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6-minute walk test distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis

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Running Head: 6-Minute Walk Test Prognostic Utility in IPF

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Most important findings from the study:

6-minute walk distance indices independently predict mortality in IPF and improve the performance of the previously published clinical prediction model.

ABSTRACT:

6-minute walk test distance (6MWD) has recently been shown to be associated with the risk of mortality in patients with IPF; however, the independent contribution of 6MWD to the prediction of mortality risk has not been evaluated in a large, well-defined population of patients with IPF.

A Cox proportional hazards model was used to characterise the relationship between risk factors of interest and all-cause mortality in IPF patients who completed a week 24 study visit in a clinical trial evaluating interferon gamma-1b (N=748). Risk factors of interest included the independent predictors of mortality in the previously published clinical prediction model together with 6MWD and 24-week change in 6MWD.

Baseline 6MWD<250 m was associated with a 2-fold increase in the risk of mortality (HR 2.12; 95% CI 1.15–3.92) and a 24-week decline in 6MWD>50 m was associated with a nearly 3-fold increase in mortality risk (HR 2.73; 95% CI 1.60–4.66). Inclusion of 6MWD data improved model discrimination compared with the original model (C-statistic, 0.80 [95% CI 0.76–0.85] vs.0.75 [0.71–0.79]).

Both 6MWD and change in 6MWD are independent predictors of mortality in patients with IPF. The addition of 6MWD to the clinical prediction model improves model discrimination compared with the original model.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and ultimately fatal fibrotic lung disease characterised by progressive pulmonary insufficiency and diminished exercise capacity [1]. Periods of transient clinical stability may occur; however, continued disease progression is inevitable [2]. The prognosis is poor, with an estimated 5-year survival rate that is comparable to several neoplastic disorders, including cancers of the lung, liver, and brain [3,4].

Several studies have identified independent predictors of mortality in patients with IPF, including age, respiratory hospitalisation, percent predicted forced vital capacity (%FVC), and longitudinal change in %FVC [5–16]. Six-minute walk test distance (6MWD), a practical and widely used measure of clinical status in patients with a variety of cardiopulmonary diseases, [17–22] has recently been shown to be associated with the risk of mortality in patients with IPF [23–25]; however, the independent contribution of 6MWD to the risk of mortality has not been formally evaluated in a large, well-defined population of patients with IPF.

We previously reported the test performance characteristics of the 6-minute walk test (6MWT) in patients with IPF [23]. A novel finding of our study was the observation that 6MWD and 24-week change in 6MWD were highly predictive of 1-year mortality despite relatively weak correlations between 6MWD and various measures of pulmonary function known to be independent predictors of mortality. Based on this observation, we

hypothesized that the 6MWT might interrogate a separate domain of the disease process and provide incrementally informative data regarding the prognosis of patients with IPF. The aim of the present study, therefore, was (1) to evaluate the contribution of 6MWD to the prediction of risk of all-cause mortality in patients with IPF, independent of other indices we have previously reported to predict mortality, and (2) to assess the change in model performance when 6MWD is added to the previously published clinical model [7].

METHODS

Source and Study Populations

The source population included all randomised patients in a prospective, double-blind, placebo controlled Phase 3 trial evaluating treatment with interferon gamma-1b in patients with IPF (GIPF-007 [N=826]) [26]. From the source population, we selected for inclusion all patients who completed a baseline and week 24 study visit (N=748); patients who died (n=20) or had a lung transplant (n=1) between baseline and week 24 were thus excluded from the analysis. Clinical efficacy outcomes in the original trial revealed no evidence of a treatment effect; therefore, the analysis included data from both treatment groups to maximize study power [26].

Criteria for enrolment in the original trial have been previously described [26]. Briefly, eligible patients had a confident IPF diagnosis according to the criteria of the American Thoracic Society/European Respiratory Society, [27,28] FVC ≥55% of the predicted value, carbon monoxide diffusing capacity (DL_{CO}) ≥35% of predicted, either FVC or

DL_{CO} ≤90% of predicted, and a 6MWT distance ≥150 m. Patients with a history of unstable or deteriorating cardiac, vascular, or neurologic disease within the previous 6 months and patients on a waiting list for lung transplantation at the time of randomisation were excluded from enrolment.

Study Protocol

Eligible patients underwent a complete physical examination and assessments of physiologic function (FVC, DL_{CO}, resting A-a gradient), dyspnea (University of California San Diego Shortness of Breath Questionnaire) health-related quality of life (HRQL; St. George's Respiratory Questionnaire), and exercise capacity (6MWT) at the baseline study visit and at 24-week intervals thereafter.

