Patient Characteristics and Survival for Progressive Pulmonary Fibrosis Using Different Definitions

To the Editor:

Background

Patients with fibrotic interstitial lung disease (ILD) exhibit heterogeneous disease courses, with idiopathic pulmonary fibrosis (IPF) being the prototypic subtype with a mean survival of 4 years (1). A large proportion of patients with non-IPF fibrotic ILD have similar courses and nearly identical therapeutic responses to antifibrotic therapy compared with patients with IPF (2–5). These patients are now labeled as having progressive pulmonary fibrosis (PPF) (6); however, its optimal definition remains uncertain. Different thresholds and combinations of symptom, physiological, and radiological criteria with varying observation durations have been used to define PPF in clinical trials (3–5) and a recent clinical practice guideline (6). In this multicenter cohort study, we examined the characteristics of patients with PPF according to recent guideline and clinical trials and compared their survival with that of patients with IPF, hypothesizing that patient characteristics and survival would vary across definitions of PPF. Some of the results of this study have been previously reported in the form of an abstract (7).

Methods

This study included consecutive patients aged ⩾18 years old with non-IPF fibrotic ILD, with serial clinical, lung function, and radiological assessments after diagnosis from the prospective Austin Health ILD Registry (Melbourne, Australia) and the multicenter Canadian Registry for Pulmonary Fibrosis (CARE-PF) (2, 8) between 2015 and 2020. Demographics, ILD subtype per multidisciplinary discussion, use of ILD-targeted therapy, and survival or lung transplantation status were collected. Consecutive patients with IPF were included for survival comparison. For both cohorts, only patients who survived and had follow-up ⩾2 years were included to ensure comparability and to address immortal time bias, given varying lead times of 6 months to 2 years to define PPF. Ethics approval was obtained from the Austin Health Human Research Ethics Committee (LNR/19/Austin/45) and the University of British Columbia Research Ethics Board (H19–01368).

Four non-independent cohorts of non-IPF PPF were determined with anchoring to the date of ILD diagnosis, on the basis of the following: *1*) guideline (6)—a combination of two or more of the following criteria over 1 year: worsening respiratory symptoms, physiological progression (absolute decline in forced vital capacity [FVC] ⩾5% predicted and/or diffusing capacity for carbon monoxide ⩾10% predicted), or radiological progression; *2*) the INBUILD trial (3)—relative FVC decline ⩾10% predicted or a combination of two or more of the following criteria over 2 years despite standard therapy: relative FVC decline ⩾5% to <10% predicted, worsening symptoms, or imaging progression; *3*) the unclassifiable ILD (uILD) trial (4)—absolute FVC decline >5% predicted or significant symptom progression within 6 months; and *4*) the RELIEF trial (5): annual FVC decline ⩾5% predicted on the basis of three or more measurements within 6–24 months despite standard therapy. Patients were included if data for all definitions were available, with an additional 3 months of observation allowed to account for variation in clinical follow-up intervals. The degree of lung fibrosis on computed tomography was not evaluated, reflecting the absence of this criterion from the guideline definition and for reimbursement purposes in most regions. Descriptive analyses were presented as means ± standard deviation, median (and interquartile range), or frequency (and percentage). Landmark analysis was used to address immortal time bias, with time zero being 2 years after diagnosis. Transplantfree survival of patients with PPF was evaluated using the Kaplan-Meier method and compared with the IPF cohort using the log-rank test. Cox proportional hazards models were used to examine the association between PPF with mortality and lung transplantation in patients with non-IPF fibrotic ILD, adjusting for age, sex, baseline lung function, ILD subtype (connective tissue disease–associated ILD, fibrotic hypersensitivity pneumonitis, unclassifiable ILD, other), and study site.

Results

A total of 753 patients with non-IPF fibrotic ILD were included, with a comparator IPF cohort of 712 patients (Table 1). At least one of the four definitions of PPF was met in 403 (54%) patients, with 68 (17%) patients meeting all four definitions (Figure 1). A large proportion of patients (54/276, 20%) who met the INBUILD trial definition for PPF did so on the basis of achieving only ⩾10% FVC decline. The PPF cohorts had comparable demographics and baseline lung function. Connective tissue disease–associated ILD was the most common ILD subtype in the total cohort and the subgroups with PPF. The most commonly prescribed immunosuppressants were mycophenolate and prednisone. Patients excluded because of having <2 years of follow-up had worse FVC and diffusing capacity for carbon monoxide compared with included patients (Table 1). The excluded patients with PPF had a higher proportion of males and were less likely to be treated with immunosuppressants, compared with those who were included.

