Predicting Pulmonary Fibrosis Disease Course From Past Trends in Pulmonary Function

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Background: The clinical course of idiopathic pulmonary fibrosis (IPF) is characterized by progressive decline in lung function and eventual mortality. We sought to determine if future declines in pulmonary function, mortality, or both can be predicted from prior trends in pulmonary function tests (PFTs).

Methods: Data from 1981 to 2008 on 4,431 PFTs and mortality were analyzed from 734 subjects with IPF. The Kaplan-Meier method was used for mortality analyses. Mixed models were used to describe longitudinal pulmonary function dynamics, since PFTs were observed at varying time points from baseline.

Results: During the first year of follow-up, 135 subjects (73%) had stable FVC while 50 subjects (37%) showed a decline in FVC. During months 12 to 24 (1-2 years after diagnosis), a stable FVC occurred with the same frequency among both subjects whose FVC had declined during year 1 and whose FVC had remained stable (84.0% and 80.7%, respectively; $P = .59$). Among subjects alive at the end of year 1, those with a stable FVC were more likely to be alive at the end of year 2 than those whose FVC declined (hazard ratio [HR], 0.91 [95% CI, 0.87-0.94] and HR, 0.71 [95% CI, 0.62-0.78], respectively).

Conclusions: PFT decline predicts early mortality, but not future declines in physiology, regardless of time since diagnosis.

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Abbreviations: DLCO = diffusion capacity of the lung for carbon monoxide; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic, diffuse parenchymal lung disease. Although the median survival is often described as 2 to 3 years, the more recent IPF consensus state-

ment highlighted that the disease course of an individual patient is variable, with some patients surviving for many years, others progressing more rapidly, and still others having acute exacerbations.¹ This heterogeneity complicates the ability to provide clear prognostic information to patients and complicates the design of therapeutic clinical trials. With no cure, IPF has been the focus of multiple therapeutic studies over the last decade.²⁻¹² Unfortunately, effective treatments have been elusive. While there are many considerations as to why any given trial may not show

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significance, one is that the natural history of the disease has not been defined well enough to allow for the creation of inclusion criteria that result in an adequate number of clinical end points over the duration of the trial.

Several characteristics of patients with IPF are associated with increased mortality, including older age, male sex, increased severity of dyspnea, worse pulmonary function, decreased exercise capacity, and radiographic findings such as increased fibrosis.¹³⁻¹⁷ Six- and 12-month longitudinal declines in pulmonary function and exercise tests have also been reported to predict mortality.¹⁸⁻²³ Unfortunately, there are no clear variables that allow for the prediction of how these characteristics will change for individual patients or for populations of patients enrolled in clinical trials. To both provide better prognostic information to patients with IPF and understand implications for future clinical trials, we wanted to determine if an individual's prior trend in pulmonary function predicts future trends, 1-year mortality, and progression-free survival.

MATERIALS AND METHODS

We identified pulmonary function tests (PFTs) for patients with IPF through interstitial lung disease databases from the Royal Brompton and Harefield National Health Service Foundation Trust, National Jewish Health, and the University of Michigan Health System from 1981 through 2008. Patients were diagnosed with IPF either through surgical lung biopsy or characteristic chest CT scan.^{1,24} For each patient, sex, age, and every PFT they had performed at their home center were captured for analysis. Percent predicted values of FVC and diffusion capacity of the lung for carbon monoxide (DLCO) were analyzed. Mortality data were confirmed through the Social Security Death Registry Index or the UK National Health Service censured by 3 months to account for reporting lag. The study was approved by the University of Michigan institutional review board (study HUM00018279), the ethics committee at the Royal Brompton (study 01-246), and the National Jewish institutional review board (Study HS-1603).