The 6MWT was performed indoors on a flat, straight corridor with a hard surface. An oxygen titration procedure was performed at the screening visit to establish a baseline flow rate for patients who required supplemental oxygen; all subsequent tests during the study period were performed using the baseline oxygen flow rate established during the titration procedure. Before each 6MWT, patients were required to have resting oxygen saturation as measured by pulse oximetry of at least 83% after 10 minutes of rest breathing room air or at the baseline O_2 flow rate. Patients were instructed to walk as far as they could without jogging or running; if they needed to slow down or stop to rest they were permitted to do so and encouraged to resume walking as soon as they were able. The test was stopped if the patient experienced chest pain, intolerable dyspnea, leg cramps, diaphoresis, or desaturation below 83%.

Two observation periods were used to maximize the number of events and enhance the power of the study to detect significant relationships between predictor variables and 1-year mortality. 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. These periods served as the “run-in” phases during which changes in longitudinal predictors of mortality were measured; all deaths occurring over the subsequent 48-week periods were identified and flagged accordingly (**Figure 1**). All data from the two periods were pooled into a single dataset for analysis; therefore, patients may have contributed up to two unique observations to the study database.

Statistical Analysis

A multivariate Cox proportional hazards model was used to characterise the relationship between risk factors of interest and all-cause mortality. Risk factors of interest included the independent predictors of mortality in the previously published clinical model (age, respiratory hospitalisation, %FVC, and 24-week change in %FVC), [7] as well as 6MWD and 24-week change in 6MWD. Categorical thresholds were retained for risk factors of interest from the original clinical model; categorical thresholds for baseline 6MWD and 24-week change in 6MWD were selected based on prior research [23].

The presence of multicollinearity, hazards assumptions, and model discrimination were evaluated using published methods [29,30]. Model discrimination was quantified based on the C-statistic and compared against the previously published clinical model. The C-statistic is a measure of 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.

Values range from 0.5 (model discrimination is no better than chance) to 1.0 (perfect discrimination). Values between 0.70 and 0.80 were assumed to signify “acceptable” model discrimination; values exceeding 0.80 were assumed to represent “excellent” discrimination. Model performance was also evaluated by calculating the net reclassification improvement (NRI) for the model including 6MWD and change in 6MWD compared with the original model (based on patients in study GIPF-007). The NRI can be quantified as a sum of differences in proportions of individuals moving up in risk categories minus the proportion moving down for people who develop events, and the proportion of individuals moving down minus the proportion moving up for people who do not develop events [30].

RESULTS

A total of 748 patients completed a week 24 study visit in the original clinical trial and therefore qualified for inclusion in the study population. Demographics and baseline characteristics are summarised in **Table 1**. The mean (±SD) age at study entry was 66 (±7.6) years and 71.5% of patients were male. Mean values for percent predicted FVC and percent predicted DL_{CO} were 72.5 (±12.8) and 47.5 (±9.2), respectively. The mean distance walked during the 6MWT was 397 (±107) m. A total of 86 (11.5%) patients required supplemental oxygen during the 6MWT; among these, the mean baseline oxygen flow rate was 2.84 L/min.

There was a total of 79 deaths during the two periods of observation (n [patient visits]=1,156; see online data supplement, **Table E1**); 59 deaths occurred between the week 24 and week 72 study visits (mean duration of follow-up, 43 weeks) and 20 deaths occurred during the 48-week period following the week 72 study visit (mean duration of follow-up, 31 weeks). The crude 1-year risk of all-cause mortality was 6.8% (95% confidence interval [CI] 5.4%–8.3%). Death was judged by clinical investigators to be IPF-related in 67 patients (crude 1-year risk, 5.8%; 95% CI 4.6%–7.1%).

The unadjusted risk of 1-year all-cause mortality and Kaplan-Meier survival distributions by baseline 6MWD and 24-week change in 6MWD are summarised in **Table 2** and **Figure 2**, respectively**.** In the unadjusted analyses, both baseline 6MWD and 24-week change in 6MWD were associated with the risk of 1-year mortality. Patients with a >50 m decline in 6MWD at 24 weeks (vs. ≤25 m decline) had the largest relative risk (HR 3.76, 95% CI 2.26−6.27, p<0.001).

In the multivariate analysis, all risk factors of interest were found to be statistically significant independent predictors of all-cause mortality, including age, respiratory hospitalisation, %FVC, 6MWD, and 24-week changes in %FVC and 6MWD (**Table 3**). Baseline 6MWD <250 m was independently associated with a 2-fold increase in the risk of 1-year mortality (HR 2.12; 95% CI 1.15–3.92; p=0.02) and a 24-week decrement in 6MWD >50 m was independently associated with a nearly 3-fold increase in the risk of mortality at 1 year (HR 2.73; 95% CI 1.60–4.66; p<0.01). Additionally, inclusion of 6MWD and 24-week change in 6MWD improved model discrimination compared with the original clinical model (C-statistic, 0.80 [95% CI 0.76–0.85] vs. 0.75 [95% CI 0.71–0.79]). The addition of 6MWD and 24-week change in 6MWD to the original model resulted in a net reclassification improvement of 26.1% (p<0.001); 10.1% of events and 16.0% of non-events were reclassified correctly compared with the original model (**Table 4**).

