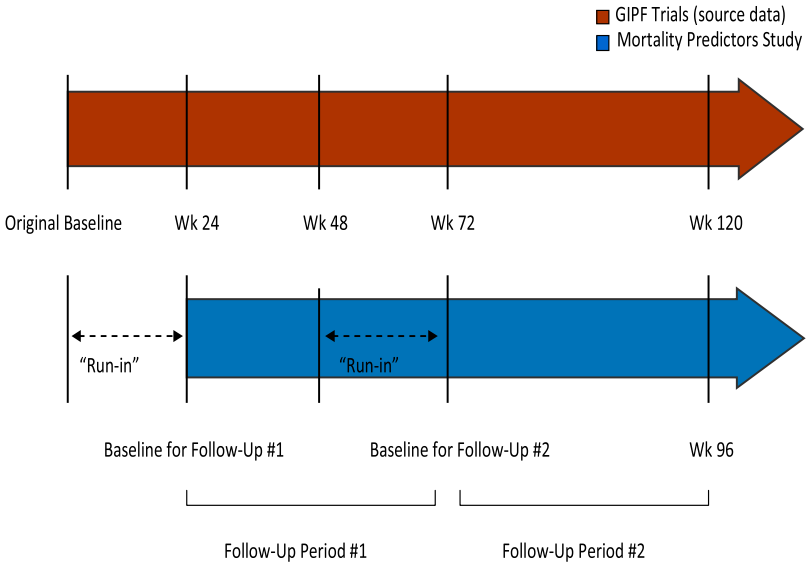

Figure 1. Schematic of study design.

A mortality risk scoring system was developed using methodology set forth by Wilson and coworkers (23) and used in other studies (24, 25). Specifically, β coefficients from the abbreviated Cox model were converted to scores by multiplying each by 10 and rounding to the nearest integer. A mortality risk score was calculated for each study subject by summing the individual scores corresponding to his or her characteristics; the baseline hazard function from the Cox model was then used to convert the total risk score to a 1-year probability of death as follows: $p(\text{death}) = 1 - 0.988^{\exp[0.1*\text{total risk score}]}$, where 0.988 is the estimated 1-year probability of survival, and thus 1 – 0.988 is the estimated 1-year probability of death for persons with the lowest risk (i.e., those with a total risk score equal to 0). To verify that estimates of risk produced by the scoring system were consistent with observed data, subjects were stratified into quintiles based on their risk scores, and average risks calculated from the scoring system were compared with observed risks (using the Kaplan-Meier method). Calibration and discrimination were evaluated using the chi-square statistic and C statistic, respectively.

RESULTS

Patient Characteristics

Among the 1,156 patients with IPF who were enrolled in the two clinical trials of IFN-γ1b, 1,099 participated in the week-24 trial visit and thus qualified for inclusion in the study population (Table 1). Mean age was 65 (SD = 8) years, 70% were male, and 75% were United States residents. Mean baseline percent predicted FVC was 68 (SD = 14), and percent predicted D_{LCO} was 42 (SD = 12). Among the 1,099 patients, 830 participated in the week-72 visit; thus, the study database included a total of 1,929 patient-visits.

Predictors of Mortality

There were a total of 152 deaths; 98 deaths occurred between the week-24 and week-72 trial visits (mean duration of follow-up, 43 wk), whereas the remainder (n = 54) occurred during the 48-week period after the week-72 trial visit (mean duration of follow-up, 29 wk). Crude 1-year risk of mortality was 9.7% (95% confidence interval [CI], 8.2–11.2). Unadjusted risks of mortality were systematically different ($P < 0.10$) across one or more strata for the following variables: age; supplemental oxygen use; history of surgical lung biopsy; 24-week history of respiratory hospitalization; prednisone use; azathioprine use; percent predicted FVC; 24-week change in percent predicted FVC; percent predicted D_{LCO}; 24-week change in percent predicted D_{LCO}; dyspnea score (assessed by UCSD SOBQ); 24-week change in dyspnea score; HRQL (assessed by SGRQ); and 24-week change in HRQL (Table 2).