The PFTs were grouped into baseline and follow-up categories of first year, second year, third year, and fourth year. To be included in an interval, the PFT had to be dated within 3 months prior to or 3 months after the interval. Patient-specific regression lines were generated from baseline to 1 year, 1 year to 2 years, 2 years to 3 years, and 3 years to 4 years. All PFTs within a given interval were included to build the regression lines. A patient had to be alive with data at the start and finish of an interval to be included in it. Predicted PFT values were then obtained from the regressions to standardize across patients at exactly 1, 2, 3, or 4 years. Mean change was defined as (% predicted PFT at end of interval – % predicted PFT at start of interval)/(% predicted PFT at start of interval). The actual PFT value was used for the start of each interval, while the 12-month value was estimated from an individual regression line for each patient. The Kaplan-Meier method was used to analyze if a prior year's mean change in PFT predicted mortality in the next year. Mixed models were used to describe longitudinal pulmonary function dynamics, since PFTs were observed at varying time points from baseline. All statistics were performed with SAS, version 9.2 (SAS Institute Inc).

RESULTS

Patient Population

A total of 4,431 PFTs were analyzed from 734 patients (characteristics are in Table 1). Fewer patients had baseline DLCO measurement performed than FVC: 657 vs 730, respectively. If a patient had subsequent DLCO measured, their data would return to the analysis for later years. An aggregate mean FVC and DLCO were recorded for each year of the analysis and were remarkably consistent between the years: within 5% predicted for FVC and 4% predicted for DLCO.

Due to losses to follow-up, we compared the baseline demographics depending on the patients' eventual outcome during year 1 (Table 2). There were 109 deaths (14.9%) within the first year of follow-up. There were more male patients in the declined/dead group (77.2%) vs the stable/lost-to-follow-up group (65.5%, $\chi^2 P = .001$), although survival at 1 year was similar for male patients and female patients (log-rank test $P = .1643$). One-year survival in male patients was 0.84 and in female patients was 0.88. In general, the baseline pulmonary function of the patients lost to follow-up approximated that of those who declined during the year and was better than those who ultimately died. The lost-to-follow-up group was older with a higher proportion of women than any of the other groups.

Predicting Future Trends in Pulmonary Function

Among the 85% of subjects who survived year 1, FVC remained stable in the majority of patients over the subsequent year, regardless of the prior year's trend in pulmonary function (Tables 3, 4). Whether the FVC was stable or declined during year 1, 80.7% and 84.0%, respectively, were stable over year 2 ($P = .60$). Three-quarters of the patients with a stable FVC between years 1 and 2 would continue to be stable between years 2 to 3. The prior year's trend in pulmonary function did not differentiate between those whose pulmonary function would decline the following year and those whose pulmonary function would remain stable.

To further clarify pulmonary function dynamics over time, Figure 1 shows the trends in pulmonary function trajectory by mixed model analysis grouped by prior year stability or decline. In Figure 1, the graph of patients with a stable FVC baseline to year 1 demonstrates a greater decline (solid line with greater downward slope) in FVC over time compared with those who had declined in year 1 (line with tick marks) ($P < .0001$). After year 1, the rate of decline (slope of curves) in FVC is similar, regardless of the stability or decline of the prior year ($P = .78$) (Fig 1).

Table 1—Patient Characteristics by Year in the Analysis

Characteristic	Baseline	Year 1	Year 2	Year 3	Year 4
FVC analysis					
No.	730	388	186	110	71
Age, y	63.1 (10.1)	62.2 (9.9)	60.9 (9.6)	60.5 (9.8)	59.6 (10.7)
Male patients, No. (%)	507 (69.5)	279 (71.9)	133 (71.5)	78 (70.9)	51 (71.8)
% predicted FVC	67.8 (17.0)	65.7 (17.7)	66.5 (17.9)	65.2 (17.8)	62.9 (15.8)
DLCO analysis					
No.	657	312	154	81	56
Age, y	62.9 (10.0)	62.0 (9.9)	61.5 (9.9)	61.0 (9.8)	60.4 (10.2)
Male patients, No. (%)	461 (70.2)	228 (73.1)	109 (70.8)	59 (72.8)	42 (75.0)
% predicted DLCO	45.6 (16.0)	42.5 (16.3)	41.7 (15.7)	41.9 (16.4)	42.7 (15.6)

Data are given as mean (SD) unless otherwise indicated. DLCO = diffusion capacity of the lung for carbon monoxide.