Hazard ratios for risk factors of interest from the original clinical model were comparable to previously published estimates. Consistent with the original clinical model, %FVC and 24-week change in %FVC remained the most important predictors of 1-year mortality; the hazard ratio for all-cause mortality was 6.86 (95% CI, 1.99–23.60; p<0.01) among patients with a baseline FVC ≤50% (vs. ≥80%) and 5.86 (95% CI, 3.33–10.81; p<0.01) among patients with a ≥10% decline in FVC at 24 weeks (vs. >–5%) .

Since the original clinical model included a subset of 330 patients from the GIPF-001 study for whom 6MWT data were not collected, a multivariate analysis using the predictor variables in the original clinical model was repeated in the subset of patients

(N=748) who were included in the present analysis (see online data supplement; **Table E2**). Hazard ratios and model discrimination were largely unchanged compared with the original clinical model. Consistent with the original clinical model, the addition of 6MWD and change in 6MWD improved model discrimination in this cohort (C-statistic 0.80 [95% CI 0.76–0.85] vs. 0.76 [0.71–0.82]).

DISCUSSION

The hallmark clinical features of IPF include progressive pulmonary insufficiency and reduced exercise capacity. While declines in lung function and exercise capacity are inevitable, considerable variability may be observed in the rate of disease progression—both within and between patients. Moreover, longitudinal changes in the various measures used to assess clinical status in patients with IPF are only weakly correlated; periods of transient stability in one measure may coincide with marked declines in others [23,31]. As a result of the highly variable and enigmatic clinical course, formulating an accurate prognosis in the individual patient represents a distinct challenge for clinicians. The identification of accurate predictors of mortality that are readily and reliably ascertainable in the typical clinical setting therefore has obvious and important implications for the clinical management of patients with IPF.

We previously reported that a simplified clinical risk prediction model comprised of four predictors that are widely accessible in the clinical setting accurately predicts near-term mortality in patients with IPF [7]. The predictors included age, history of respiratory hospitalisation within the preceding 24 weeks, %FVC, and 24-week change in %FVC. In

the present study, we further demonstrate that 6MWD and 24-week change in 6MWD are independent predictors of near-term mortality in patients with IPF and that a novel clinical risk prediction model comprised of age, respiratory hospitalisation, %FVC, 6MWD, and 24-week changes in %FVC and 6MWD improves the ability to discriminate between patients on the basis of risk compared with the previously published clinical model.

The 6MWT has several potential advantages as a measure of clinical status in patients with IPF. The test is practical, inexpensive, and reliable; it requires no special equipment or advanced training and can be performed by all but the most severely impaired patients [32]. Additionally, 6MWD is highly reproducible in patients with IPF [23,33] and changes in 6MWD have been shown to correlate with changes in measures of physiologic function and health related quality of life [23]. Since the 6MWT is self-paced, it is both better tolerated and more reflective of activities of daily living than other walk tests [34]. Finally, the 6MWT may be incrementally informative in the assessment of disease progression in IPF patients with comorbid emphysema by capturing functional deficits that would otherwise be masked due to the spurious preservation of FVC [33].

Only two previous studies have demonstrated an independent association between 6MWD and the risk of mortality in patients with IPF [24, 25]. In a retrospective review of data from 44 patients with IPF, 29 of whom had an additional evaluation at 12 months, Caminati and coworkers [24] reported that both baseline 6MWD (<212 m) and change in 6MWD at 12 months were independently associated with an increased risk of

mortality. The study was limited by the modest sample size and the retrospective nature of the analysis, as well as the exclusion of patients who were unable to perform the 6MWT without the use of supplemental oxygen. However, the findings were generally consistent with a previous study by Lederer et al. [25] that evaluated the prognostic utility of 6MWD in 454 patients with IPF who were on a waiting list for lung transplantation. In this study, baseline 6MWD (<207 m) was strongly and independently associated with an increased risk of mortality at 6 months and performed better than baseline %FVC as a predictor of waiting list survival. Of note, longitudinal change in 6MWD was not evaluated as a potential predictor of mortality, and the 6MWT was not performed according to a standardised protocol across study sites. Moreover, patients listed for lung transplantation represent a distinct cohort; on average, patients in this study were younger and had more severe physiologic impairment and a higher prevalence of comorbid pulmonary hypertension than IPF patients who are not candidates for lung transplantation. As a result, the degree to which the findings can be generalised to the broader population of patients with IPF is unknown.

