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Investigation of clinical predictors of survival in idiopathic pulmonary fibrosis patients: A cohort study in Taiwan

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Abstract

Background: Two antifibrotic medications, pirfenidone and nintedanib, have been approved as treatments for idiopathic pulmonary fibrosis (IPF)—a life-threatening interstitial lung disease. However, there are insufficient current data regarding clinical predictors of survival for patients with IPF in the era of antifibrotics.

Methods: We retrospectively analyzed the medical records of patients with IPF treated between April 2017 and May 2020. Univariate and multivariate Cox proportional hazard models were used to identify independent predictors of mortality among these patients with IPF.

Results: A total of 40 patients with IPF (average age, 75.58 ± 8.34 years) were included in the study, 27 (67.5%) of whom were treated with antifibrotic drugs. In the entire cohort, 14 (35%) patients died, and the overall survival of the study population was 48.52 ± 5 months (median, not applicable [NA] [29-NA] months). The univariate and multivariate Cox proportional hazard models indicated that chest tightness, finger clubbing, acute exacerbation after medication, decreased percentage forced vital capacity (%FVC), and decreased percentage 1-second forced expiratory volume were clinical factors linked to all-cause mortality among all patients, although without statistical significance at the multivariate level. Meanwhile, only finger clubbing was a significant mortality predictor among patients who received antifibrotic medications. A mortality scoring system was built upon the aforementioned risk factors, with the exclusion of %FVC, whose individual mortality score was nearly zero.

Conclusion: Chest tightness, finger clubbing, acute exacerbation after medication, and decreased %FVC were clinical factors associated with mortality in patients with IPF, although without statistical significance. A scoring system including these factors can be used to predict all-cause mortality in patients with IPF. The mere intake of antifibrotic medications was not a significant mortality predictor in this study. This might be owed to the retrospective nature of the study, where many patients started the medications after the deterioration of their pulmonary function rather than from the start.

Keywords: Humans; Idiopathic pulmonary fibrosis; Medical records; Mortality; Risk factors

1. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a life-threatening, chronic fibrotic interstitial lung disease characterized by the progressive deterioration of lung function.[1,2] The most common cause of death from IPF is respiratory failure, accounting for a substantial majority of IPF-related fatalities, although other causes of death from IPF, including infection, heart failure, ischemic heart disease, and pulmonary embolism, have also been identified.[3] The prognosis of IPF is typically quite poor, with a lower median duration of survival among patients not treated with antifibrotic medications.[4]

Two antifibrotic medications, pirfenidone and nintedanib, have been approved as treatments for IPF in many countries over the past decade following various clinical trials successfully demonstrating their effectiveness in decreasing the loss of lung function experienced by patients with IPF.[5–8] For example, in the A Study of Cardiovascular Events in Diabetes (ASCEND) and INPULSIS trials, where patients were treated for a total duration of 52 weeks, pirfenidone and nintedanib decreased the forced vital capacity (FVC) declined in by roughly 50%.[7,8] In the Remote COVID-19 Assessment in Primary Care study, which was a follow-up for the ASCEND trial, It was reported that the median duration of survival for patients on pirfenidone was 6.4 years.[9] Another two survival studies reported that pirfenidone achieved a mean life expectancy of 8.72 (7.65-10.15) years vs 6.24 (5.38-7.18) years with best supportive care, and nintedanib achieved a mean life expectancy of 11.6 (9.6-14.1) compared to 3.7 (2.5-5.4) years in placebo-treated patients.[10,11]

Relatedly, several past studies have sought to identify clinical predictors of survival for IPF. For example, numerous studies

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have found that a loss of FVC is both indicative of disease progression and predictive of decreased survival time.[12–15] Among those studies, a 2003 study by Collard et al[13] further found that 6-month changes in oxygen saturation, total lung capacity, dyspnea score, thoracic gas volume, 1-second forced expiratory volume (FEV_1), partial pressure of arterial oxygen, diffusing capacity of carbon monoxide (DLCO), and alveolar-arterial oxygen gradient were also predictive of survival duration, with 12-month changes in oxygen saturation, total lung capacity, dyspnea score, partial pressure of arterial oxygen, and alveolar-arterial oxygen gradient likewise being predictive. A more recent study published by du Bois et al[16] in 2011 undertook a similar analysis to identify independent predictors of 1-year mortality among patients with IPF and identified age, percent predicted FVC (%FVC), percent predicted DLCO (%DLCO), respiratory hospitalization, 24-week change in FVC, 24-week change in health-related quality of life, and 24-week change in %DLCO as such predictors.

