Delayed Access and Survival in Idiopathic Pulmonary Fibrosis

A Cohort Study

Daniela J. Lamas¹, Steven M. Kawut²⁻⁴, Emilia Bagiella⁵, Nisha Philip¹, Selim M. Arcasoy¹, and David J. Lederer¹

¹Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York; ²Penn Cardiovascular Institute, ³Department of Medicine, and ⁴Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and ⁵Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York

Rationale: Idiopathic pulmonary fibrosis is often initially misdiagnosed. Delays in accessing subspecialty care could lead to worse outcomes among those with idiopathic pulmonary fibrosis.

Objectives: To examine the association between delayed access to subspecialty care and survival time in idiopathic pulmonary fibrosis.

Methods: We performed a prospective cohort study of 129 adults who met American Thoracic Society criteria for idiopathic pulmonary fibrosis evaluated at a tertiary care center. Delay was defined as the time from the onset of dyspnea to the date of initial evaluation at a tertiary care center. We used competing risk survival methods to examine survival time and time to transplantation.

Measurements and Main Results: The mean age was 63 years and 76% were men. The median delay was 2.2 years (interquartile range 1.0–3.8 yr), and the median follow-up time was 1.1 years. Age and lung function at the time of evaluation did not vary by delay. A longer delay was associated with an increased risk of death independent of age, sex, forced vital capacity, third-party payer, and educational attainment (adjusted hazard ratio per doubling of delay was 1.3, 95% confidence interval 1.03 to 1.6). Longer delay was not associated with a lower likelihood of undergoing lung transplantation.

Conclusions: Delayed access to a tertiary care center is associated with a higher mortality rate in idiopathic pulmonary fibrosis independent of disease severity. Early referral to a specialty center should be considered for those with known or suspected interstitial lung disease.

Keywords: access to healthcare; healthcare disparities; idiopathic pulmonary fibrosis; interstitial lung disease; survival

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease (ILD) characterized by progressive fibrosis preferentially involving

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Delays in accessing care occur frequently among patients with idiopathic pulmonary fibrosis (IPF). The harms of delayed access to an interstitial lung disease (ILD) center have not been previously examined.

What This Study Adds to the Field

Delayed access to a tertiary care center is associated with a higher risk of death in IPF independent of disease severity. Early referral to an ILD center should be considered for those with suspected or known interstitial lung disease.

the periphery of the secondary pulmonary lobule that leads to respiratory failure and death a median of 3 years after diagnosis (1, 2). Affected individuals typically present with progressive exertional dyspnea, which is often initially misdiagnosed until physiological and imaging tests suggest the presence of an ILD. A delay in receiving an accurate diagnosis might lead to initiation of ineffective or harmful interventions (such as inhaled bronchodilators and high-dose corticosteroids) and may delay evaluation for lung transplantation, the only effective treatment for this disease (3), resulting in worse outcomes. On the other hand, prompt recognition of IPF after symptom onset and access to an ILD specialty center could minimize harm, promote early institution of standard therapies such as supplemental oxygen, and allow timely access to clinical trials and lung transplantation evaluation. It is not known whether early access to an ILD program improves outcomes in IPF.

We investigated the association between the timing of subspecialty care and the risk of death in IPF. We hypothesized that a longer time from the onset of dyspnea to the time of first evaluation at a tertiary (or quaternary) center would be associated with an increased risk of death independent of established measures of disease severity. Some of the results of this study have been previously reported in the form of an abstract (4).

METHODS

Setting, Study Design, and Study Participants

We performed a prospective cohort study of adults with IPF at the New York Presbyterian/Columbia University Medical Center (New York, NY) Lung Transplant and Interstitial Lung Disease Programs between February 2007 and June 2010. During the study period, 505 adults seen by a pulmonologist at our center with suspected or known ILD were referred for enrollment in our study (Figure 1). Of these, 418 consented. We excluded those with an ILD other than IPF, such as those with evidence of connective tissue disease, a history of occupational or

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Correspondence and requests for reprints should be addressed to David J. Lederer, M.D., M.S., Division of Pulmonary, Allergy, and Critical Care Medicine, College of Physicians and Surgeons, Columbia University, 622 W 168th Street, PH-14, Room 104, New York, NY 10032. E-mail: davidlederer@columbia.edu

