J Korean Med Sci. 2025 Sep 1;40(34):e212
https://doi.org/10.3346/jkms.2025.40.e212
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article

Respiratory Diseases & Critical Care Medicine

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Development of a Prediction Model for Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Study of the Korea IPF Cohort Registry

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OPEN ACCESS

Received: Oct 6, 2024
Accepted: Feb 10, 2025
Published online: Jul 8, 2025

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Disclosure

The authors have no potential conflicts of interest to disclose.

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ABSTRACT

Background: Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) has the most disastrous impact on prognosis as a major cause of morbidity and mortality. However, there is no proven treatment, and the occurrence of AE is unpredictable. This study aimed to develop a prediction model for AE in patients with IPF using the nationwide Korea IPF Cohort (KICO) registry.

Methods: This is a retrospective study of Korean patients with IPF who were enrolled from June 2016 to February 2022 in the KICO registry. We developed a prediction model for AE based on risk factors found in the multivariable logistic regression model.

Results: Of 678 patients with IPF, the mean age was 69.4 years, and 82.0% were male. AE occurred in 165 patients (24.3%) during follow-up (median: 40.7 months). The median time from IPF diagnosis to AE was 11.6 (interquartile range: 3.6–23.5) months. Lower forced vital capacity (FVC), shorter six-minute walking distance (6MWD), and the use of home oxygen were independently associated with AE in the multivariable logistic analysis. In a risk-predicting model using variables of FVC, 6MWD, and the use of home oxygen, there was a significant predictive power for AE in both score (area under the curve [AUC], 0.746; 95% confidence interval [CI], 0.705–0.783; $P < 0.001$) and stage (AUC, 0.696; 95% CI, 0.654–0.736; $P < 0.001$).

Conclusion: Our results suggest that a model using FVC, 6MWD, and home oxygen use may be useful in predicting AE in patients with IPF.

Keywords: Idiopathic Pulmonary Fibrosis; Acute Exacerbation; Prognosis; Mortality

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a prototype of chronic progressive fibrosing interstitial pneumonia, characterized by variable course and poor prognoses.[1,2] Acute exacerbation (AE) has the most serious impact on prognosis in patients with IPF and is the most common cause of death in this population.[3-5] AE can occur at any stage during the disease course, with an annual incidence of 5–15%, and is associated with a high mortality rate (30–85%) in patients with IPF.[3,6-10] The etiology and pathogenesis are not well understood.[10,11] The known risk factors for AE are lower forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLco) at baseline, shorter six-minute walking distance (6MWD), infections, and presence of pulmonary hypertension.[9,12-15]

Despite considerable progress in the management of IPF, there is no proven treatment for AE of IPF.[16,17] Only corticosteroids had been weakly recommended in the international guidelines, and this recommendation was based on expert opinion without specific guidance on dose, duration, or tapering.[2,18] Therefore, prediction and prevention based on the risk factors of AE might be important, as well as alternative ways to manage AE in patients

Validation: Lee HK, Yang SH, Lee H, Kim SH, Lee EJ, Choi HS, Kang HK, Heo EY, Lee WY. Writing - original draft: Lee JH, Jang JH, Kim SY, Park MS, Chung MP, Yoo H, Jeong SH, Lee HL, Song JW. Writing - review & editing: Lee JH, Jang JH, Kim SY, Park MS, Chung MP, Yoo H, Jeong SH, Lee HL, Choi SM, Kim YW, Kim YH, Park SW, Park JS, Jegal Y, Jo YS, Yoon HY, Kim TH, Kim YH, Shin B, Lee HK, Yang SH, Lee H, Kim SH, Lee EJ, Choi HS, Kang HK, Heo EY, Lee WY, Song JW.

with IPF in clinical practice. However, previous studies on the prediction of AE in patients with IPF have limitations, such as small numbers of patients (n = 110–121) and insufficient data.[19,20] The aim of the present study was to develop a risk prediction model using data from the Korea IPF Cohort (KICO) registry.