Nevertheless, while those earlier studies were certainly of considerable value, the increasingly widespread use of nintedanib and pirfenidone in the intervening years, as well as the significantly longer survival duration of patients treated with those agents vs those not treated with either antifibrotic medication, has raised questions regarding how patients' survival can be best predicted in the era of antifibrotics. Therefore, this study was conducted to provide updated data regarding the clinical predictors of mortality in patients with IPF by investigating a cohort of patients including both patients receiving antifibrotic treatments and patients not receiving such treatments.

2. METHODS

2.1. Study population

This retrospective observational study included all patients with IPF admitted at a general hospital in Taiwan between April 2017 and September 2019. The follow-up period extended to May 2020 or till the patient's death, which is closer. Patients were diagnosed and treated per the 2011 version of the ATS/ERS/JRS/ALAT guidelines[2] before September 2018, while patients seen after September 2018 were diagnosed and treated per the 2018 update to the ATS/ERS guidelines.[17] All the patients' diagnoses and treatment options were determined through multidisciplinary discussions, including a pulmonologist, a radiologist, and a rheumatologist. diagnosis through imaging met at least a definite or a probable usual interstitial pneumonia-IPF. If otherwise, a biopsy was performed.

2.2. Predictors of mortality

Potential predictors of mortality were evaluated throughout the full study period from April 2017 to May 2020 based on the deaths that occurred among the study population during that period. More specifically, the medical records of the included patients regarding the potential predictors of mortality were pooled together in a single database to determine the relationship, if any, between a given potential predictor and subsequent death, with any of the study population patients who died within the study period being flagged accordingly.

The patient and clinical characteristics regarded as possible predictors of mortality were identified beforehand based on clinical rationale and biologic plausibility. More specifically, the characteristics evaluated as possible predictors of mortality were patient age, sex, smoking status, bronchiectasis status, coronary artery disease status, chronic obstructive pulmonary disease status, diabetes mellitus status, gastroesophageal reflux disease status, hypertension status, nausea, abnormal liver function, diarrhea, itchy skin, exhaustion, headache, acute exacerbation after medication, use of antidiarrheal drugs, FVC at baseline (baseline FVC), C-reactive protein level, %FVC, and %DLCO.

2.3. Statistical analyses

The patient data were analyzed using SPSS Statistics, version 25.0, and Jamovi, version 2.2.2. Continuous data were presented as means ± SDs, and categorical data were presented as numbers (%). Categorical data that were not normally distributed were presented as medians and interquartile ranges. Student's *t* test and the Mann-Whitney U test were used for comparisons of the continuous data, while the Chi-square test was used for comparisons of the categorical data. Two-tailed p value <0.05 was considered significant.

A multivariate Cox proportional hazards model was built to identify predictors of all-cause mortality. For approaching such a model, independent variables with p values <0.1 in univariate analyses were included in the model. This model was approached for all patients with IPF and for the subgroup of patients who received antifibrotic medications.

A mortality risk scoring system was built using the methodology adopted by du Bios et al.[16] β-coefficients from the final Cox model were converted to scores by multiplying each by 10. the baseline hazard function from the Cox model was then used to convert the total risk score to a 1-year probability of death using the following formula:

$p(\text{death}) = 1 - 0.95 \times \text{experimental density}(0.1 \times \text{total risk score})$, where 0.95 is the estimated 1-year probability of survival and thus 1 – 0.95 is the estimated 1-year probability of death for people with the lowest risk (ie, those with a total risk score equal to 0).