In the present analysis, we examined the specific contribution of 6MWD to the risk of near-term mortality in a large and well-defined population of patients with a confident diagnosis of IPF and broad range of impairment in physiologic measures of disease status. Baseline 6MWD <250 m was independently associated with a 2-fold increase in the risk of 1-year mortality, and a 50 m decrement in 6MWD at 24 weeks conferred a nearly 3-fold increase in the risk of mortality during the subsequent year, even after controlling for age, respiratory hospitalisation, %FVC, and 24-week change in FVC. This latter finding is particularly noteworthy, as it establishes for the first time in a large,

multinational study that longitudinal change in 6MWD is strongly and independently associated with the risk of near-term mortality in patients with IPF. While our results also demonstrated a significant relationship between a 24-week decrement in 6MWD of 26−50 m and the risk of 1-year mortality, we chose to focus on the threshold of a 50 m decrement based on prior work in which the minimal clinically important difference for the 6MWT was estimated as 24−45 m [23]. We selected the higher threshold because we did not wish to sacrifice specificity in order to improve sensitivity.

A further noteworthy finding of this study is the observation that the addition of 6MWD to a parsimonious clinical model based on four widely available and inexpensive measures of disease status provides data that is incrementally informative in the prognostic evaluation of individual patients with IPF. Model discrimination, as measured by the C-statistic, improved from 0.75 (95% CI, 0.71–0.81) to 0.80 (95% CI, 0.76–0.85) when 6MWD and 24-week change in 6MWD were added to a model comprised of age, respiratory hospitalisation, %FVC, and 24-week change in %FVC. The magnitude of improvement in model discrimination is notable, as large independent associations with the dependent variable are required for the addition of a predictive marker to result in a meaningful increase in the C-statistic [29]. For example, Pencina et al. [29] evaluated the improvement in model performance by the introduction of HDL cholesterol into a standard prediction model for a first coronary heart disease (CHD) event in 3264 subjects who were part of the Framingham Heart Study. HDL cholesterol was independently associated with the risk of a CHD event (HR 0.64; $p<0.001$); however, the addition of HDL cholesterol to a standard model comprised of age, sex, smoking status, and systolic blood pressure had a negligible effect on model discrimination (C-statistic, 0.77 vs. 0.76; p=NS). In addition, consistent with the original clinical model, the

discriminative ability of the novel model compared favorably with several well-established cardiovascular disease models based on the Framingham Heart Study; C-statistics for these models ranged from 0.66–0.79 (**Table 5**) [35–39].

Our findings have several potential implications for both clinical practice and clinical trial design. The 6MWT is a practical, safe, and inexpensive measure that can be performed in virtually any setting without the need for specialised equipment or advanced training. Our results demonstrate that data obtained from this simple and inexpensive test can be used to further inform prognosis and facilitate clinical decision making. Additionally, the ability to further discriminate between patients on the basis of risk may facilitate refinement of enrolment criteria for therapeutic clinical trials, thereby enriching study populations and potentially decreasing the necessary size, duration, and cost of clinical trials. Finally, the strong independent association between longitudinal changes in FVC and 6MWD and the risk of mortality, coupled with the favorable test performance characteristics and relatively weak correlations between changes in FVC and 6MWD suggest that a composite endpoint for disease progression defined on the basis of categorical change in FVC and 6MWD might substantially increase the rate of clinically meaningful events and further improve the efficiency of clinical trials.

The findings of our study should be interpreted in the context of several important limitations. First, source data for our analysis was obtained from a clinical trial that enrolled patients with mild to moderate impairment in baseline measures of lung function and exercise capacity. Patients with severe functional impairment or those with selected comorbidities including severe emphysema and unstable cardiovascular

disease were excluded from enrolment. While the study population likely included patients with mild to moderate emphysema, as well as patients who developed severe impairment in physiologic function during the interval preceding the second observation period (week 72 to week 120), the degree to which our findings can be generalised to these populations is uncertain.

Second, risk factors of interest and the corresponding categorical thresholds in our model were identified *a priori* based on prior research. Since the primary aims of the study were to assess the independent contribution of 6MWD to the risk of mortality and evaluate the predictive value of 6MWD when added to the previously published clinical prediction model, no formal model specification procedures were undertaken in the primary analysis to specify the model *de novo*. Third, as noted in our prior publication, [7] hospitalisations were designated as respiratory in nature based on the clinical judgment of the primary investigator and were not formally adjudicated. We note, however, that our original intent was to develop a risk prediction model that could be used in the clinical setting to quickly and accurately formulate a prognosis based on readily available data. Accordingly, we believe that the manner in which hospitalisations were characterised is more reflective of typical clinical practice, thereby potentially enhancing the clinical utility of the model. Finally, the 6MWT was performed with strict adherence to a standardised protocol following a formal oxygen titration procedure; the replication of such rigorous methods in the typical clinical setting, while possible, cannot be assured. Indeed, our decision not to develop a revised risk scoring system was based largely on the likely inconsistent clinical application of standardised procedures for the 6MWT. Nonetheless, we believe the strength of the relationship between 6MWD

and the risk of mortality warrants consideration in the clinical assessment of patients with IPF and has important implications for the design and execution of clinical trials.

In conclusion, the findings of the present study demonstrate that both 6MWD and longitudinal change in 6MWD are strong independent predictors of mortality in patients with IPF. Additionally, a clinical risk prediction model comprised of age, respiratory hospitalisation, %FVC, 6MWD, and 24-week changes in %FVC and 6MWD reliably predicts 1-year mortality in patients with IPF and may be used to further refine the prognosis of individual patients and guide clinical decision making. Further research is warranted to validate the model in other large and independent patient populations.