Survival and Prior Trends in Pulmonary Function

The trend in pulmonary function in the prior year did predict subsequent survival. Table 5 illustrates subsequent-year survival based on prior-year stability or decline in pulmonary function, by Kaplan-Meier method. If there was a 10% relative decline in FVC or 15% relative decline in DLCO the prior year, survival dropped roughly 20% in the subsequent year. A decline in FVC of 5% was not predictive of subsequent mortality (hazard ratio [HR], 1.32; 95% CI, 0.86-2.01; $P = .23$), while a decline in DLCO of 10% was significant (HR, 1.83; 95% CI, 1.20-2.79; $P = .005$). Combinations of less substantial changes in FVC (5%) and DLCO (10%) also predicted the subsequent risk of mortality (HR, 2.35; 95% CI, 1.67-3.31; $P < .001$). Given that these data span several decades during which the definitions and approach to the diagnosis of IPF changed, we evaluated if there were differences in the ability of PFT changes to predict mor-

tality by the decades of 1980 to 1990, 1990 to 2000, or after 2000. We did not see any difference in results for FVC ($P = .2809$) or DLCO ($P = .2773$).

Progression-free survival is a frequently used combined end point in IPF clinical trials, defined as survival with < 10% decline in FVC or 15% decline in DLCO during the trial follow-up period.⁷ From baseline to year 1, 48.3% of patients had either died ($n = 77$) or shown a decline in FVC ($n = 126$). During year 1 to 2, the percentage of patients meeting this outcome dropped to 31.7%. Therefore, typical clinical trial outcomes occurred with greatest frequency within the first year of follow-up, declining by a third the second year after diagnosis. The small number of patients with FVC < 50% predicted ($n = 40$) precluded rigorous analysis of this subset of patients who are often excluded from therapeutic trials in IPF. Pulmonary function in the prior year did differentiate among patients. Of patients who were stable from baseline to

Table 2—Baseline Demographics Grouped by Outcome Over the First Year

Demographics	FVC Analysis			
	PFT Stable	PFT Declined ^a	Lost to Follow-up ^b	Death
FVC analysis				
Patients, No.	246	137	238	109
Age, y	61.9 (10.3)	62.7 (9.3)	64.8 (10.3)	62.5 (9.6)
Male patients, No. (%)	167 (67.9)	108 (78.8)	150 (63.0)	82 (75.2)
% predicted FVC	70.3 (17.4)	69.2 (15.1)	68.1 (17.9)	59.8 (13.9)
% predicted DLCO	47.8 (14.9)	47.5 (14.5)	45.5 (17.3)	39.7 (15.2)
DLCO analysis				
Patients, No.	175	132	244	109
Age, y	61.6 (10.0)	62.3 (9.9)	64.5 (10.0)	62.5 (9.6)
Male patients, No. (%)	123 (70.3)	101 (76.5)	156 (63.9)	82 (75.2)
% predicted FVC	72.8 (16.9)	68.9 (15.9)	67.7 (17.7)	59.8 (13.9)
% predicted DLCO	49.0 (14.9)	46.8 (14.5)	45.1 (17.0)	39.7 (15.2)

Data are given as mean (SD) unless otherwise indicated. PFT = pulmonary function test. See Table 1 legend for expansion of other abbreviation.

^aA decline in PFT was defined as at least a 10% relative decline in FVC or a 15% relative decline in DLCO.

^bLost to follow-up defined as patients who had a baseline FVC, did not die, and did not have enough PFTs to get progression status during the first year.