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

Characteristics	N (%)
Demographic	
Age, yr	
<60	240 (21.8)
60–69	473 (43.1)
⩾70	386 (35.1)
Male	772 (70.2)
Race	
White	1,013 (92.2)
Other	86 (7.8)
Country of residence	
United States	826 (75.2)
Other	273 (24.8)
Clinical	
Honeycombing on HRCT	947 (86.2)
Surgical lung biopsy	638 (58.1)
History of cardiovascular disease	299 (27.2)
Treatment assignment	
Placebo	418 (38)
IFN-γ1b	681 (62)
Study	
GIPF-007	801 (72.9)
GIPF-001	298 (27.1)

Definition of abbreviation: HRCT = high-resolution computed tomography.

In the multivariate model, statistically significant independent predictors of all-cause mortality included age, history of respiratory hospitalization, percent predicted FVC, 24-week change in percent predicted FVC, percent predicted D_{LCO}, 24-week change in percent predicted D_{LCO}, and 24-week change in HRQL (Table 3). This comprehensive model was found to be robust across alternative approaches for eliminating variables from the model, with each yielding the same set of predictors. Model discrimination, based on the C statistic, was 0.77 (95% CI, 0.72–0.81).

From the comprehensive model, an abbreviated clinical model including only those factors that are readily and reliably evaluable in the typical clinical setting was derived. These included age, 24-week history of respiratory hospitalization, percent predicted FVC, and 24-week change in percent predicted FVC (Table 3). Among these, the strongest independent predictor of mortality was the 24-week change in percent predicted FVC. Of note, a 24-week change of −5% to −9.9% was associated with a more than twofold increase in the risk of death over the subsequent 12 months (hazard ratio [HR], 2.60 [95% CI, 1.75–3.85; $P < 0.001$]), whereas a decline greater than or equal to 10% was associated with an eightfold increase in the risk of 1-year mortality (HR, 7.99 [95% CI, 5.26–12.14; $P < 0.001$]). Model discrimination for the clinical model was 0.75 (95% CI, 0.71–0.79), indicating that the discriminatory power was comparable with that of the comprehensive model. Multicollinearity between independent variables and nonproportional hazards were determined not to be significant in any of the multivariate models, and results were robust across models when focusing on the subset of patient visits (n = 1,444) with data available for all potential predictors. Consideration of interaction terms in the clinical model selected by the stepAIC method failed to improve model discrimination.

Mortality Risk Scoring System

A simplified mortality risk scoring system was developed based on the β coefficients for each predictor in the abbreviated Cox model. The mortality risk scoring system is presented in Table 4. Overall, the scoring system overestimated mortality risk by, in relative terms, less than 2% (observed risk, 9.7% vs. estimated risk from scoring system, 9.9%) (Table 5). The ratio of risk from the scoring system to observed risk ranged from 0.65–1.13 across patient quintiles; absolute differences ranged from 0.3–2%. Calibration (P value = 0.316) and discrimination (C statistic = 0.75 [95% CI, 0.71–0.80]) of the scoring system were good.

The expected 1-year risk of mortality for an individual patient can be ascertained by summing the scores for each of the four predictors and comparing the total score with the corresponding expected 1-year risk of mortality (Table 4). For example, the total score for a 66-year-old patient with a history of respiratory hospitalization, a percent predicted FVC of 68%, and a 24-week change in percent predicted FVC of less than −5% is 26 (4 + 14 + 8 + 0), which corresponds to a 10–20% risk of 1-year mortality. By contrast, the total score for a patient with the same age, baseline FVC, and history of respiratory hospitalization, yet with a 24-week change in percent predicted FVC between −5 and −9.9%, is 36 (4 + 14 + 8 + 10), which corresponds to a 30–40% risk of 1-year mortality.