Transplant-free survival at 1 and 3 years for PPF cohorts were 91% and 68%, respectively, for the guideline definition; 91% and 68%, respectively, for the INBUILD trial definition, 91% and 75%, respectively, for the uILD trial definition; and 89% and 66%, respectively, for the RELIEF trial definition. Compared with IPF, only PPF, as defined according to the uILD trial, had a better transplant-free survival ($P = 0.02$), with the other three PPF definitions having similar transplant-free survival ($P > 0.05$) (Figure 1). The presence of

Supported by a grant from the National Health and Medical Research Council (ID: 2008255 to Y.H.K.). The Canadian Registry for Pulmonary Fibrosis (CARE-PF) is funded by Boehringer Ingelheim, which had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Author Contributions: Y.H.K. and C.J.R. were responsible for trial conception and development of the study protocol. Y.H.K., M.F., N.H., M.K., C.J.R., and the other listed investigators were responsible for data acquisition. Y.H.K. and C.J.R. were responsible for data analysis and interpretation. All authors critically revised the manuscript and approved the final version for publication.

This letter has a related editorial.

Originally Published in Press as DOI: 10.1164/rccm.202205-0910LE on August 9, 2022

Table 1. Patient Characteristics of Included Patients and Excluded Patients with <2 Years of Follow-up

Characteristic	Non-IPF (*n* = 753)	PPF				IPF (*n* = 712)
		Guideline (*n* = 224)	INBUILD Trial (*n* = 276)	RELIEF Trial (*n* = 173)	uILD Trial (*n* = 243)	
Included Patients						
Age at diagnosis, years, *Mdn* (IQR)	61 (51–68)	61 (53–68)	59 (49–67)	61 (51–67)	61 (52–68)	70 (64–75)
Males, *n* (%)	318 (42)	84 (38)	111 (40)	69 (40)	98 (40)	512 (72)
BMI at diagnosis, kg/m^2, *Mdn* (IQR)	28 (25–33)	29 (25–33)	29 (25–33)	29 (25–32)	29 (25–33)	29 (26–32)
Smoking history at baseline						
Ever-smokers, *n* (%)	399 (53)	128 (57)	153 (55)	98 (57)	137 (56)	536 (75)
Pack-years among smokers, *Mdn* (IQR)	16 (7–33)	16 (7–33)	15 (7–30)	16 (8–33)	16 (9–32)	26 (11–39)
Pulmonary function at diagnosis, mean ± SD						
FEV_1/FVC	80 ± 9	80 ± 8	81 ± 7	80 ± 8	79 ± 8	80 ± 8
FEV_1, % predicted	77 ± 19	76 ± 19	73 ± 18	76 ± 18	75 ± 19	83 ± 18
FVC, % predicted	76 ± 19	76 ± 20	72 ± 19	76 ± 19	76 ± 19	79 ± 18
DLCO, % predicted	61 ± 20	60 ± 20	55 ± 17	56 ± 17	58 ± 19	57 ± 18
Non-IPF ILD subtypes, *n* (%)*						
CTD-ILD	372 (49)	120 (32)	163 (44)	99 (27)	130 (35)	—
Fibrotic HP	73 (10)	29 (40)	30 (41)	19 (26)	26 (36)	—
Idiopathic NSIP	10 (1)	2 (20)	4 (40)	2 (20)	4 (40)	—
Sarcoidosis	46 (6)	11 (24)	5 (11)	2 (4)	9 (20)	—
Unclassifiable ILD	169 (22)	47 (28)	57 (34)	42 (25)	51 (30)	—
Other	83 (11)	15 (18)	17 (20)	9 (11)	23 (28)	—
Immunosuppressant use during evaluation period for PPF, *n* (%)†						
Azathioprine	—	49 (22)	103 (37)	57 (33)	39 (16)	—
Cyclophosphamide	—	28 (13)	57 (21)	27 (16)	27 (11)	—
Mycophenolate	—	90 (40)	212 (77)	120 (69)	76 (31)	—
Prednisone	—	83 (37)	170 (62)	101 (58)	72 (30)	—
Rituximab	—	13 (6)	30 (11)	16 (9)	7 (3)	—
Time to meet PPF definition, months, *Mdn* (IQR)	—	11 (7–13)	10 (6–16)	12 (8–16)	5 (3–7)	—