Table 3—Subsequent Change in FVC Over the Next Year, Based on the Previous Year's Change

PFT in Prior Year	PFT in Next Year			P Value
	No.	FVC Stable	FVC Declined ^a	
Baseline to year 1				.60
FVC stable	135	109 (80.7)	26 (19.3)	
FVC declined	50	42 (84.0)	8 (16.0)	
Year 1 to 2				.11
FVC stable	85	63 (74.1)	22 (25.9)	
FVC declined	12	6 (50.0)	6 (50.0)	
Year 2 to 3				.89
FVC stable	48	33 (68.8)	15 (31.3)	
FVC declined	12	8 (66.7)	4 (33.3)	

See Table 1 and 2 legends for expansion of abbreviations.

^aDeclined was defined as at least a 10% relative decline in FVC or 15% relative decline in DLCO.

year 1 (n = 133), 73.7% had progression-free survival the subsequent year compared with 55.4% of those who had declined the year prior (n = 56, $P = .02$) (Table 6). Progression in year 2 for patients with a stable FVC from baseline to year 1 was more likely to be defined by a decline in FVC, while patients with a decline in FVC of at least 10% from baseline to year 1 were more likely to have progression defined by mortality (Table 6).

DISCUSSION

In a large, multicenter, retrospective cohort of patients with IPF, we report (1) the change in pulmonary function in the prior year does not predict the change in pulmonary function in the subsequent year, (2) declines in the pulmonary function in the prior year predicts mortality in the following year, and (3) commonly used study end points such as mor-

tality and decline in pulmonary function occur with greatest frequency the first year after presentation.

Attempts to enrich study populations for a greater probability of decline in pulmonary function during the study led some investigators to consider inclusion criteria that required a decline in pulmonary function prior to study entry. Our data highlight that the change in pulmonary function in the prior year is a poor predictor in subsequent changes in pulmonary function. Furthermore, patients with stable lung function during the first year of follow-up seemed to have a more progressive subsequent course, although overall trends in pulmonary function after 2 years of follow-up seemed similar regardless of prior stability or decline. Thus, prior changes in pulmonary function should not be used to try to enrich study populations for subjects likely to show additional decline in pulmonary physiology.

Our data demonstrate that the frequency of death or physiologic decline was greatest during the first year of being evaluated at a tertiary referral center. Our data do not allow us to discriminate between the patients for whom this is the first year after diagnosis vs patients who may have been diagnosed prior and subsequently referred. Clear guidance is lacking on the optimal time from diagnosis to enroll patients with IPF into clinical trials. Thus, mechanisms to facilitate the rapid enrollment of these patients into clinical trials may be most useful for researchers looking to understand the pathobiology of patient deterioration as well as to study novel therapeutics aimed at disease stabilization. Further research is needed to identify biomarkers that can predict which patients are likely to remain stable over time. Tools of this nature will aid both the effective recruitment for clinical trials, as well as the appropriate triage of patients for procedures such as lung transplantation.

Short-term changes in pulmonary function have been shown to predict the subsequent risk of mortality.¹⁸⁻²² Our data confirm these findings. We also show that combinations of smaller declines in FVC and DLCO can also predict mortality with risk estimates similar to larger, individual changes in FVC or DLCO. The combination of smaller changes in heterogeneous outcomes that move in parallel may be a useful way to confirm relatively small changes that truly reflect disease progression. In future studies, the combination of these smaller changes in physiology may be useful outcome measures along with other measures of disease progression such as symptoms, function, and radiographic findings.

The best primary end point for clinical trials in IPF has been the topic of recent debate.^{25,26} Although mortality can be argued as the gold standard for clinical trials, the potential use of surrogates for mortality,

Table 4—Subsequent Change in DLCO Over the Next Year, Based on the Previous Year's Change

PFT in Prior Year	PFT in Next Year			P Value
	No.	DLCO Stable	DLCO Declined ^a	
Baseline to year 1				.76
DLCO stable	87	53 (60.9)	34 (39.1)	
DLCO declined	36	23 (63.9)	13 (36.1)	
Year 1 to 2				.74
DLCO stable	44	23 (52.3)	21 (47.7)	
DLCO declined	23	13 (56.5)	10 (43.5)	
Year 2 to 3				.94
DLCO stable	28	19 (67.9)	9 (32.1)	
DLCO declined	12	8 (66.7)	4 (33.3)	

See Table 1 and 2 legends for expansion of abbreviations.