TABLE 2. UNADJUSTED ANALYSES OF PREDICTORS OF ALL-CAUSE MORTALITY AMONG PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

Covariates	Subject Visits (*n*)	Deaths (*n*)	Deaths (%)	HR	95% CI	*P* Value
Demographic						
Age						
<60	417	22	5.3	0.51	0.32–0.83	0.006
60–69	817	59	7.2	0.71	0.50–1.00	0.053
⩾70	690	71	10.3	—	—	—
Sex						
Male	1,347	113	8.4	1.23	0.86–1.77	0.262
Female	577	39	6.8	—	—	—
Race						
White	1,775	139	7.8	0.95	0.54–1.69	0.865
Other	149	13	8.7	—	—	—
Country						
United States	1,459	109	7.5	0.79	0.56–1.13	0.202
Other	465	43	9.2	—	—	—
Clinical						
Current smoker						
Yes	92	4	4.3	0.49	0.18–1.32	0.157
No	1,832	148	8.1	—	—	—
Oxygen use						
Yes	485	58	12	1.85	1.34–2.57	<0.001
No	1,431	94	6.6	—	—	—
Honeycombing on HRCT						
Yes	1,652	132	8	1.07	0.67–1.71	0.790
No	271	20	7.4	—	—	—
Surgical lung biopsy						
Yes	1,126	72	6.4	0.62	0.45–0.86	0.004
No	795	80	10.1	—	—	—
History of cardiovascular disease						
Yes	520	41	7.9	1.00	0.70–1.43	0.991
No	1,404	111	7.9	—	—	—
History of respiratory hospitalization						
Yes	77	26	33.8	6.22	4.07–9.49	<0.001
No	1,847	126	6.8	—	—	—
Prednisone use						
>10 mg per day	296	40	13.5	2.16	1.48–3.15	<0.001
⩽10 mg per day	295	29	9.8	1.54	1.01–2.35	0.047
0	1,338	83	6.2	—	—	—
Azathioprine use						
Yes	17	5	29.4	4.82	1.97–11.75	0.001
No	1,907	147	7.7	—	—	—
Physiologic						
% Predicted FVC						
⩽50	99	14	14.1	4.45	2.14–9.44	<0.001
51–65	726	75	10.3	3.02	1.69–5.33	<0.001
66–79	677	48	7.1	2.18	1.28–4.18	0.005
⩾80	412	14	3.4	—	—	—
24-Week change in % predicted FVC						
⩽ −10	166	39	23.5	7.06	4.21–11.84	<0.001
−5 to −9.9	373	45	12.1	3.43	2.07–5.66	<0.001
0 to −4.9	678	34	5	1.37	0.81–2.33	0.237
>0	638	23	3.6	—	—	—
% Predicted DLco						
⩽35	397	50	12.6	2.68	1.75–4.12	<0.001
36–45	716	61	8.5	1.84	1.22–2.78	0.004
>45	772	36	4.7	—	—	—
24-Week change in % predicted DLco						
⩽ −15	103	18	17.5	4.61	2.53–8.38	<0.001
−14.9 to −10	124	15	12.1	2.86	1.52–5.39	0.001
−9.9 to 0	938	62	6.6	1.56	0.99–2.44	0.056
>0	612	27	4.4	—	—	—
Dyspnea and HRQL						
UCSD SOBQ						
>80	97	14	14.4	3.37	1.74–6.51	<0.001
61–80	249	24	9.6	1.89	1.07–3.33	0.029
41–60	433	41	9.5	1.99	1.20–3.30	0.007
21–40	576	46	8	1.62	0.99–2.65	0.057
⩽20	491	24	4.9	—	—	—
24-Week change in UCSD SOBQ						
>10	490	71	14.5	2.73	1.96–3.82	<0.001

(*Continued*)

TABLE 2. (CONTINUED)

Covariates	Subject Visits (*n*)	Deaths (*n*)	Deaths (%)	HR	95% CI	*P* Value
⩽10	1,255	68	5.4	—	—	—
SGRQ (summary)						
⩾60	334	39	11.7	2.33	1.38–3.93	0.002
46–59	488	40	8.2	1.56	0.93–2.63	0.093
31–45	527	43	8.2	1.60	0.95–2.67	0.075
<30	413	22	5.3	—	—	—
24-Week change in SGRQ (summary)						
>20	81	25	30.9	5.92	3.74–9.37	<0.001
11–20	209	32	15.3	2.80	1.84–4.25	<0.001
⩽10	1,242	71	5.7	—	—	—

Definition of abbreviations: CI = confidence interval; DL_{co} = carbon monoxide diffusing capacity; HR = hazard ratio; HRCT = high-resolution computed tomography; HRQL = health-related quality of life; SGRQ = St. George's Respiratory Questionnaire; UCSD SOBQ = University of California San Diego Shortness of Breath Questionnaire.