3. RESULTS

3.1. Patient characteristics

A total of 40 patients with IPF were treated during the study period. Their average age was 75.6 ± 8.3 years, and most of the patients (77.5%) were male. Nineteen (47.5%) of the patients were smokers. Twenty-seven (67.5%) of the patients were treated with antifibrotic drugs. In the entire cohort, 14 (35%) patients died, and the overall survival of the study population was 48.52 ± 5 months (median, not applicable (NA) [29-NA] months). The mean %FVC of the patients was 67.85 ± 14.09%, the mean percentage FEV_1 (%FEV_1) was 79 ± 17.2%, and the mean %DLCO was 38.4 ± 13.8%. The most common comorbidity was hypertension, affecting 57.5% of the patients. Thirty (75%) of the patients had a left ventricular ejection fraction >55%, and 15 (37.5%) of the patients had coronary artery disease. COPD affected 9 (22.5%) patients. Twenty-seven (67.5%) of the patients were treated with antifibrotic drugs and 13 (32.5%) were not. Of those 13 patients, 4 (30.77%) patients developed GIT adverse events (nausea and diarrhea) and could not tolerate antifibrotic medication, while 9 (69.23%) patients did not receive antifibrotic medication due to financial issues. Twenty-eight (70%) patients were treated with bronchodilators. The most common side effect of medication was diarrhea (52.5%), followed by nausea (12.5%), exhaustion (7.5%), itchy skin (2.5%), and headache (2.5%). Acute exacerbation after medication occurred in 15 (37.5%) patients. Fourteen (35%) of the patients died, and their median time from diagnosis to death was 34 months (Table 1).

3.2. Predictors of mortality

Thirty-eight independent variables were initially investigated as potential predictors of all-cause mortality using univariate Cox proportional hazard model (Table 2). Of those variables, only 5 were statistically significant, namely chest tightness (HR, 5.79 [0.76-44.38]; p = 0.09), finger clubbing (HR, 6.3 [2.18-18.29];

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Table 1

Patients' baseline, clinical, pulmonary, and treatment characteristics

Characteristics	All patients with IPF (n = 40)
Age, y	75.6 ± 8.3
Sex: male	31 (77.5%)
BMI	25.2 ± 3.3
Smoking	
Nonsmoker	21 (52.5%)
Smoker	18 (45%)
Ex-smoker	1 (2.5%)
Smoking index	46.7 ± 29.4
Pulmonary function	
%FVC	67.9 ± 14.1
$\%FEV_1$	79 ± 17.2
%DLCO	38.4 ± 13.8
%DLCO/VA	62.1 ± 16.2
RVSP	34.9 ± 10.2
LVEF (>55%)	30 (75.0%)
Diagnosis	
Imaging	32 (80%)
Biopsy	8 (20%)
Using bronchodilators: yes	28 (70%)
Using antifibrotic drugs: yes	27 (67.5%)
Time from diagnosis to death, mo	34 (23-55)
Survival outcomes	
Overall survival (time from diagnosis to death, mo)	Mean, 48.52 ± 5; median, NA (29-NA)
Deaths	14 (35%)
Symptoms	
Cough	36 (90.0%)
Sputum	16 (40.0%)
Chest tightness	29 (72.5%)
Breath shortness after exertion	40 (100.0%)
Limited daily activities	25 (62.5%)
Tiredness	21 (52.5%)
Clubbing digits	8 (20.0%)
Bibasilar crackles	35 (87.5%)
Comorbidity	
CAD	15 (37.5%)
HTN	23 (57.5%)
COPD	9 (22.5%)
Bronchiectasis	6 (15.0%)
TB	1 (2.5%)
DM	9 (22.5%)
CKD	6 (15.0%)
GERD	9 (22.5%)
Others	13 (32.5%)
Dose regulation	5 (12.5%)
Side effects	
Diarrhea	21 (52.5%)
Nausea	5 (12.5%)
Itchy skin	1 (2.5%)
Headache	1 (2.5%)
Exhaustion	3 (7.5%)
Abnormal liver function	5 (12.5%)
Using antidiarrheal drugs	20 (50.0%)
Acute exacerbation after medication[a]	15 (37.5%)

%DLCO = percent predicted carbon monoxide diffusing capacity; $\%FEV_1$ = percentage 1-second forced expiratory volume; %FVC = percentage forced vital capacity; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DLCO/VA = diffusing capacity divided by the alveolar volume; DM = diabetes mellitus; GERD = Gastroesophageal reflux disease; HTN = hypertension; IPF = idiopathic pulmonary fibrosis; LVEF = left ventricular ejection fraction; NA = not available; TB = tuberculosis.