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Figure 1. Study flow. ILD = interstitial lung disease.

environmental exposures known to cause pneumoconioses, and those with suspected drug-induced lung disease. There were 151 participants who met American Thoracic Society/European Respiratory Society criteria for idiopathic pulmonary fibrosis, including 44 confirmed by biopsy and 85 diagnosed on the basis of clinical–radiological criteria alone (5). We excluded 15 who did not complete questionnaires and 7 who did not have spirometry performed at the time of their initial evaluation, leaving 129 study participants included in the analysis. The Columbia University Medical Center Institutional Review Board approved the study. All participants gave written informed consent.

Data and Measurements

Demographic and clinical data were collected by trained research staff using preformatted case report forms. We reconstructed a timeline of dyspnea onset and evaluations at ILD and transplant centers before study enrollment, using a structured questionnaire and review of the medical record. We assessed the time of dyspnea onset by asking “When was the first time you experienced shortness of breath?” Because the onset of dyspnea in IPF is typically insidious, we defined the onset of symptoms as the midpoint of the most accurately recalled time interval during which symptoms began. We defined the initial visit at a tertiary care center as the date of the first visit to a pulmonologist practicing at an academic medical center. Body height and weight were measured with clinical stadiometers and scales at the time of evaluation at our center. Smoking status was ascertained by asking the following question: “Have you smoked at least 100 cigarettes in your lifetime?” Race and ethnicity were self-assigned, using categories established by the Office of Management and Budget (6). Health insurance coverage was determined by asking the following questions adapted from the 2006 National Health Interview Survey (7): “Are you covered by any kind of health insurance or some other kind of health care plan?” and “What kind of health insurance or health care coverage do you have?” with 11 possible responses: private health insurance, Medicare, Medicaid, SCHIP (State Children’s Health Insurance Program), military health care, Indian Health Service, state-sponsored health plan, other government program, single service plan, and no coverage of any type. The start date of each plan was recorded. Educational attainment was ascertained by asking “What is the highest degree or level of schooling you have completed?” and recording one of nine responses: no schooling, grades 1–8, grades 9–11, completed high school (12th grade) or GED, some college but no degree, technical school certificate, associate degree, bachelor’s degree, graduate or professional school. Spanish language questionnaires were used for Spanish-speaking study participants. Pulmonary function testing was performed at the time of the initial visit at a tertiary care center. Published reference values

were used to report pulmonary function test results (8, 9). Dates of death and transplantation were determined on the basis of the Social Security Death Index, the New York Presbyterian Hospital electronic medical record, and telephone contact with study participants and their families. All participants were monitored until January 2011.

Statistical Analysis

The measure of exposure was the time from the onset of dyspnea to the initial visit at a tertiary care center (“delay”). Delay was log₂-transformed in continuous analyses and divided into quartiles for categorical analyses. We used Spearman correlation coefficients to examine associations between delay and continuous measures. We used Kruskal-Wallis tests and Wilcoxon rank-sum tests to compare delay between groups. We examined associations between delay and the rates of death and transplantation, using cause-specific semipropportional hazards competing risk models with left truncation from the time of the initial visit at a tertiary care center until study enrollment (10, 11). We included purposefully selected covariates to account for lead time (age and forced vital capacity expressed as a percentage of the predicted value [FVC%] at the time of evaluation at a tertiary care center) and to examine the role of barriers to accessing care (third-party payer and educational attainment). We also adjusted for sex, because delay varied somewhat by sex, and male sex is a known risk factor for a greater risk of death in IPF (2). We also explored whether comorbidities, functional status, prednisone use, oxygen use, and site of initial evaluation explained our findings in *post hoc* analyses. We performed two sensitivity analyses. First, we examined survival beginning at study enrollment (instead of the initial visit at a tertiary care center) to examine the impact of immortal time bias on our findings (12). Second, we included survival time after lung transplantation in our analyses and adjusted for lung transplantation status by including one time-varying covariate for the first posttransplantation year and another for time after the first posttransplantation year (13, 14). The proportional hazards assumption was examined by inspection of Schoenfeld residual plots (15) for models without time-varying covariates and by testing for interactions with time for models with time-varying covariates. The proportional hazards assumption was met in all cases. All models were complete case analyses. Statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC) and the “mstate” package in R version 2.8.1 (R Foundation, Vienna, Austria). *P* values less than 0.05 were considered statistically significant.