Characteristic	—	PPF				IPF (*n* = 309)
		Guideline (*n* = 76)	INBUILD Trial (*n* = 99)	RELIEF Trial (*n* = 68)	uILD Trial (*n* = 71)	
Excluded Patients with <2 Yr Follow-up‡						
Age at diagnosis, years, *Mdn* (IQR)	—	64 (58–72)	64 (57–72)	63 (56–70)	64 (58–72)	72 (65–77)
Males, *n* (%)	—	43 (57)	51 (51)	39 (57)	40 (56)	231 (75)
BMI at diagnosis, kg/m^2, *Mdn* (IQR)	—	29 (25–33)	28 (24–32)	29 (25–33)	29 (25–33)	28 (25–32)
Smoking history at baseline						
Ever-smokers, *n* (%)	—	48 (63)	64 (65)	43 (63)	47 (66)	224 (72)
Pack-years among smokers, *Mdn* (IQR)	—	21 (10–35)	21 (9–33)	20 (7–34)	20 (7–31)	26 (13–44)
Pulmonary function at diagnosis, mean ± SD						
FEV_1/FVC	—	81 ± 9	81 ± 9	82 ± 8	80 ± 10	81 ± 11
FEV_1, % predicted	—	67 ± 19	69 ± 19	69 ± 18	68 ± 18	80 ± 20
FVC, % predicted	—	64 ± 18	67 ± 19	66 ± 19	66 ± 19	74 ± 20
DLCO, % predicted	—	47 ± 18	49 ± 18	49 ± 17	47 ± 16	48 ± 16
Non-IPF ILD subtypes, *n* (%)‡						
CTD-ILD	—	29 (38)	42 (42)	28 (41)	27 (38)	—
Fibrotic HP	—	15 (20)	16 (16)	13 (19)	13 (18)	—
Idiopathic NSIP		1 (1)	1 (1)	1 (1)	1 (1)	—
Sarcoidosis	—	0 (0)	0 (0)	0 (0)	0 (0)	—
Unclassifiable ILD	—	23 (30)	27 (27)	19 (28)	22 (31)	—
Other	—	8 (11)	13 (13)	7 (10)	8 (11)	—
Immunosuppressant use during evaluation period for PPF, *n* (%)						
Azathioprine	—	14 (18)	15 (15)	11 (16)	10 (14)	—
Cyclophosphamide	—	4 (5)	5 (5)	5 (7)	4 (6)	—
Mycophenolate	—	46 (61)	60 (61)	43 (63)	45 (63)	—
Prednisone	—	41 (54)	49 (949)	37 (54)	39 (55)	—
Rituximab	—	4 (5)	6 (6)	5 (7)	4 (6)	—

Definition of abbreviations: BMI = body mass index; CTD-ILD = connective tissue disease–associated interstitial lung disease; DLCO = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; NSIP = nonspecific interstitial pneumonia; PPF = progressive pulmonary fibrosis.

Data are expressed as mean ± standard deviation (SD), median (and IQR), or *n* (and %).

Numbers of patients with non-IPF fibrotic ILD excluded for incomplete serial assessments: 967 for the guideline definition, 1,005 for the INBUILD trial definition, 832 for the RELIEF trial definition, and 893 for the uILD definition, with 531 being excluded for inadequate assessments for any of the four definitions.

*Presented as percentages based on the total numbers of patients with non-IPF fibrotic ILD for different PPF groups.

†Presented as percentages based on the total numbers of each PPF group.

‡Patients with <2 years of follow-up because of loss of follow-up, death, or lung transplantation.

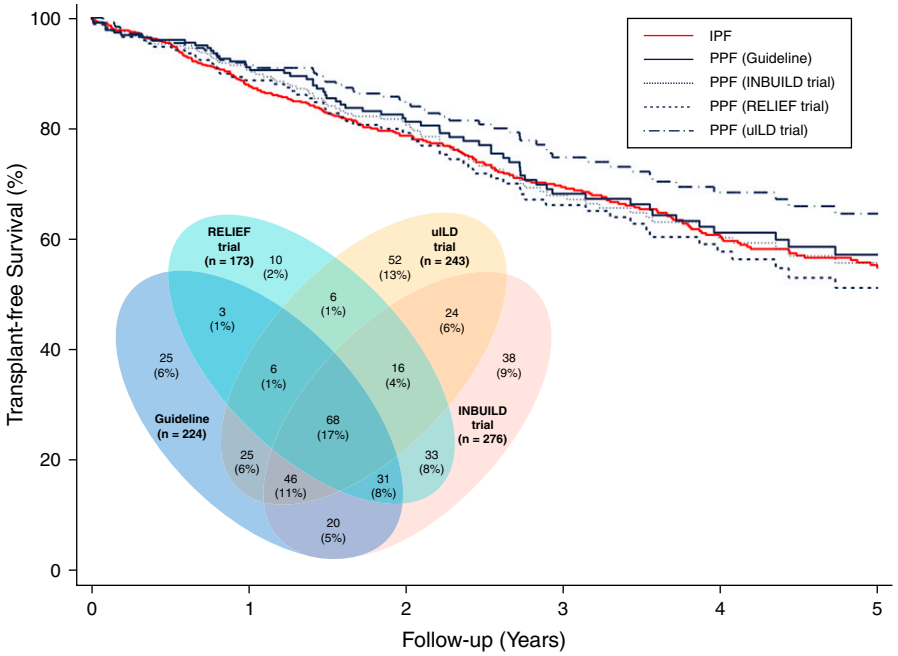

Figure 1. Overlap of PPF criteria and Kaplan-Meier survival curves of patients with PPF compared with patients with IPF. IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis. *Time zero was defined as 2 years postdiagnosis for both PPF and IPF.