[a]Acute exacerbation after medication is defined as the need to use oral steroids, seek emergency treatment, or hospitalization due to IPF-induced respiratory tract illnesses.

$p < 0.001$), %FVC (HR, 0.95 [0.91-0.99]; $p = 0.03$), $\%FEV_1$ (HR, 0.97 [0.93-1]; $p = 0.06$), and acute attack after medication (HR, 4.54 [1.42-14.56]; $p = 0.01$). Use of antifibrotic medication was not a significant predictor for mortality ($p = 0.15$). For subgroup of patients who received antifibrotic medications, two variables were statistically significant in the univariate analysis, which were finger clubbing (HR, 5.96 [1.96-18.13]; $p = 0.002$) and %FVC (HR, 0.95 [0.90-0.99]; $p = 0.02$).

A multivariate Cox model was then constructed to predict all-cause mortality using the abovementioned five predictors (Table 3). In this model, chest tightness, finger clubbing, and occurrence of acute attack after medication were risk factors for mortality (HR for death, >1) without statistical significance ($p > 0.05$). Patients with chest tightness had a 3.56 (0.39-32.64) times risk of death when other factors were constant ($p = 0.26$). Patients with finger clubbing had 3.75 (0.69-20.45) times mortality risk than patients without clubbing ($p = 0.13$). Patients who developed acute attack after medication (defined as the need to use oral steroids, seek emergency treatment, or hospitalization due to IPF-induced respiratory tract illnesses) had 2.01 (0.5-8.14) times the mortality risk of patients who did not develop an attack ($p = 0.33$). Each 1% decrease in FVC was associated with increase in mortality risk by 4% (multivariate HR, 0.96 [0.88-1.05]; $p = 0.39$). Each 1% decrease in FEV_1 was associated with increase in mortality risk by 1% (multivariate HR, 0.99 [0.96-1.1]; $p = 0.42$).

For patients with IPF who received antifibrotic medications, patients with finger clubbing had 4.69 (1.03-21.39) times mortality risk than patients without clubbing ($p = 0.05$). Each 1% decrease in FVC was associated with an increase in mortality risk by 2% (multivariate HR, 0.98 [0.93-1.05]; $p = 0.65$).

A mortality risk scoring system was established based on the multivariate Cox predictive model. In this system (Table 4), both chest tightness and finger clubbing had a risk score of 13 points. Occurrence of acute exacerbation after medication had a risk score of 7. One percent decrease in %FVC increased the risk score by 5 points. Notably, %FEV did not affect risk score and was hence excluded from the scoring system. For a patient with all four risk factors, his total risk score would be 36. The 1-year probability of death was estimated from risk scores and compared against actual 1-year mortality rates of corresponding subgroups from the study cohort. This system overestimated the probability of death by only 0.85% for patients with chest tightness and underestimated it by only 2.06% for finger clubbing and 1.98% for acute attack after an exacerbation.

Comparing our model with that developed by du Bois et al[16] (Table 5), the latter depended on four predictors: age, history of respiratory hospitalization, basal %FVC, and 24-week change in %FVC. Our model had a higher level of statistical significance ($p = 0.009$ vs $p = 0.011$) and could account for higher percent of variations in all-cause mortality for patients with IPF (32% vs 20%).

4. DISCUSSION

Previous studies have demonstrated the effective mechanisms by which nintedanib and pirfenidone can improve the outcomes of patients with IPF.[18–22] Both drugs have been reported to successfully prolong survival and decrease the likelihood of sudden declines in lung function by slowing the speed with which IPF progresses.[10,11,23–26] Another point that should favor nintedanib and pirfenidone is the absence of "absolute contraindications" for their prescription in patients with IPF.[27]

The present study was established to revisit the clinical predictors of IPF survival, being necessitated by the growing use of such new and clinically effective antifibrotic therapies over the past decade. Several recent studies have emerged to fulfill this purpose, providing updated real-world evidence through comparison of patients treated and not treated with antifibrotic

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Table 2

Univariate Cox hazard proportional model for potential predictors of all-cause mortality among patients with IPF