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REFERENCES

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
2. Ley B, Collard HR, King TE, Jr. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2011;183:431–440.
3. Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. *Am J Respir Crit Care Med* 2007;176:277–284.
4. SEER cancer statistics review, http://seer.cancer.gov Date last updated: April 15, 2009.
5. King TE Jr., Tooze JA, Schwarz MI, Brown K, Cherniack RM. Predicting Survival in Idiopathic Pulmonary Fibrosis Scoring System and Survival Model. *Am J Respir Crit Care Med* 2001;164:1171–1181.
6. Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, Kim WS, Kim WD, Lee JS, Travis WD, Kitaichi M, Colby TV. Physiology Is a Stronger Predictor of Survival than Pathology in Fibrotic Interstitial Pneumonia. *Am J Respir Crit Care Med* 2005;171:639–644.
7. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE Jr. Ascertainment of Individual Risk of Mortality in Patients with Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2011;184:459–66.

8. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE Jr., Collard HR. A Multidimensional Index and Staging System for Idiopathic Pulmonary Fibrosis. *Annal of Intern Med* 2012; 156:684–91.
9. Wells AU, Desai SR, Rubens MB, Goh NS, Cramer D, Nicholson AG, Colby TV, du Bois RM, Hansell DM. Idiopathic Pulmonary Fibrosis: A Composite Physiologic Index Derived from Disease Extent Observed by Computed Tomography. *Am J Respir Crit Care Med* 2003;167:962–969.
10. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, Veeraraghavan S, Hansell DM, Wells AU. Fibrotic Idiopathic Interstitial Pneumonia: The Prognostic Value of Longitudinal Functional Trends. *Am J Respir Crit Care Med* 2003;168:531–537.
11. Collard HR, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2003;168:538–542.
12. Flaherty KR, Andrei AC, Murray S, Fraley C, Colby TV, Travis WD, Lama V, Kazerooni EA, Gross BH, Toews GB, et al. Prognostic Implications of Physiologic and Radiographic Changes in Idiopathic Interstitial Pneumonia. *Am J Respir Crit Care Med*2003;168:543–548.
13. Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, Hansell DM, du Bois RM, Wells AU. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;35:830–6.

14. Hook JL, Arcasoy SM, Zemmel D, Bartels MN, Kawut SM, Lederer DJ. Titrated oxygen requirement and prognostication in idiopathic pulmonary fibrosis. *Eur Respir J* 2012; 39:359–365. doi: 10.1183/09031936.00108111. Epub 2011 Sep 1.
15. Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, Taglieri A, Mezzasalma F, Rottoli P, Saltini C, Rogliani P. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study *Eur Respir J* 2012;40:101–109. doi: 10.1183/09031936.00106011. Epub 2012 Jan 12.
16. Maldonado F, Moua T, Rajagopalan S, Karwoski RA, Raghunath S, Decker PA, Hartman TE, Bartholmai BJ, Robb RA, Ryu JH. Automated quantification of radiologic patterns predicts survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2013 Apr 5 [Epub ahead of print].
17. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six-minute walking test for assessing exercise capacity in chronic heart failure. *Br Med J* (Clin Res Ed) 1986;292:653–655.
18. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996;110:325–332.
19. Gomberg-Maitland M, Huo D, Benza RL, McLaughlin VV, Tapson VF, Barst RJ. Creation of a model comparing 6-minute walk test to metabolic equivalent in evaluating treatment effects in pulmonary arterial hypertension. *J Heart Lung Transplant* 2007;26:732–738.
20. Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman L, Jones NL, Fallen EL, Taylor DW. Effect of encouragement on walking test performance. *Thorax* 1984;39:818–822.

21. Bernstein ML, Despars JA, Singh NP, Avalos K, Stansbury DW, Light RW. Reanalysis of the 12-minute walk in patients with chronic obstructive pulmonary disease. *Chest* 1994;105:163–167.
22. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007;132:207–213.
23. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE Jr. Six-Minute-Walk Test in Idiopathic Pulmonary Fibrosis: Test Validation and Minimal Clinically Important Difference. *Am J Respir Crit Care Med* 2011;183:1231–1237.
24. Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. *Respir Med* 2009;103: 117–123.
25. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006;174:659–64.
26. King TE Jr., Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009;374:222–228.
27. American Thoracic Society, European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;161:646–664.

28. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.
29. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157–72.
30. Allison PD. Survival analysis using the SAS System: a practical guide. Cary, NC: SAS Institute Inc.; 1995. p. 292.
31. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, King TE Jr., Lancaster L, Noble PW, Sahn SA, Thomeer M, Valeyre D, Wells AU. Forced Vital Capacity in Patients with Idiopathic Pulmonary Fibrosis: Test Properties and Minimal Clinically Important Difference. *Am J Respir Crit Care Med* 2011;184:1382–1389.
32. American Thoracic Society. ATS Statement. Guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
33. Eaton T, Young P, Milne D, Wells AU. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. *Am J Respir Crit Care Med* 2005; 171:1150–1157.
34. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001;119:256–270.
35. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, et al. Development of a

risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;373:739–745.

36. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–753.
37. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW, Kritchevsky SB; Health ABC Study. Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circ Heart Fail* 2008;1:125–33.
38. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ.A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;290:1049–1056.
39. Rathore SS, Weinfurt KP, Foody JM, Krumholz HM. Performance of the Thrombolysis in Myocardial Infarction (TIMI) ST-elevation myocardial infarction risk score in a national cohort of elderly patients. *Am Heart J* 2005;150:402–10.

Tables and Figures

Table 1. Demographics and Baseline Characteristics

Characteristic	**Value (N=748)**
Demographic	
Age, mean (SD)	66 (7.6)
Sex, n (%) Male Female	 535 (71.5) 213 (28.5)
Race, n (%) Caucasian Other	 703 (94.0) 45 (6.0)
Country of residence, n (%) US Other	 521 (69.7) 227 (30.3)
Treatment assignment Interferon gamma-1b Placebo	 496 (66.3) 252 (33.7)
Clinical, n (%)	
Honeycombing on HRCT	653 (87.3)
Surgical lung biopsy	411 (54.9)
History of cardiovascular disease	213 (28.5)
Supplemental oxygen use	115 (15.4)
Physiologic, mean (SD)	
FVC, % predicted	72.5 (12.8)
DL_{CO}, % predicted	47.5 (9.2)
6MWT distance, m	397 (107)

HRCT=high resolution computed tomography; FVC=forced vital capacity; DL_{CO}=carbon monoxide diffusion capacity; 6MWT=6-minute walk test

Table 2. Unadjusted 1-year risk of all-cause mortality by baseline 6-minute walk distance and 24-week change in 6-minute walk distance

	N*	Deaths, n (%)	HR (95% CI)	P-value
Baseline 6MWD, m				
<250	125	15 (12.0)	2.33 (1.30−4.18)	0.005
250 to 349	244	19 (7.8)	1.42 (0.83−2.43)	0.201
≥350	787	45 (5.7)	1.00	−
24-week change in 6MWD, m				
<–50	308	38 (12.3)	3.76 (2.26−6.27)	<0.001
–50 to –26	165	17 (10.3)	3.15 (1.69−5.86)	<0.001
≥–25	683	24 (3.5)	1.00	−

HR=hazard ratio; CI=confidence interval; 6MWD=6-minute walk distance

*Patient visits

Table 3. Multivariate analysis of predictors of all-cause mortality in patients with idiopathic pulmonary fibrosis

Predictor Variable	Original Clinical Model [7]*			Novel Clinical Model†		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age						
≥70	2.21	1.35–3.62	0.002	2.35	1.14–4.82	0.02
60 to 69	1.49	0.90–2.46	0.12	2.29	1.13–4.63	0.02
<60	1.00	–	–	1.00	–	–
Respiratory Hospitalisation	4.11	2.57–6.58	<0.001	3.54	1.80–6.97	<0.01
Baseline %FVC						
≤50	5.79	2.55–13.15	<0.001	6.86	1.99–23.60	<0.01
51 to 65	3.54	1.95–6.44	<0.001	2.92	1.39–6.13	<0.01
66 to 79	2.20	1.19–4.09	0.012	2.17	1.02–4.63	0.05
≥80	1.00	–	–	1.00	–	
24-week change in %FVC						
≤–10	7.99	5.26–12.14	<0.001	5.86	3.33–10.81	<0.01
–5 to –9.9	2.60	1.75–3.85	<0.001	2.74	1.61–4.68	<0.01
>-5	1.00	–	–	1.00	–	–
Baseline 6MWD, m						
<250				2.12	1.15–3.92	0.02
250 to 349				1.28	0.74–2.21	0.38
≥350				1.00	–	–
24-week change in 6MWD, m						
<–50				2.73	1.60–4.66	<0.01
–50 to –26				2.94	1.56–5.53	<0.01
≥–25				1.00	–	–
C-statistic (95% CI)	0.75 (0.71–0.79)			0.80 (0.76–0.85)		

HR=hazard ratio; CI=confidence interval; FVC=forced vital capacity; DL_{CO}=carbon monoxide diffusion capacity; 6MWD=6-minute walk distance

*n (patient visits) = 1,854; n (deaths) = 142
†n (patient visits) = 1,156; n (deaths) = 79

Table 4.