DISCUSSION

The clinical course of patients with mild to moderate IPF is characterized by physiologic deterioration (as measured by FVC, DL_{co}, and alveolar–arterial oxygen gradient); worsening severity of dyspnea; and frequent hospitalizations for respiratory disorders (3). Hospitalization for a respiratory condition is a particularly ominous event, with up to half of the IPF-related deaths occurring after such an event (3). In addition, although most patients experience an insidious decline in lung function that ultimately proves fatal, considerable intersubject and intrasubject variability may be observed (3). As a result, formulating an accurate prognosis for an individual patient with IPF represents a distinct clinical challenge. Two clinical prediction models have been developed for patients with IPF (4, 5). To date, however, use of these prediction models and corresponding risk scoring systems has been confined to clinical research, largely based on the inclusion of factors that are not widely accessible in the clinical setting or for which the measurement characteristics preclude widespread clinical use.

In the present study, we identified significant predictors of mortality among a well-defined cohort of patients with IPF and developed a simplified scoring system that may be easily used in clinical practice to assess the 1-year risk of mortality for an individual patient. Development of the scoring system was based on data from two of the largest clinical trials to date in patients with IPF; the study population included more than 1,000 patients from the United States and Europe with a wide range of demographic, clinical, and physiologic characteristics. Additionally, although all patients had mild to moderate functional impairment at baseline, many progressed during the period of observation. Consequently, our scoring system should be generalizable to the population of patients typically treated in respiratory clinical practice. We note that because our objective was to use all available data to develop a robust risk scoring system that is sensitive to the potential importance of relatively small differences in variable values, we chose not to split our sample for purposes of validation, and we were unable to validate the risk scoring system using data from a different source. Thus, whether the scoring system would perform comparably in other populations of patients with IPF is currently unknown, and validation using data from other large populations of patients with IPF are therefore needed.

We included only four predictors in our scoring system, each of which can be readily and reliably ascertained in the typical clinical setting. These predictors included age, history of respiratory hospitalization within the previous 24 weeks, percent predicted FVC, and 24-week change in percent predicted FVC. Importantly, we found that a decline in percent predicted FVC as small as 5% at 6 months was associated with a more than twofold increase in the risk of death over the subsequent 12 months. This finding is particularly noteworthy because it highlights the prognostic significance of changes in FVC that were previously regarded as within the range of test variability and thus evidence of clinically stable disease. Only one other study to date has reported a similar finding regarding the predictive value of categorical changes in FVC less than 10%. In a study that included 84 patients with

TABLE 3. MULTIVARIATE ANALYSES OF PREDICTORS OF ALL-CAUSE MORTALITY AMONG PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

	HR for Death					
	Comprehensive Model*			Clinical Model†		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age						
⩾70	2.19	1.22–3.95	0.009	2.21	1.35–3.62	0.002
60–69	1.64	0.91–2.94	0.10	1.49	0.90–2.46	0.120
<60	1.00	—	—	1.00	—	—
History of respiratory hospitalization						
Yes	2.82	1.61–4.97	<0.001	4.11	2.57–6.58	<0.001
% Predicted FVC						
⩽50	3.90	1.49–10.19	0.006	5.79	2.55–13.15	<0.001
51–65	2.35	1.18–4.78	0.016	3.54	1.95–6.44	<0.001
66–79	1.46	0.73–2.92	0.291	2.20	1.19–4.09	0.012
⩾80	1.00	—	—	1.00	—	—
24-Week change in % predicted FVC						
⩽ −10	3.65	2.03–6.57	<0.001	7.99	5.26–12.14	<0.001
−5 to −9.9	1.95	1.24–3.09	0.004	2.60	1.75–3.85	<0.001
> −5	1.00	—	—	1.00	—	—
% Predicted DLco						
⩽35	1.74	1.01–2.99	0.046			
36–45	1.29	0.78–2.13	0.319			
>45	1.00	—	—			
24-Week change in % predicted DLco						
⩽ −15	2.41	1.19–4.87	0.015			
−14.9 to −10	1.61	0.79–3.28	0.190			
−9.9 to 0	1.29	0.78–2.13	0.317			
>0	1.00	—	—			
24-Week change in HRQL (SGRQ)						
>20	3.63	2.08–6.34	<0.001			
11–20	1.59	0.98–2.58	0.058			
⩽10	1.00	—	—			

Definition of abbreviations: CI = confidence interval; DLco = carbon monoxide diffusing capacity; HRQL = health-related quality of life; HR = hazard ratio; SGRQ = St. George's Respiratory Questionnaire.