	Among all patients with IPF				Among IPF received antifibrotic medications			
Variable	**HR**	**Lower CI**	**Upper CI**	***p***	**HR**	**Lower CI**	**Upper CI**	***p***
Age, y	0.97	0.91	1.03	0.34	0.97	0.90	1.04	0.37
Sex: male-female	0.92	0.26	3.33	0.90	1.56	0.34	7.07	0.56
BMI	0.92	0.77	1.10	0.36	0.93	0.79	1.10	0.42
Smoking: smoker	1.31	0.45	3.81	0.62	1.44	0.48	4.30	0.52
Smoking: ex-smoker	NA	NA	NA	NA	NA	NA	NA	NA
Bronchodilator: yes	0.69	0.21	2.22	0.53	0.73	0.22	2.39	0.61
Cough: yes	>10	0.00	Inf	1.00	>10	0.00	Inf	1.00
Phlegm: yes	2.13	0.74	6.16	0.16	2.12	0.69	6.53	0.19
Chest tightness: yes	5.79	0.76	44.38	0.09	3.92	0.51	30.26	0.19
Restricted daily activities: yes	1.23	0.41	3.73	0.71	1.34	0.41	4.36	0.63
Fatigue: yes	1.42	0.47	4.24	0.53	1.30	0.40	4.22	0.67
Clubbing fingers: yes	6.31	2.18	18.29	<0.001	5.96	1.96	18.13	0.002
Moist crackles: yes	1.25	0.16	9.62	0.83	1.01	0.13	7.81	0.99
CHF: yes	0.00	0.00	Inf	1.00	0.00	0.00	Inf	1.00
CAD: yes	0.29	0.06	1.29	0.10	0.39	0.09	1.78	0.23
HTN: yes	0.76	0.26	2.16	0.60	0.89	0.30	2.66	0.84
COPD: yes	1.23	0.33	4.54	0.76	2.53	0.66	9.74	0.18
Bronchiectasis: yes	0.92	0.25	3.34	0.90	0.92	0.25	3.37	0.90
Old TB: yes	0.00	0.00	Inf	1.00	0.00	0.00	Inf	1.00
DM: yes	0.51	0.11	2.27	0.37	0.70	0.15	3.16	0.64
CKD: yes	1.28	0.28	5.80	0.75	1.23	0.27	5.61	0.79
GERD: yes	0.92	0.26	3.32	0.90	0.68	0.15	3.08	0.62
%FVC	0.95	0.91	0.99	0.03	0.95	0.90	0.99	0.02
$\%FEV_1$	0.97	0.93	1	0.06	0.97	0.94	1.01	0.16
FEV_1 L	0.51	0.13	2.04	0.34	0.63	0.15	2.73	0.54
FEV_1/FVC L	0.32	0.0	792.57	0.78	0.32	0.00	2258.97	0.80
%DLCO	0.99	0.95	1.04	0.72	1.02	0.96	1.07	0.59
%DLCO/VA	0.99	0.95	1.02	0.41	1.00	0.96	1.03	0.86
CRP	1.23	0.90	1.68	0.19	1.14	0.83	1.57	0.43
Antifibrotic medication: yes	4.56	0.59	35.27	0.15	NA	NA	NA	NA
Diarrhea: yes	0.68	0.23	1.99	0.48	0.49	0.16	1.52	0.22
Nausea: yes	1.45	0.40	5.23	0.57	1.27	0.35	4.66	0.71
Itchy skin: yes	0.00	0.00	Inf	1.00	0.00	0.00	Inf	1.00
Headache: yes	0.00	0.00	Inf	1.00	0.00	0.00	Inf	1.00
General weakness: yes	2.86	0.60	13.58	0.19	3.31	0.68	15.98	0.14
Abnormal liver function: yes	2.00	0.55	7.21	0.29	1.53	0.42	5.61	0.52
Antidiarrheals: yes	0.94	0.33	2.73	0.91	0.82	0.27	2.53	0.73
Acute attack after medication: yes	4.54	1.42	14.56	0.01	2.57	0.79	8.38	0.12

%DLCO = percent predicted carbon monoxide diffusing capacity; $\%FEV_1$ = percentage 1-second forced expiratory volume; %FVC = percentage forced vital capacity; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; CRP = C-reactive protein; FEV = forced expiratory volume; COPD = chronic obstructive pulmonary disease; DLCO/VA=diffusing capacity divided by the alveolar volume; DM = diabetes mellitus; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; HR = hazard ratio; HTN = hypertension; Inf = inference; IPF = idiopathic pulmonary fibrosis; NA = not available; TB = tuberculosis.

medications. Our study came to fulfill the same purpose and to add to its predecessors.