RESULTS

The mean (SD) age of study participants was 63 (8) years, 76% were men, and 84% were self-identified as non-Hispanic white, 7% as Hispanic, and 5% as non-Hispanic black. At the time of evaluation at a tertiary care center, the mean FVC% was $53 \pm 21\%$ and the mean diffusing capacity for carbon monoxide expressed as a percentage of the predicted value (DL_{CO}%) was $39 \pm 13\%$.

The median delay was 2.2 years (interquartile range, 1.0–3.8 yr). Correlations of delay with age, FVC%, and DL_{CO}% were small and not significant ($r < 0.07$ and $P \geq 0.50$ for each). Age, race, FVC%, and DL_{CO}% did not vary across quartiles of delay (Table 1). Men tended to have a longer delay than women (median delay of 2.5 yr for men and 1.5 yr for women; $P = 0.11$). Participants with coronary artery disease, diabetes mellitus, and gastroesophageal reflux disease tended to have longer delays than others (median delay of 2.5 yr for those with coronary artery disease and 2.1 yr for others, $P = 0.25$; median delay of 3.5 yr for those with diabetes and 2.1 yr for others, $P = 0.049$; median delay of 2.8 yr for those with gastroesophageal reflux disease and 1.8 yr for others, $P = 0.01$). Those using prednisone tended to have somewhat shorter delays (median delay of 1.8 yr for prednisone users and 2.4 yr for others; $P = 0.14$). Medicaid beneficiaries ($n = 9$) tended to have longer delays than others (median delay of 3.2 yr for Medicaid beneficiaries vs. 2.1 yr for others; $P = 0.30$). The median delay for non-Hispanic white

TABLE 1. PARTICIPANT CHARACTERISTICS

	No.	Quartile of Delay			
		<1 yr	1–2 yr	2–4 yr	4 yr
No.		33	32	33	31
Age, yr	129	64 (6)	62 (10)	62 (8)	65 (6)
Male	129	69%	66%	91%	77%
Race/ethnicity					
Non-Hispanic white		88%	78%	81%	90%
Non-Hispanic black		3%	3%	9%	3%
Hispanic (any race)		6%	9%	9%	3%
Other		3%	9%	0%	3%
Body mass index, kg/m ²	129	30 (6)	27 (4)	28 (6)	28 (4)
Former or current smoker*	128	48%	66%	73%	63%
Cigarette pack-years*	128	18 (13–41)	18 (5–38)	17 (6–24)	24 (14–47)
FVC, % predicted	129	54 (21)	50 (21)	54 (18)	54 (23)
DL _{CO} , % predicted	123	41 (9)	38 (14)	41 (17)	38 (11)
NYHA class	129				
I–II		64%	47%	52%	45%
III–IV		36%	53%	48%	55%
Months from evaluation to enrollment†	129	4 (0–16)	7 (0–21)	2 (0–10)	1 (0–9)
Site of initial tertiary care	129				
Columbia		91%	88%	82%	84%
Other		9%	12%	18%	16%
Timing of oxygen initiation	129				
Before tertiary care		55%	56%	61%	68%
After tertiary care		33%	31%	30%	29%
Not initiated		12%	13%	9%	3%
Therapies	129				
Prednisone		42%	38%	24%	33%
Azathioprine		9%	13%	6%	3%
N-Acetylcysteine		30%	38%	30%	29%
Other‡		3%	3%	3%	6%
Comorbidities	129				
Coronary artery disease		15%	19%	18%	26%
Diabetes mellitus		18%	13%	12%	39%
History of malignancy		15%	19%	15%	10%
Gastroesophageal reflux		21%	28%	27%	65%
Health insurance	129				
Private		76%	75%	61%	58%
Medicaid		6%	3%	9%	10%
Medicare		45%	56%	45%	61%
Educational attainment	129				
Less than high school		6%	13%	12%	6%
Completed high school		39%	41%	39%	36%
Associate's degree		9%	9%	12%	13%
Bachelor's degree or higher		45%	38%	36%	45%

Definition of abbreviations: DL_{CO} = diffusing capacity for carbon monoxide; NYHA = New York Heart Association.