PPF was independently associated with increased mortality and lung transplantation, except for those based on the uILD trial definition (hazard ratio [95% confidence interval]: for guideline, 2.08 [1.49–2.90], $P < 0.01$; for INBUILD, 2.44 [1.73–3.44], $P < 0.01$; for RELIEF, 2.27 [1.61–3.20], $P < 0.01$; for uILD, 1.35 [0.97–1.88], $P = 0.07$), with the proportional hazards assumption being examined and met using Schoenfield residuals.

Discussion

This retrospective study evaluated key definitions proposed for PPF using comprehensive real-world data in well-characterized patients with fibrotic ILD. Baseline patient characteristics and relative proportions of ILD subtypes were similar across different PPF cohorts. The proposed 1-year evaluation using a combination of symptom, physiological, and radiological criteria for PPF in the recent guideline identified patients with similarly poor prognosis compared with other PPF criteria and to the IPF cohort. However, the requirement for demonstrated progression of two or more domains, as proposed by the guideline, resulted in a lower percentage of patients with PPF, compared with other definitions that include single-domain criteria. This suggests dissociation in physiological, symptom, and radiological progression in patients with fibrotic ILD.

Only a small proportion of patients met all four definitions for PPF, demonstrating the major impact on overall case counts for apparently minor modifications to the criteria and the need for guidelines and policymakers to be cautious in how these criteria are recommended and implemented in clinical practice. Nevertheless, the presence of disease progression was a consistently poor prognostic factor across different definitions, except for the uILD trial definition with no demonstrated prognostic relevance. A 6-month evaluation based on a single criterion without the requirement of failed standard therapy in the uILD trial may include patients with different disease behavior. This highlights the implications of case definitions of PPF for patient care and future research. Our findings support the use of multi-domain assessment over a relatively short observation period. Compared with relative changes and annual rates of change for the lung function criteria, the evaluation of absolute change is more easily applied in clinical practice. Although we excluded a large number of patients with non-IPF fibrotic ILD because of incomplete serial assessments to support direct comparison across the different sets of criteria, real-world patients would be continually assessed for such criteria rather than waiting a full 2 years. Future research needs to determine thresholds for each criterion and their associations with prognosis and the minimum observation period to define PPF, taking into account the frequency of assessments in clinical practice. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Antifibrotics and Reduced Mortality in Idiopathic Pulmonary Fibrosis: Immortal Time Bias

To the Editor:

Pirfenidone and nintedanib, antifibrotic medications approved for the treatment of patients with mild to moderate idiopathic pulmonary fibrosis (IPF), have been shown to slow the decline in lung function and are recommended by international treatment guidelines (1).

Meta-analyses of randomized trials of this treatment have investigated their effects on reducing mortality in patients with IPF, with rather divergent conclusions (2–6). Indeed, whereas a meta-analysis concluded that neither pirfenidone nor nintedanib is associated with lower mortality (2), others found reduced mortality only with nintedanib but not pirfenidone (3), or vice-versa (6). Meta-analyses conducted specifically among trials for only one of the antifibrotic drugs concluded a mortality benefit (4, 5).

On the other hand, observational studies have consistently reported remarkable reductions in mortality with antifibrotic medications (7). Such remarkable effects from observational studies are often the result of time-related biases, such as immortal time bias that tends to considerably exaggerate the benefit of drugs, including those used to treat respiratory diseases (8).

Given these inconsistencies, we reviewed the observational studies examining the effect of antifibrotics on mortality in IPF, focusing on time-related biases that could explain these discrepancies.

The Observational Studies

We searched the literature using MEDLINE and Embase for all observational studies of any antifibrotic reporting on mortality in patients with IPF (until January 24, 2022) and identified 14 studies reporting relative risks of death associated with antifibrotic use (9–22). The pooled relative risk of all-cause mortality with antifibrotic use was 0.62 (95% confidence interval [CI], 0.56–0.69) compared

Author Contributions: S.S. and K.S. contributed to the conception, analysis, and writing of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202207-1301LE on August 11, 2022