A. Patients who died

		Model with 6MWD/∆6MWD: Predicted Mortality Risk			
		<0.02	**0.02−0.04**	**0.04−0.07**	**≥0.07**
Model without 6MWD/∆6MWD: Predicted Mortality Risk	**<0.02**	16	2	0	0
	0.02−0.04	2	12	4	3
	0.04−-0.07	0	4	4	6
	≥0.07	0	1	0	25

B. Patients who did not die

		Model with 6MWD/∆6MWD: Predicted Mortality Risk			
		<0.02	**0.02−0.04**	**0.04−0.07**	**≥0.07**
Model without 6MWD/∆6MWD: Predicted Mortality Risk	**<0.02**	234	47	3	0
	0.02−0.04	103	112	32	9
	0.04−0.07	0	178	29	82
	≥0.07	0	29	35	184

C. Summary

	Percent	**p-value**
Events Reclassified Correctly	10.1%	0.088
Non-events Reclassified Correctly	16.0%	<0.001
Net Reclassification Improvement	26.1%	<0.001

6MWD=6-minute walk distance; Δ6MWD=24-week change in 6-minute walk distance

*Stratification based on quartiles of the distribution for 6MWD and Δ6MWD

Table 5. Model discrimination for selected cardiovascular risk prediction models based on the Framingham Heart Study [35-39]

Risk Prediction Model	N	C Statistic
Framingham Heart Study General Cardiovascular Risk [33]	8491	0.76–0.79
Framingham Heart Study Atrial Fibrillation Risk [32]	4764	0.78
Incident Heart Failure Risk in the Elderly [34]	2935	0.73
Framingham Stroke Risk in Patients with Atrial Fibrillation [35]	868	0.66
TIMI ST-elevation Myocardial Infarction (STEMI) Risk Score [36]	47882	0.67

Figure 1.