METHODS

Study population

This is a post hoc analysis using data from the KICO registry, an ongoing observational nationwide cohort study of IPF, which has recruited patients from 34 referral hospitals in Korea since 2016. A total of 707 patients with IPF who were registered from June 2016 to February 2022 in the KICO registry were screened. Among them, 29 patients were excluded due to unavailable data of AE (n = 23) or follow-up loss (n = 6), and 678 patients were ultimately included in the analysis (**Fig. 1**). All IPF patients met the criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association.[2,21,22]

Clinical data

Clinical and survival data were obtained from the KICO web-based registry (http://IPF.crf.kr). Information was collected from each center and was recorded into a central electronic Case Report Form. FVC and DLco by spirometry or plethysmography were measured at the time of diagnosis according to the ATS/ERS recommendations.[23,24] The six-minute walk test (6MWT) was also conducted at the time of diagnosis according to the ATS/ERS guidelines.[25]

AE was defined, using the criteria suggested by Collard et al.,[26] as acute, clinically significant deterioration of dyspnea, typically less than 30 days, with new bilateral lung infiltration that is not fully explained by heart failure or fluid overload without identified extra-parenchymal cause (pneumothorax, pleural effusion, or pulmonary embolism).

Development of a prediction model for AE

Baseline variables at IPF diagnosis and follow-up data were evaluated as predictive factors for AE in patients with IPF. Binary logistic regression analysis was used to identify risk factors for AE. The prediction model was developed using a nomogram consisting of identified

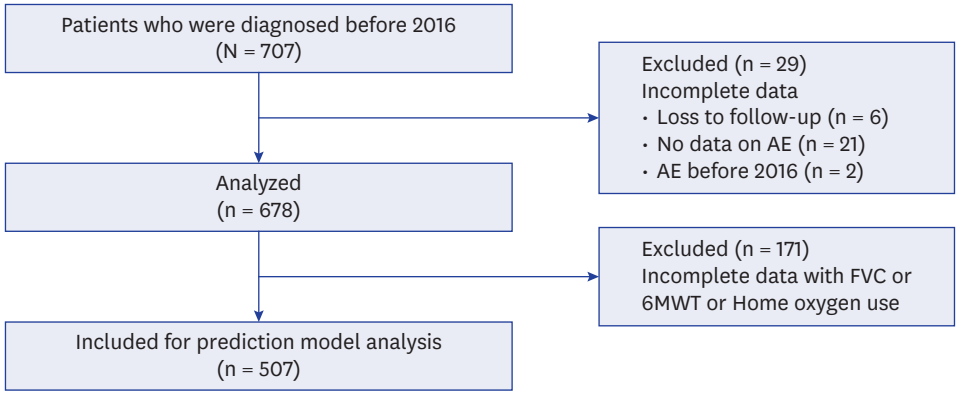


Fig. 1. Flow chart of study participants and analyzed population.
AE = acute exacerbation, FVC = forced vital capacity, 6MWT = six-minute walk test.

https://doi.org/10.3346/jkms.2025.40.e212

variables with point contributions to predicting AE in patients with IPF. Categorical ranges were established based on values commonly used in clinical practice and shown to be clinically meaningful and significant for prognosis in previous studies.[27-29] We classified the patients into three categories based on the scores. We evaluated the performance of the model for predicting AE using the receiver operating characteristic (ROC) curve analysis. We also analyzed the differences in survival according to stage to assess the usefulness of the scoring system in predicting prognosis using Kaplan-Meier survival curve analysis and the log-rank test.

Statistical analysis

Data are presented as percentages for categorical variables and mean ± standard deviation for continuous variables. Differences in study participant characteristics were compared between subgroups using the χ^2 test or Fisher's exact test for categorical variables and an independent *t*-test or Mann-Whitney *U* test for continuous variables. The Shapiro-Wilk test was used to test for normal distribution.

Overall survival probability was estimated using the Kaplan-Meier survival curve analysis. The difference between groups was assessed using the log-rank test. The time interval was calculated from the day of IPF diagnosis to death or the last follow-up. Time to AE was calculated from the day of IPF diagnosis to the event. Unadjusted and multivariable analyses, using binary logistic regression, were performed to identify predicting factors for AE. The nomogram was developed by identifying patient characteristics predicting AE in the multivariable logistic regression model. A bootstrap resampling method was used for internal validation. Bootstrap-corrected ROC curve analysis using bootstrap resampling (times = 1,000) was performed. All statistical analyses were carried out using SPSS 26.0 (IBM Corp. released 2019, IBM SPSS Statistics for Windows, Version 26.0; IBM Corp., Armonk, NY, USA), R 4.1.2 (R Core Team (2021), R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/), and MedCalc Statistical Software version 19.2.6 (2020; MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org), and *P* values less than 0.05 were considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of Haeundae Paik Hospital (approval No. 2021-07-017), and the requirement for written informed consent was waived due to the retrospective nature of the study. The preparation of the manuscript was carried out in accordance with the Strengthening the Reporting of Observational studies in Epidemiology guidelines for observational studies.