While 67.5% of patients in our cohort received antifibrotic therapy, other recent studies reported a lower percentage of 60%,[28–30] suggesting different treatment considerations from our study. Such considerations include the potential side effects of antifibrotic medications such as nausea and diarrhea,[31] relative contraindications including moderate-to-severe hepatic,[11]

Table 3

Predictive Cox model for all-cause mortality among patients with IPF

	Among all patients with IPF				Among IPF received antifibrotic medications			
	Univariate analysis		**Multivariate analysis[a]**		**Univariate analysis**		**Multivariate analysis[a]**	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Chest tightness: yes	5.79 (0.76-44.38)	0.09	3.56 (0.39-32.64)	0.26	…	…	…	…
Clubbing fingers: yes	6.3 (2.18-18.29)	<0.001	3.75 (0.69-20.45)	0.13	5.96 (1.96-18.13)	0.002	4.69 (1.03-21.39)	0.05
Acute attack after medication: yes	4.54 (1.42-14.56)	0.01	2.01 (0.5-8.14)	0.33	…	…	…	…
%FVC	0.95 (0.91-0.99)	0.03	0.96 (0.88-1.05)	0.39	0.95 (0.9-0.99)	0.02	0.98 (0.93-1.05)	0.65
$\%FEV_1$	0.97 (0.93-1)	0.06	0.99 (0.96-1.1)	0.42	…	…	…	…

$\%FEV_1$ = percentage 1-second forced expiratory volume; %FVC = percentage forced vital capacity; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis.
[a]$R^2 = 0.317$; $p = 0.009$.

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Table 4

Proposed mortality risk scoring system and 1-year probability of death for patients with IPF

Variable	Mortality risk score[a]	Cumulative risk score	The 1-y probability of death	The expected cumulative 1-y probability of death, %	The observed cumulative 1-y mortality rate, %	Difference in probability
Chest tightness: yes	13	13	18.35%	18.35%	17.5%	0.85%
Clubbing fingers: yes	13	26	18.35%	36.68%	38.74%	–2.06%
%FVC	5 (for each 1% decrease)	29	3.03%	39.89%	…	…
Acute attack after medication: yes	7	36	10.1%	54.9%	56.88%	–1.98%

FEV_1 = 1-second forced expiratory volume; %FVC = percentage forced vital capacity; IPF = idiopathic pulmonary fibrosis.
[a]Mortality score for each 1% decrease in FEV_1 was nearly zero and hence omitted.

cost/reimbursement issues, uncertainty regarding the diagnosis of IPF, and/or underestimation of the patient's need to antifibrotic medication.[27,29]

Our study investigated 38 independent factors as potential predictors of all-cause mortality among patients with IPF. Baseline pulmonary function tests were among the included factors but follow-up pulmonary tests were not; as IPF is a chronic, irreversible, progressively destructive lung disease, many patients have a poorer status after preventing them from performing the follow-up test. Antifibrotic medications are mainly used to decrease the loss of lung function experienced by patients with IPF. For example, in the INPULSIS trial, nintedanib significantly reduced the decline in FVC, which is consistent with a slowing of disease progression.[25] The remaining number of patients who completed their follow-up was too statistically low to be included in the model. Among the 38 included factors, 3 clinical factors and 2 pulmonary functions were significantly correlated in the univariate analysis, namely chest tightness, finger clubbing, acute attack after medication, lower %FVC, and lower %FEV_1. However, all of those factors failed to reach statistical significance in the multivariate model. In addition, the mortality score of %FEV_1 was found to be nearly zero and hence excluded from our proposed mortality scoring system. Regarding the subgroup of patients who received antifibrotic medication, only finger clubbing and decrease in %FVC were significantly correlated at the univariate level, and only finger clubbing was a significant mortality predictor at the multivariate level. To furtherly validate our model, we compared the expected and the observed cumulative 1-year probability of death (%) for the study population, and they were very close (Table 4).