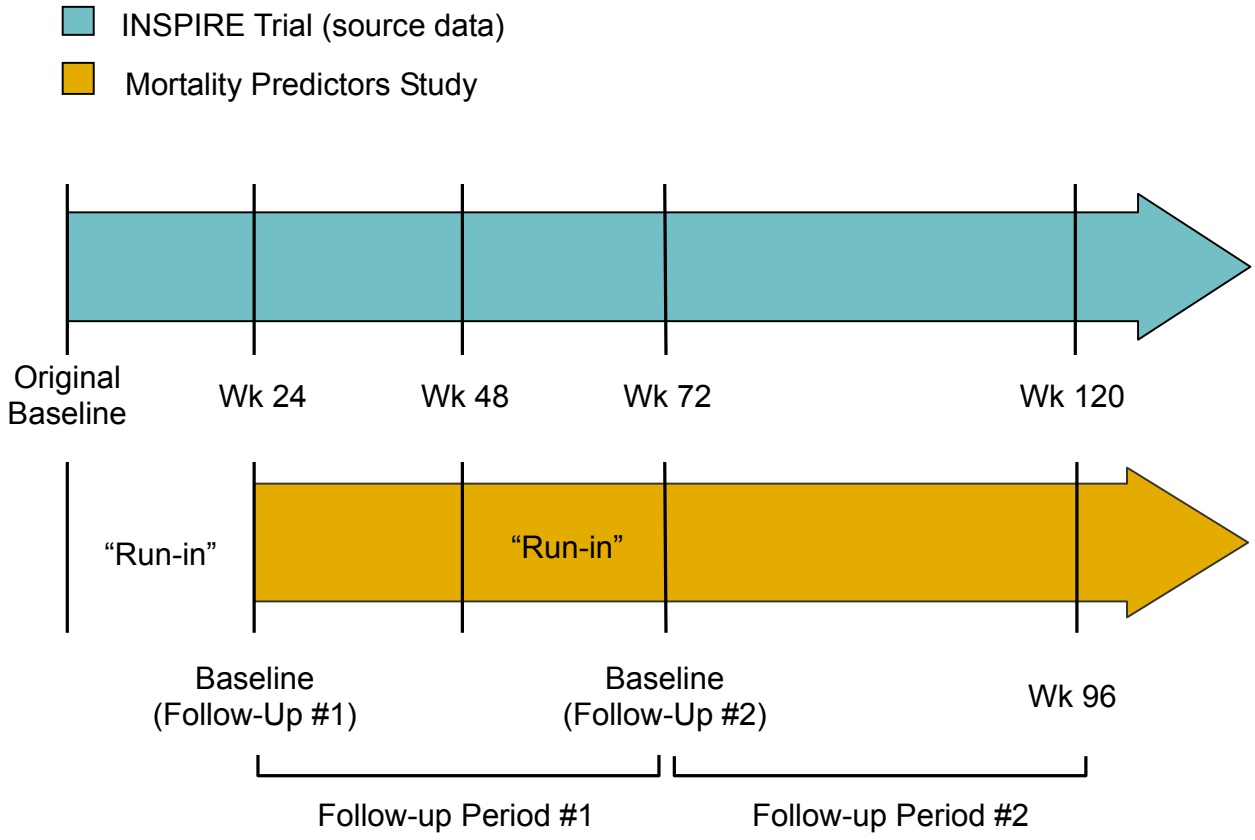
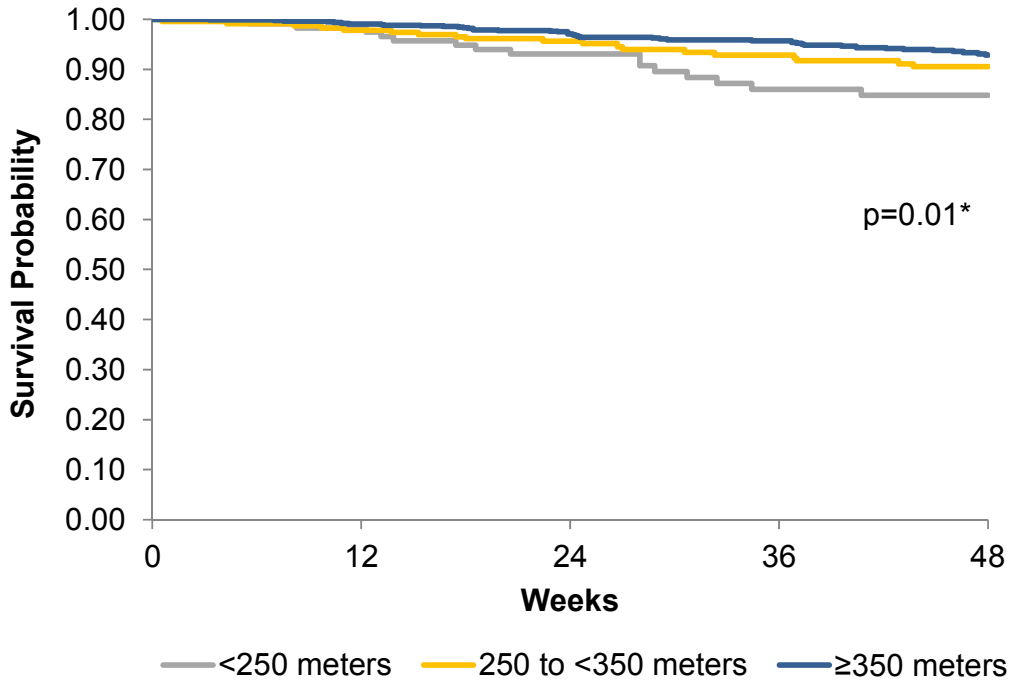
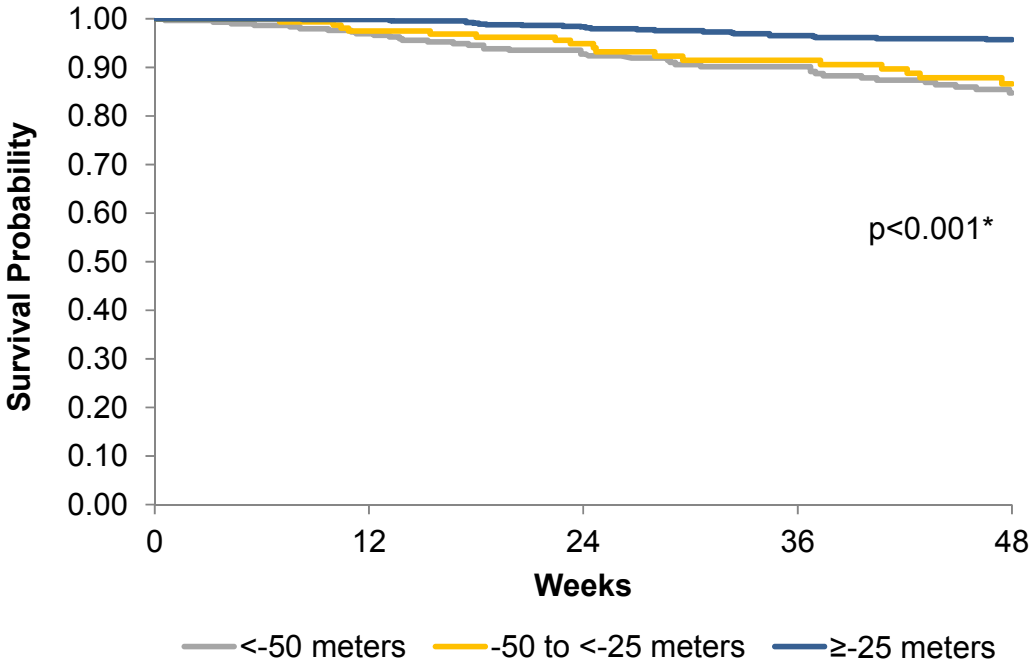

INSPIRE Trial (source data)
Mortality Predictors Study
Original Baseline
Wk 24
Wk 48
Wk 72
Wk 120
"Run-in"
"Run-in"
Baseline (Follow-Up #1)
Baseline (Follow-Up #2)
Wk 96
Follow-up Period #1
Follow-up Period #2

Figure 2.

A



B



*Log-rank test