RESULTS

Baseline characteristics

Of 678 patients, the mean age was 69 years, and 82.0% were male (**Table 1**). Most of the patients (88.4%) had received antifibrotic treatment, and the mean duration of antifibrotic use was 418.2 ± 358.5 days. During follow-up (median: 40.7 months, interquartile range [IQR]: 38.9–42.4 months), 203 (29.9%) patients died, and the one- and three-year mortality rates were 7.7% and 28.6%, respectively. AE occurred in 165 patients (24.3%), and the median time from diagnosis of IPF to AE occurrence was 11.6 (IQR: 3–23.5) months. The one- and three-year cumulative incidence rates of AE were 12.7% and 26.9%, respectively.

https://doi.org/10.3346/jkms.2025.40.e212

Table 1. Comparison of baseline characteristics of the AE and no AE groups among patients with idiopathic pulmonary fibrosis

Characteristics	Overall	AE	No AE	*P* value
All patients	678	165	513	
Male	556 (82.0)	137 (83.0)	419 (81.7)	0.694
Age, yr	69.37 ± 8.23	69.40 ± 8.02	69.37 ± 8.30	0.964
BMI, kg/m^2	24.48 ± 3.16	24.39 ± 3.52	24.52 ± 3.05	0.333
Ever smoker	428 (64.4)	110 (70.1)	318 (62.6)	0.887
PaO_2, mmHg	99.00 ± 39.58	89.95 ± 23.06	103.24 ± 44.73	0.007
BNP, pg/mL	211.34 ± 513.14	251.25 ± 562.94	188.85 ± 483.46	0.079
RVSP, mmHg	29.77 ± 9.84	32.95 ± 11.71	28.06 ± 8.23	0.012
PFT				
FVC, % predicted	85.88 ± 17.51	79.75 ± 17.99	87.85 ± 16.90	< 0.001
DLco, % predicted	61.10 ± 20.57	50.05 ± 17.81	64.64 ± 20.15	< 0.001
6MWT				
Distance, m	403.95 ± 111.38	370.60 ± 116.78	414.98 ± 107.42	< 0.001
Nadir SpO_2, %	90.09 ± 6.57	87.04 ± 7.46	91.10 ± 5.92	< 0.001
GAP stage				< 0.001
Stage I	355 (53.5)	59 (36.0)	296 (59.3)	
Stage II	242 (36.5)	75 (45.7)	167 (33.5)	
Stage III	66 (10.0)	30 (18.3)	36 (7.2)	
Home oxygen use	99 (16.2)	64 (40.3)	35 (7.7)	< 0.001
Lung cancer	60 (8.9)	22 (13.5)	38 (7.5)	0.018
Antifibrotics use	536 (88.4)	141 (89.2)	395 (88.2)	0.717

Data are presented as mean ± standard deviation or number (%), unless otherwise indicated.
AE = acute exacerbation, BMI = body mass index, PaO_2 = arterial partial pressure of oxygen, BNP = brain natriuretic peptide, RVSP = right ventricular systolic pressure, PFT = pulmonary function test, FVC = forced vital capacity, DLco = diffusing capacity of lung for carbon monoxide, 6MWT = six-minute walk test, SpO_2 = percutaneous oxygen saturation, GAP = gender, age, and physiology.

Risk factors

The AE group had more frequent history of lung cancer, more severe dyspnea, lower arterial partial pressure of oxygen (PaO_2; at rest in room air), lower lung function (FVC and DLco), shorter 6MWD, higher gender-age-physiology index, higher frequency of home oxygen use, and higher right ventricular systolic pressure than the non-AE group (**Table 1**). In the multivariable logistic regression analysis, lower FVC, shorter 6MWD, and use of home oxygen were independent risk factors for AE (**Table 2**).

Development of a prediction model

Among 678 patients, 507 with complete datasets were included in model development. We developed a prediction model for AE in patients with IPF using variables of FVC, 6MWD, and use of home oxygen. The thresholds for the categorical variables of 6MWD and FVC were determined based on the results of previous studies,[29-31] and were significant for predicting AE in our study. When converted to categorical variables, 6MWD < 250 m, (odds ratio [OR], 2.091; 95% confidence interval [CI], 1.038–4.214; $P = 0.039$), FVC (% predicted) between 50 and 75 (OR, 1.828; 95% CI, 1.151–2.904; $P = 0.011$) and < 50 (OR, 3.819; 95% CI, 1.406–10.370; $P = 0.009$), and use of home oxygen (OR, 6.541; 95% CI, 3.843–11.133; $P < 0.001$) were independent risk factors for AE (**Table 3**).