* n (patient visits) = 1,444, n (deaths) = 110, C statistic (95% CI), 0.77 (0.72–0.81).

† n (patient visits) = 1,854, n (deaths) = 142, C statistic (95% CI), 0.75 (0.71–0.79).

TABLE 4. MORTALITY RISK SCORING SYSTEM FOR PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

(1) Sum individual scores corresponding to level of each risk factor for a given patient*		(2) Find expected 1-year probability of death corresponding to total risk score	
Risk Factors	Score	Total Risk Score	Expected 1-Year Risk of Death
Age			
⩾70	8		
60–69	4	0–4	<2%
<60	0	8–14	2–5%
History of respiratory hospitalization		16–21	5–10%
Yes	14	22–29	10–20%
No	0	30–33	20–30%
% Predicted FVC		34–37	30–40%
⩽50	18	38–40	40–50%
51–65	13	41–43	50–60%
66–79	8	44–45	60–70%
⩾80	0	47–49	70–80%
24-Week change in % predicted FVC		>50	>80%
⩽ −10	21		
−5 to −9.9	10		
> −4.9	0		

* For example: total score for a patient aged 70 years, with no history of respiratory hospitalization, a % predicted FVC of 51–65, and a 24-week change in % predicted FVC of −5 to −9.9, is 31 (8 + 0 + 13 + 10) and predicted 1-year probability of death, 20–30%.

biopsy-proven IPF, Zappala and coworkers (18) observed a significant increase in the risk of mortality among patients who experienced a 5–10% decline in percent predicted FVC over 6 months (HR, 2.31 [95% CI, 1.19–4.50]). Although this study was limited by a relatively small sample size and potential confounding by a range of variables for which we controlled in our study, the magnitude of the observed risk associated with a 5–10% decline in FVC was strikingly similar to that of the present study (HR, 2.60 [95% CI, 1.75–3.85]). The discriminative ability of our mortality risk model compares favorably with others, including predictive models for long-term survival after lung transplantation (26). These models, which considered selected pretransplant demographic and clinical characteristics as potential predictors, and separately, post-transplant parameters included in the Lung Allocation System, performed poorly in predicting long-term survival, with C statistics for the various models all less than 0.60. C statistics for several cardiovascular disease models based on data from the Framingham Heart Study range from 0.66–0.79 (23, 27–30).

Consistent with prior research, we also found that baseline percent predicted DL_{co} was an important predictor of mortality (4, 5, 7, 8, 31, 32). However, we decided not to include DL_{co} in the risk scoring system because it exhibits considerable variability in clinical practice and is not as widely available as the other measures that were included in the abbreviated clinical model. Based on these factors, we concluded that its inclusion would likely limit the use of our scoring system among clinicians. Importantly, excluding baseline and longitudinal measures of percent predicted DL_{co} (and change in HRQL) had no meaningful impact on model discrimination, suggesting that measures of DL_{co} may not be incrementally informative in differentiating between patients with IPF based on their mortality risk (Table 6).

Our findings have several potentially important implications for both clinical practice and clinical trial design. First, although there is considerable variability in prognosis among patients with IPF, our data suggest that an IPF patient's prognosis may be readily and accurately assessed, and such information may be used as a basis for management decisions that are significantly informed by discussions with patients about the relative risks of treatment against the risks of progressive disease. Additionally, our findings may aid in the identification of appropriate candidates for enrollment in clinical trials and facilitate accurate stratification, both of which may contribute to a more efficient and properly "powered" clinical trial.