Findings in this study shared ground of agreement with those reported by du Bois et al,[16] 2011, who conducted their study on 1156 patients pooled from two clinical trials, investigating 20 independent variables, and using a very similar methodology to ours. In concordance with this study, the severity of respiratory illness was an important mortality predictor, where the history of respiratory hospitalization hurt a patient's survival chances. In addition, %FVC <80 and/or declining %FVC were also associated with a higher risk of mortality.

However, this study differed from that of du Bois in some points. First, our study investigated mortality predictors among patients with IPF treated with antifibrotic medications, while patients in the study by du Bois were treated with interferon-gamma. Second, acute attack after medications was not reported in the study by du Bois as a separate entity. Furthermore, unlike the current study, age was a significant mortality predictor in the model by du Bois. In addition, clinical predictors in our study had more impact on mortality risk score than pulmonary functions, which was not the case in the model by du Bois. Our model achieved more statistical significance than that of du Bois (p = 0.009 vs p = 0.011) and a higher predictive power (R^2 = 0.317 vs R^2 = 0.2).

Alhamad et al[31] conducted a retrospective study investigating 212 patients with IPF and provided closely similar results to ours where antifibrotic therapy, final saturation <85%, acute exacerbation, and walking distance <300 m were all predictors of IPF survival. Furthermore, Kang et al conducted a retrospective analysis on 1213 patients with IPF. They used propensity score matching to compare those who received antifibrotic medications with those who did not. Their results indicated that the risks of hospitalization, acute exacerbation, all-cause mortality, and mortality after acute exacerbation were all significantly reduced by antifibrotic treatment.[32]

The mere intake of antifibrotic medications was not a significant mortality predictor in our study. This might be owed to the retrospective nature of the study, where many patients started the medications after the deterioration of their pulmonary function rather than from the start. Hence, it should be stressed that drug treatment should be administered as early as possible following diagnosis.

Relatedly, the sample size of this study was relatively small. Therefore, further studies utilizing data from other populations of IPF patients are warranted to validate the applicability of our mortality risk model, especially as the utilization of antifibrotic medications may increase still further in the future.

In conclusion, this study came to investigate potential factors affecting all-cause mortality among patients with IPF in general and those treated with antifibrotic medications in particular. The univariate and multivariate Cox proportional hazard models indicated that chest tightness, finger clubbing, acute exacerbation after medication, decreased %FVC, and decreased %FEV_1 were

Table 5

Comparison between our model and that of du Bois

	Present model	du Bois's model
Risk scoring system	Chest tightness: 13 Finger clubbing: 13 Decrease FVC by 1%: 5 Acute exacerbation after medication: 7	Age >60 y: 4-8 H/o of respiratory hospitalization: 14 %FVC <80: 8-18 24-wk change in %predicted FVC by >–4.9: 10-21
1-y probability of death for each increase in score by 1 point	= (1 – 0.950) × EXP(risk score × 0.1)	= (1 – 0.988) × EXP(risk score × 0.1)
R^2	0.317	0.2
p	0.009	0.011

%FVC = percentage forced vital capacity; exp = experimental density; FVC = forced vital capacity; H/o = null hypothesis.

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clinical factors linked to all-cause mortality among all patients, although without statistical significance at the multivariate level. Meanwhile, only finger clubbing was a significant mortality predictor among patients who received antifibrotic medications. A mortality scoring system was built upon the aforementioned risk factors, with the exclusion of %FVC, whose individual mortality score was nearly zero. Such a system was internally validated by comparing the expected and the observed cumulative 1-year probability of death (%) for the study population and externally validated by comparing it with that developed by du Bois et al.

The two main limitations of this study were its retrospective nature and relatively small sample size. Many patients in this study started antifibrotic medications after the deterioration of pulmonary functions, which might explain the fact that the mere intake of those medications was not a significant mortality predictor in this study.