Data represent means (standard deviation), medians (interquartile range), and percentages.

All participants had health insurance.

*One participant with a delay over 4 years was a current smoker. Pack-year data are shown for former/current smokers only (n = 80).

†The time from evaluation at a tertiary care center to enrollment in the study was the entry time into the cohort in time-to-event analyses.

‡Other medications: pirfenidone (n = 3), cyclophosphamide (n = 1), IFN-γ (n = 1).

subjects was 2.2 years compared with 2.7 years for non-Hispanic black subjects and 2.1 years for Hispanic subjects ($P = 0.79$).

The median follow-up time was 1.1 years, and there were 168 person-years of follow-up time in total. No subjects were lost to follow-up. Forty (31%) underwent lung transplantation, 35 (27%) died without undergoing lung transplantation, and 4 (3%) died after lung transplantation. A longer delay was associated with an increased risk of death independent of age, sex, FVC%, third-party payer, and educational attainment (adjusted hazard ratio per doubling of delay was 1.3; 95% confidence interval, 1.03 to 1.6; Table 2). Those in the fourth quartile of delay had a 3.4-fold higher multivariable-adjusted mortality rate compared with those in the first quartile (Table 2). Figure 2 shows predicted survival curves adjusted for age and lung function. Delay did not appear to have an impact on the likelihood of undergoing lung

transplantation (Table 2). Additional adjustment for comorbidities, cigarette pack-years, prednisone use, body mass index, functional class, site of initial visit, or timing of oxygen initiation did not meaningfully change the effect estimates (see Table E1 in the online supplement). Neither varying the method of accounting for immortal time bias nor adjusting for transplantation as a time-dependent covariate changed our findings (Figure 3 and Tables E2 and E3). There was no evidence that the association between delay and survival varied by age, sex, race, third-party payer, or lung function (P for interaction > 0.20 for each).

DISCUSSION

The results of this single-center prospective study demonstrate that a longer delay from the onset of dyspnea until evaluation

TABLE 2. ASSOCIATIONS OF DELAY WITH SURVIVAL AND LUNG TRANSPLANTATION IN IDIOPATHIC PULMONARY FIBROSIS

	Quartile of Delay				<i>P</i> Value for Trend	Hazard Ratio (95% CI) per Log ₂ (time)*	<i>P</i> Value
	<1 yr	1–2 yr	2–4 yr	>4 yr			
No.	33	32	33	31			
Person-years†	48.1	38.7	41.0	40.7			
Survival							
Mortality rate‡	8.3	18.1	26.8	31.9			
Unadjusted hazard ratio	Ref.	1.9	2.6	3.3	0.04	1.3 (1.02–1.6)	0.03
Model 1 hazard ratio§	Ref.	2.0	2.8	3.6	0.03	1.3 (1.03–1.6)	0.03
Model 2 hazard ratio	Ref.	2.0	2.5	3.4	0.04	1.3 (1.03–1.6)	0.03
Transplantation							
Transplantation rate‡	18.7	31.0	24.4	22.1			
Unadjusted hazard ratio	Ref.	1.5	1.0	0.8	0.31	NA	
Model 1 hazard ratio§	Ref.	1.5	0.9	0.8	0.33	NA	
Model 2 hazard ratio	Ref.	1.6	1.1	1.0	0.68	NA	

Definition of abbreviations: CI = confidence interval; NA = not applicable (nonlinear association); Ref. = reference.

*Represents the hazard ratio for each doubling of delay.

†Censored at transplantation.

‡Per 100 person-years.

§Model 1 = adjusted for age, sex, and FVC % predicted.

||Model 2 = adjusted for age, sex, FVC % predicted, private insurance, and college education.

at a tertiary care center is associated with a higher rate of death from IPF independent of disease severity. This finding did not appear to be explained by differences in the rate of lung transplantation, third-party payer, socioeconomic status, comorbidities, or functional status. In addition, delay was not associated with the rate of lung transplantation. These findings are noteworthy in that they persisted even after accounting for measures of lead time and the effect of transplantation.