Some limitations of our study are noteworthy. First, these clinical trials enrolled a group of patients with mild to moderate impairment of pulmonary function at baseline. The study did not include patients who were too ill or considered at high risk for dying during the course of the trial (2, 20). We acknowledge in particular the exclusion of patients with severe emphysema, because emerging evidence suggests that comorbid emphysema may have a potentially important impact on survival and

TABLE 5. OBSERVED ONE-YEAR RISK OF DEATH AMONG PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS AND ESTIMATES FROM RISK SCORING SYSTEM

Risk Group (*score*)	N	Observed Risk (%)	Risk from Scoring System (%)	Ratio*
All patients	1,854	9.7	9.9	1.02
Quintiles of patients, by risk score				
1st (⩽ 11)	368	3.4	2.2	0.65
2nd (12–15)	359	4.4	4.1	0.93
3rd (16–17)	361	5.4	6	1.12
4th (18–24)	384	9.3	9	0.96
5th (⩾ 25)	382	25	27.1	1.08

* Observed risk versus risk from scoring system.

TABLE 6. ALTERNATIVE CLINICAL MODEL SPECIFICATIONS

Model	Independent Variables	C Statistic (*95% CI*)
Clinical model	Age, respiratory hospitalization, FVC, ΔFVC	0.75 (0.71–0.79)
Model B	Age, respiratory hospitalization, DL_{co}, ΔDL_{co}	0.70 (0.66–0.75)
Model C	Age, respiratory hospitalization, FVC, DL_{co}	0.71 (0.66–0.75)
Model D	Age, FVC, DL_{co}, ΔFVC, ΔDL_{co}	0.75 (0.71–0.80)
Model E	Age, FVC, DL_{co}	0.66 (0.62–0.70)

Definition of abbreviations: ΔDL_{co} = 24-week change in carbon monoxide diffusing capacity; ΔFVC = 24-week change in FVC; CI = confidence interval; DL_{co} = carbon monoxide diffusing capacity.

longitudinal measures of pulmonary function in patients with IPF. Although the trial populations undoubtedly included some patients with mild to moderate emphysema, further assessment of the prognostic significance of comorbid emphysema was not possible and remains for future research. The generalizability of study results (e.g., the importance of a 5–9% decline in FVC vis-à-vis mortality) and the applicability of the risk scoring system to patients excluded from the trial populations are unknown.

Second, although the study database included a broad range of demographic, clinical, and physiologic parameters for a large number of study subjects, potential predictors of mortality that have been reported to be independently significant in several recent small studies were not included in our analysis. Brain natriuretic protein, a noninvasive marker for pulmonary hypertension, was recently shown in one study to be a predictor of mortality in patients with IPF (16). In another recent small study, CT visual scores were found to be a useful predictor of mortality in IPF (14). Additionally, 6-minute walk distance has been reported to be an independent predictor of mortality in patients with IPF on a waiting list for lung transplantation (10). More recently, both baseline 6-minute walk distance and the change in 6-minute walk distance at 12 months were identified as independent predictors of mortality in a small cohort of patients with IPF (17). Whether further research will establish these and possibly other measures as important predictors of mortality in IPF and whether the addition of these predictors to our model would significantly enhance its predictive accuracy is unknown.

Third, although using categorical variables for continuous measures is typically less desirable (vs. considering continuous measures and corresponding higher-order effects), we did so to aid in the interpretation and use of study results. Fourth, hospitalizations were designated as respiratory in nature based on assessments by principal investigators, and such designations were not formally adjudicated. Finally, although our analyses would have ideally been limited to patients randomized to placebo in the clinical trials, we concluded based on the absence of evidence for any treatment effect that the enhanced power of the study to identify independent predictors of mortality justified the inclusion of all randomized patients.

In conclusion, we found that among a large and well-characterized population of patients with IPF several parameters were important independent predictors of mortality, including changes in percent predicted FVC that were previously regarded as evidence of clinically stable disease. We also found that an abbreviated clinical model comprising four predictors that are readily and reliably ascertainable in clinical practice performed well in discriminating between patients with IPF based on their risk of death, and that a risk scoring system based on these characteristics may be used to accurately assess an individual patient's risk of death and facilitate clinical decision making. Additional research using data from other large populations of patients with IPF is needed to validate the applicability and accuracy of our scoring system.

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