REFERENCES

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. *Am J Respir Crit Care Med* 2000;161:646–64.
2. 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.
3. Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, et al; IPF Study Group. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005;**142**(12 Pt 1):963–7.
4. Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. *Adv Ther* 2018;**35**:724–36.
5. Maher TM, Strek ME. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. *Respir Res* 2019;**20**:205.
6. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011;**365**:1079–87.
7. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–82.
8. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;**370**:2083–92.
9. Costabel U, Albera C, Lancaster LH, Lin CY, Hormel P, Hulter HN, et al. An open-label study of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (RECAP). *Respiration* 2017;**94**:408–15.
10. Fisher M, Nathan SD, Hill C, Marshall J, Dejonckheere F, Thuresson PO, et al. Predicting life expectancy for pirfenidone in idiopathic pulmonary fibrosis. *J Manag Care Spec Pharm* 2017;**23**(3-b Suppl):17–24.
11. Fisher M, Nathan SD, Hill C, Marshall J, Dejonckheere F, Thuresson PO, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. *BMJ Open Respir Res* 2019;6:e000397.
12. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med* 2011;**184**:1382–9.
13. Collard HR, King TE Jr, 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**:538–42.
14. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;**168**:543–8.
15. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003;**168**:531–7.
16. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;**184**:459–66.
17. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;**198**:e44–68.
18. Chaudhary NI, Roth GJ, Hilberg F, Müller-Quernheim J, Prasse A, Zissel G, et al. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. *Eur Respir J* 2007;**29**:976–85.
19. Coward WR, Saini G, Jenkins G. The pathogenesis of idiopathic pulmonary fibrosis. *Ther Adv Respir Dis* 2010;**4**:367–88.
20. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015;**45**:1434–45.
21. Conte E, Gili E, Fagone E, Fruciano M, Iemmolo M, Vancheri C. Effect of pirfenidone on proliferation, TGF-β-induced myofibroblast differentiation and fibrogenic activity of primary human lung fibroblasts. *Eur J Pharm Sci* 2014;**58**:13–9.
22. Inomata M, Kamio K, Azuma A, Matsuda K, Kokuho N, Miura Y, et al. Pirfenidone inhibits fibrocyte accumulation in the lungs in bleomycin-induced murine pulmonary fibrosis. *Respir Res* 2014;**15**:16.
23. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis–FDA review of pirfenidone and nintedanib. *N Engl J Med* 2015;**372**:1189–91.
24. Guenther A, Krauss E, Tello S, Wagner J, Paul B, Kuhn S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. *Respir Res* 2018;**19**:141.
25. Collard HR, Richeldi L, Kim DS, Taniguchi H, Tschoepe I, Luisetti M, et al. Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. *Eur Respir J* 2017;**49**:1601339.
26. Ley B, Swigris J, Day BM, Stauffer JL, Raimundo K, Chou W, et al. Pirfenidone reduces respiratory-related hospitalizations in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2017;**196**:756–61.
27. Graney BA, Lee JS. Impact of novel antifibrotic therapy on patient outcomes in idiopathic pulmonary fibrosis: patient selection and perspectives. *Patient Relat Outcome Meas* 2018;**9**:321–8.
28. Maher TM, Molina-Molina M, Russell AM, Bonella F, Jouneau S, Ripamonti E, et al. Unmet needs in the treatment of idiopathic pulmonary fibrosis-insights from patient chart review in five European countries. *BMC Pulm Med* 2017;**17**:124.
29. Pesonen I, Carlson L, Murgia N, Kaarteenaho R, Sköld CM, Myllärniemi M, et al. Delay and inequalities in the treatment of idiopathic pulmonary fibrosis: the case of two Nordic countries. *Multidiscip Respir Med* 2018;**13**:14.
30. Maher TM, Swigris JJ, Kreuter M, Wijsenbeek M, Cassidy N, Ireland L, et al. Identifying barriers to idiopathic pulmonary fibrosis treatment: a survey of patient and physician views. *Respiration* 2018;**96**:514–24.
31. Alhamad EH, Cal JG, Alrajhi NN, Aharbi WM, AlRikabi AC, AlBoukai AA. Clinical characteristics, comorbidities, and outcomes in patients with idiopathic pulmonary fibrosis. *Ann Thorac Med* 2020;**15**:208–14.
32. Kang J, Han M, Song JW. Antifibrotic treatment improves clinical outcomes in patients with idiopathic pulmonary fibrosis: a propensity score matching analysis. *Sci Rep* 2020;10:1–8.

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