This is the first study to examine the effect of delays in accessing subspecialty care in ILD. King and colleagues reported a median delay of 2 years from the onset of symptoms in IPF until initial evaluation at their center (2), a finding similar to ours. We previously reported higher mortality rates among non-Hispanic black and Hispanic adults with IPF (16) and ILD (17) compared with non-Hispanic white subjects, a finding that might be rooted in racial and ethnic variation in accessing care.

In the current study, however, we found that non-Hispanic white subjects tended to have similar delays compared with non-Hispanic black and Hispanic subjects, suggesting that delayed access might not explain these differences, at least among those with IPF. The impact of other barriers to accessing care, including social, economic, provider-level, and healthcare system-level factors, should be explored in this patient population with an eye toward improving access for all patients with ILD.

It is not immediately clear why those with longer delays in accessing subspecialty care have higher mortality rates. Differences in disease severity, the rate of lung transplantation, type of health insurance, socioeconomic status, prednisone use, oxygen use, comorbidities, and New York Heart Association functional class did not appear to explain this finding. However, we did find that those with coronary artery disease, diabetes, and gastroesophageal disease tended to have longer (albeit generally nonsignificant) delays in accessing care than those without these comorbidities. Although these comorbidities did not explain our findings, it is possible that dyspnea and cough were falsely attributed to these underlying conditions in some cases, thereby delaying referral for care. Alternatively, it may be that those who are referred later are less healthy in ways that are not readily apparent. For example, differences in physical fitness, frailty, and body composition (such as adiposity or sarcopenia) might be important explanatory factors that should be explored in future studies. It is also possible that misclassification of disease severity or functional status may have limited our ability to identify the factors responsible for our findings. Right heart catheterization was not routinely performed in our study, making it difficult to determine whether pulmonary vascular disease (i.e., pulmonary hypertension) contributed to the differences in survival time; however, the similar DLCO across categories of delay suggests that pulmonary vascular disease may not have been an important factor.

Our results suggest that the recognition (or suspicion) of IPF should prompt early referral to a specialty center. However, the symptoms of early IPF are often subtle, and an accurate diagnosis of even established IPF may not be feasible for community-based physicians (18, 19). Early access would be facilitated by improved methods of early detection. At present, ILD screening efforts are limited to those with known risk factors for ILD or those with a history of familial IPF. Innovative studies of circulating biomarkers and quantitative imaging methods may hold the key to more accurately identifying early disease (20, 21).

Figure 2. Survival from the time of evaluation at a tertiary care center adjusted for age and FVC across quartiles of delay. Entry time into the cohort began at study enrollment.

Figure 3. Survival from the time of study enrollment by quartile of delay.

There were several limitations to our study. First, lead-time bias may have contributed to our findings if the higher observed mortality rate observed among those with longer delays was simply due to enrollment in the cohort at a later stage of the disease. However, disease severity (and age) were similar across quartiles of delay and our findings did not change substantially when we accounted for lead time by adjusting for age and FVC, the most widely accepted measure of disease severity in IPF (2, 22–24). Second, we started study follow-up at the time of evaluation at a tertiary care center even if it occurred before enrollment in our study. In order for these study participants to enroll in our study, they therefore must have survived from the time of evaluation until enrollment. We accounted for this “immortal time” in three ways: by left-truncating survival time, by performing a sensitivity analysis in which we started all observation times at the time of study enrollment, and by adjusting for site of initial visit. Because our findings are similar in each analysis, bias due to inclusion of immortal time seems unlikely. Third, this was an observational study; therefore, our findings cannot be considered causal. Residual and unmeasured confounders may be responsible for our findings. Fourth, we relied on recall of the timing of the onset of symptoms to ascertain delay, which may have misclassified exposure in some cases, particularly if the timing of symptom onset varied by baseline activity level. Our effect estimates, however, would be falsely inflated only if the inaccuracy of recall varied by the risk of death, a situation that appears unlikely. Fifth, by design, we enrolled only those referred to a tertiary care center. The outcome of those never referred was not examined, and might be better than those referred. Last, the results of this single center study could have been influenced by selection bias, and should be applied only cautiously to other centers.

In summary, we have shown an association between a longer delay in accessing a tertiary care center and a higher risk of death in IPF. Our findings should prompt primary care providers and pulmonologists to consider a diagnosis of ILD for unexplained dyspnea and to involve centers with expertise in diagnosing and managing ILD early in the course of disease.

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