We assigned points for each variable according to the coefficients of the logistic regression model and the nomogram. The nomogram can effectively predict the risk of AE using point-linear predictor unit mapping (**Supplementary Fig. 1**). The index score was calculated from the sum of the scores for each of the three variables; an index score of 0–1 point indicates stage I (low risk), a score of 2–4 points indicates stage II (intermediate risk), and a score of 5–6 points indicates stage III (high risk) (**Table 4**). Patients were divided into three groups with different stages based on an analysis of the incidence of AE (**Supplementary Fig. 2**). The scoring system

https://doi.org/10.3346/jkms.2025.40.e212

Table 2. Analysis of risk factors for acute exacerbation with logistic regression model

Variables	Univariate analysis			Multivariate analysis[a]		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Male	1.098	0.690–1.746	0.694			
Age, yr	1.000	0.979–1.022	0.964			
BMI, kg/m^2	0.987	0.934–1.044	0.659			
Ever smoker	1.146	0.742–1.773	0.539			
PaO_2, mmHg	0.987	0.978–0.997	0.009	-	-	-
PFT						
FVC, % predicted	0.967	0.955–0.978	< 0.001	0.970	0.948–0.992	0.008
DLco, % predicted	0.959	0.949–0.970	< 0.001	-	-	-
6MWT						
Distance, m	0.997	0.995–0.998	< 0.001	0.995	0.992–0.998	0.003
Nadir SpO_2, %	0.916	0.889–0.944	< 0.001	-	-	-
BNP, pg/mL	1.000	1.000–1.001	0.391			
GAP stage						
Stage I	1.000					
Stage II	2.253	1.525–3.329	< 0.001	-	-	-
Stage III	4.181	2.390–7.314	< 0.001	-	-	-
Home oxygen use	8.065	5.049–12.883	< 0.001	5.679	2.676–12.049	< 0.001
Lung cancer	1.938	1.110–3.385	0.020	-	-	-
Antifibrotics use	1.113	0.624–1.986	0.717			
RVSP, mmHg	1.053	1.014–1.094	0.008	-	-	-

OR = odds ratio, CI = confidence interval, BMI = body mass index, PaO_2 = arterial partial pressure of oxygen, PFT = pulmonary function test, FVC = forced vital capacity, DLco = diffusing capacity of lung for carbon monoxide, 6MWT = six-minute walk test, SpO_2 = percutaneous oxygen saturation, BNP = brain natriuretic peptide, GAP = gender, age, and physiology, RVSP = right ventricular systolic pressure.
[a]The effect of independent variables on response variable was analyzed using the multivariate logistic regression, and the statistically significant variables were included in the univariate logistic regression with 0.05 alpha level. The multivariate model was created using a backward elimination method, and the probability was set at 0.05 for removal.

Table 3. Analysis of risk factors for acute exacerbation with logistic regression model including home oxygen status, six-minute walking distance, and FVC

Variables	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Home oxygen						
Yes	8.065	5.049–12.883	< 0.001	6.541	3.843–11.133	< 0.001
No	1.000					
Distance, m						
≥ 250	1.000					
< 250	2.621	1.508–4.556	0.001	2.091	1.038–4.214	0.039
FVC, % predicted						
> 75	1.000					
50–75	1.796	1.230–2.623	0.002	1.828	1.151–2.904	0.011
< 50	5.824	2.888–11.744	< 0.001	3.819	1.406–10.370	0.009