^aDeclined was defined as at least a 10% relative decline in FVC or 15% relative decline in DLCO.

FIGURE 1. Mixed models analysis of the trend in FVC (solid lines: mean FVC, dashed lines: 95% CI) for patients with a stable FVC the year prior (solid line) vs those who declined the year prior (tick marks). * $P < .0001$ for the difference in intercept between stable and declined; $P < .0001$ for the difference in trajectory. # $P < .0001$ for the difference in intercept between stable and declined for the difference in trajectory 0.78. PFT = pulmonary function test.

such as changes in lung function, radiographic changes, or biomarkers, are attractive as the size and duration of clinical trials can be decreased. Change in pulmonary function has been used as an end point in clinical trials of novel agents for IPF, and the absence of its formal validation as a surrogate for mortality should not detract from its recognized value as a measure of disease progression. Declines in lung function correlate with increased risk of subsequent mortality, and worsening symptoms and function,^{22,27,28} with larger changes more confidently representing a true and clinically meaningful change. Unfortunately, data demonstrating that the prevention of a decline in lung function predicts improved mortality or fewer

hospitalizations/exacerbations are currently lacking. However, these data will hopefully emerge as novel, effective treatments for IPF are developed.

Our data are strengthened by the inclusion of a large number of PFTs from three tertiary referral centers in the United States and Europe. Limitations of our study include the lack of detailed information from subjects, such as treatment regimens, radiographic characteristics (ground glass, fibrosis, emphysema), duration of disease, reason for referral, the retrospective nature of data collection, and lack of prospective, complete follow-up.

CONCLUSIONS

In summary, short-term, clinically significant declines in FVC or DLCO correlate with an increased risk of mortality in the following 12 months. However, declines in these measures do not predict subsequent declines in pulmonary physiology. These data should help inform the next generation of treatment trials in IPF.

Table 5—Change in PFT the Previous Year and Subsequent 1-y Survival by Kaplan-Meier Method

PFT Status	FVC, 1-y Survival (95% CI)	DLCO, 1-y Survival (95% CI)
Baseline to year 1		
PFT stable	0.91 (0.87-0.94)	0.90 (0.84-0.93)
PFT declined ^a	0.71 (0.62-0.78)	0.72 (0.63-0.79)
P value	< .0001	< .0001
Year 1 to 2		
PFT stable	0.89 (0.82-0.93)	0.88 (0.79-0.93)
PFT declined	0.77 (0.58-0.88)	0.78 (0.64-0.87)
P value	.0528	.1161
Year 2 to 3		
PFT stable	0.96 (0.88-0.99)	0.96 (0.83-0.99)
PFT declined	0.75 (0.54-0.87)	0.75 (0.57-0.87)
P value	.0009 ^b	.0102 ^b

See Table 1 and 2 legends for expansion of abbreviations.

^aA decline in PFT was defined as at least a 10% relative decline in FVC or a 15% relative decline in DLCO.

^bP value from log-rank test comparing survival curves up to 1 y in decline vs stable.

Table 6—PFS^a in Year 2 Stratified by Change in FVC During Year 1

Year 1 Change in FVC	PFS in Year 2: No (n = 60)			PFS in Year 2: Yes (n = 129)
	Death	FVC Decline	Combined	
FVC declined 10% Patients (n = 56)	20	5	25 (44.6)	31 (55.4)
FVC stable Patients (n = 133)	18	17	35 (26.3)	98 (73.7)

Data provided as No. (%). PFS = progression-free survival.

^aPFS defined as alive with a < 10% decline in FVC ($P = .02$).

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Dr Schmidt: contributed to study conception and design; data acquisition, analysis, and interpretation; and preparation and final approval of the manuscript and served as principal author.

Ms Tayob: contributed to data analysis and revision and final approval of the manuscript.

Dr Han: contributed to data analysis and revision and final approval of the manuscript.

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