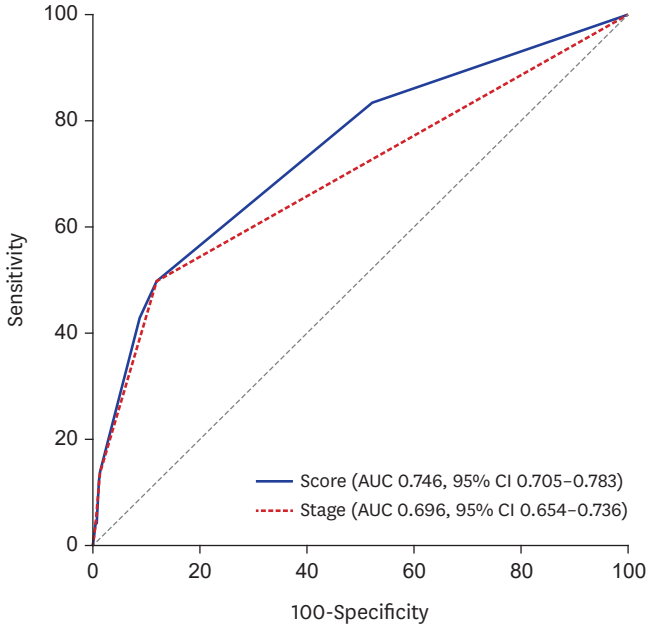
OR = odds ratio, CI = confidence interval, FVC = forced vital capacity.

showed 394 patients (77.7%) with stage I, 88 patients with stage II (17.4%), and 25 patients with stage III (4.9%) disease. We analyzed the model performance with the area under the curve (AUC) using ROC curve analysis. This model showed a statistically significant ability to predict AE in terms of both score (AUC, 0.746; 95% CI, 0.705–0.783; $P < 0.001$) and stage (AUC, 0.696; 95% CI, 0.654–0.736; $P < 0.001$) (**Fig. 2**).

Survival data

There was a significant difference in median survival time from IPF diagnosis between the AE and non-AE groups (median: 8.4 months vs. not reached, log-rank test, $P < 0.001$). The overall mortality rate after AE was 36.4%. In the multivariable Cox analysis for survival after AE, older age was the only independent risk factor for mortality (**Supplementary Table 1**). The model developed in this study was also useful for predicting survival after diagnosis.

https://doi.org/10.3346/jkms.2025.40.e212



Laboratory evaluation	Cut-point value	Group		Cut-point value	AUC (*P*)	Sensitivity, %	Specificity, %	PPV, %	NPV, %
		AE (+)	AE (–)						
Score	> 1	68	45	> 1	0.746 (< 0.001)	50.4	87.9	60.2	83.0
	≤ 1	67	327						
Stage	> 1	68	45	> 1	0.696 (< 0.001)	50.4	87.9	60.2	83.0
	≤ 1	67	327						

Fig. 2. Comparison of the model performance for predicting AE in patients with idiopathic pulmonary fibrosis with AUC using receiving operating characteristic curve analysis.
AUC = area under the curve, CI = confidence interval, AE = acute exacerbation, PPV = positive predictive value, NPV = negative predictive value.

Table 4. Distribution of patients according to the scoring system of the new prediction model

Variables	Score	No. of patients (%)
Home oxygen		
Yes	3	423 (83.4)
No	0	84 (16.6)
FVC, % predicted		
< 75	0	233 (46.0)
50–75	1	247 (48.7)
< 50	2	27 (5.3)
Distance, m		
≥ 250	0	457 (90.1)
< 250	1	50 (9.9)
Score		
0	0	200 (39.4)
1	1	194 (38.3)
2	2	23 (4.5)
3	3	29 (5.7)
4	4	36 (7.1)
5	5	18 (3.6)
6	6	7 (1.4)
Stage		
I	0–1	394 (77.7)
II	2–4	88 (17.4)
III	5–6	25 (4.9)

FVC = forced vital capacity.

https://doi.org/10.3346/jkms.2025.40.e212

In the Kaplan-Meier survival analysis, each stage showed significant differences in all-cause mortality after IPF diagnosis (**Supplementary Fig. 3**).

DISCUSSION

In this study, we developed a risk prediction model for AE in patients with IPF. Lower lung function, poor functional capacity, and use of home oxygen were independent risk factors for AE, and the scoring system using them showed good performance in predicting AE in IPF.

Lower lung function is associated with an increased risk of AE in patients with IPF.[32] In our study, only FVC was an independent risk factor for AE among variables of lung function. Previous studies supported our results.[9,33,34] Song et al.,[9] in 461 patients with IPF, showed that lower FVC was an independent risk factor (hazard ratio [HR], 0.979; 95% CI, 0.964–0.995; P = 0.011) for AE. In the previous study of 77 patients with IPF, Ohshimo et al.[34] also reported that lower FVC was significantly associated with AE (HR, 0.92; 95% CI, 0.87–0.97; P = 0.004).

In our study, lower 6MWD was significantly associated with the occurrence of AE. The 6MWT has been used widely to measure exercise tolerance and capacity and is recommended for monitoring disease severity and progression in international guidelines.[18,21,35] The 6MWD is an independent prognostic factor for mortality in patients with IPF.[36,37] In addition to indicating advanced disease, distance during the 6MWT can also provide a functional measure of overall cardiopulmonary capacity.[38,39] The 6MWD should be considered as an independent predictor of poor prognosis, including AE, as well as mortality in patients with IPF. Previous studies have supported our findings. Alhamad et al.,[40] in 667 patients with interstitial lung diseases, showed that lower 6MWD was an independent risk factor (HR, 1.615; 95% CI, 1.108–2.353; P = 0.013) for AE as well as lower FVC in the Cox proportional hazards regression analysis.

In our study, the use of home oxygen reflecting hypoxemia was an independent risk factor for AE. In 267 patients with IPF, Kondoh et al.[12] reported that baseline alveolar-arterial oxygen pressure difference was a risk factor for AE (HR, 1.062; 95% CI, 1.003–1.124; P = 0.038). In a previous study of 107 patients with IPF, the minimum peripheral oxygen saturation was a predictive factor for AE incidence (HR, 5.28; 95% CI, 1.44–19.32; P = 0.012).[41]

With regard to AE in patients with IPF, prevention after identification of risk factors and avoidance of triggering factors might be more effective than conventional treatment. Our results suggest that the risk prediction system in our study might play an important role in providing information on AE in patients with IPF, managing risk factors to reduce the incidence of AE, and achieving earlier diagnosis and treatment. Two antifibrotic agents, nintedanib and pirfenidone, have been approved and used to reduce lung function decline.[42,43] Since lower FVC was an independent factor of AE in our study, reducing FVC decline might be useful in preventing AE in patients with IPF. A recent study supports our hypothesis.[44] Petnak et al.,[44] in a systemic review and meta-analysis of the impact of antifibrotic therapy in IPF patients, reported that antifibrotic treatment was associated with reduced risks of AE (relative risk, 0.63; 95% CI, 0.53–0.76; P < 0.001) and mortality in patients with IPF. The authors suggested that, although the actual mechanism is unknown, antifibrotic treatment may reduce the FVC decline rate by down-regulating pro-inflammatory and antioxidant effects.[38,44]

https://doi.org/10.3346/jkms.2025.40.e212

This study has some limitations. First, it was retrospectively conducted exclusively on Korean participants in a multi-center cohort, and it might be difficult to generalize our findings to other races. However, baseline characteristics of IPF and clinical features of AE, including incidence and outcomes, were similar to those of previous studies.[14,45,46] Second, due to the limitations of the nature of the cohort in this study, variables related to disease progression such as decline in lung function were not included beyond baseline characteristics. Further studies are needed, including emerging biomarkers, genetic testing, and disease progression. Third, we used home oxygen use as an indicator of hypoxemia. Home oxygen use might be a less objective indicator than present hypoxemia. However, the use of home oxygen was not only a significant risk factor for AE (HR, 2.47; 95% CI, 1.37–4.47; $P = 0.002$) in 1,061 patients with IPF in the INPULSIS trial but also was an independent risk factor of mortality (HR, 1.88; 95% CI, 1.15–3.09, $P = 0.01$) after AE in previous meta-analyses including 160 patients with IPF in four studies.[33,47] Fourth, AE was not sub-classified as triggered or idiopathic as suggested in international guidelines.[26] However, in previous studies, there was no significant difference in prognosis between triggered and idiopathic AE.[41,48] Despite these limitations, this study has substantial value in proposing a new model for predicting AE using other risk factors, distinct from predicting mortality in patients with IPF.

In conclusion, our results suggest that our scoring system based on lower lung function, poor functional capacity, and use of home oxygen may have good performance in predicting the risk of AE. This model might be helpful in preventing AE, and further studies are needed for validation.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Cox proportional hazard regression analysis of risk factor for mortality in patients with acute exacerbation

Supplementary Fig. 1

Nomogram using the multivariate logistic regression model consisted of three variables; use of home oxygen, FVC, and six-minute walking distance.

Supplementary Fig. 2

Comparison of incidence of acute exacerbation in patients with idiopathic pulmonary fibrosis between scores and stages in the risk prediction model.

Supplementary Fig. 3

Comparison of survival curve after acute exacerbation between scores and groups based on the prediction model (Kaplan-Meier curves).

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