Prognostic factors for hospital mortality in patients with idiopathic pulmonary fibrosis

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Research article

Keywords: idiopathic pulmonary fibrosis, mortality, prognostic factor

Posted Date: December 9th, 2019

DOI: <https://doi.org/10.21203/rs.2.18451/v1>

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Abstract

Background: The prognostic factors for hospital mortality in patients with idiopathic pulmonary fibrosis (IPF) have not been characterised well. We aimed to determine the impact of respiratory hospitalisation on patient outcomes and the prognostic predictors for hospital mortality.

Methods: Data from patients with IPF was collected and analysed from two cohorts, Taiwan National Health Insurance Research Database (NHIRD) between 2001 and 2011 and a national medical centre (NMC) between 2001 and 2015.

Results: 122 patients in NHIRD cohort were recruited. The median survival was lower in patients with respiratory hospitalisation (25/122, 29.8%) compared with non-respiratory hospitalisation (59/122, 48.4%) in NHIRD cohort (2.3 years vs non-respiratory 9 years, $p=0.007$). In NMC cohort (N=47), patients with acute respiratory deterioration (ARD) hospitalisation (30/47, 63.8%) compared with non-ARD hospitalisation (17/47, 36.2%) had poor survival (0.9 months vs 29.6 months, $p<0.001$). The differences in survival between two cohorts were associated with age, causes of hospitalisation, mechanical ventilation and comorbidities. The patients hospitalised for ARD had statistically higher GAP score, lower oxygenation, higher C-reactive protein levels, higher neutrophil counts and lower serum albumin level compared to those non-ARD hospitalisation. For both in-hospital and 1 year mortality, multivariate analysis adjusting for patient characteristics confirmed the independent predictive factors were steroid pulse therapy, acute exacerbation and mechanical ventilation.

Conclusions: The respiratory hospitalisation negatively impacted patient outcomes, and the independent prognostic factors may be utilised to refine the management in patients with IPF.

Background

Idiopathic pulmonary fibrosis (IPF) is a progressive and life-threatening interstitial lung disease with unknown etiology[1]. The mortality burden attributable to IPF is higher than that of several cancer types[2, 3]. The median survival of patients with IPF is only 2–3 years[1, 2]. Acute respiratory deterioration (ARD) can occur at any time. Acute exacerbation of IPF (AE-IPF) is a serious condition of ARD and require hospitalisation which is associated with extremely poor outcome[4–6]. However, the presently available literature cannot provide the sufficient markers to predict outcomes after hospitalisation in patients with IPF.

Respiratory hospitalisations have been recognised as an important endpoint in IPF outcomes[7–10]. Although many individual clinical variables predict survival in IPF, the clinical characteristics of hospitalisation for ARD and the predictors of hospital mortality in patients with IPF have not been fully elucidated. The causes of respiratory hospitalisation include AE-IPF, infection and extra-parenchymal factors such as congestive heart failure, pleural effusion and pneumothorax. AE-IPF is the most common cause of death in IPF[11, 12]. The short-term mortality of AE-IPF is about 50% and typically exceeds 90% in patients admitted to an intensive care unit[13–15]. Prognostic biomarker including serum lactate

dehydrogenase [13]pro-calcitonin[16], circulating fibrocytes[17]havebeen proposed as the predictors of poor outcome in IPF.Whether these parameters can be applied topredict hospitalized patient outcomes in IPF remains unclear.

In the present study, we retrospectively analysed two IPF cohorts from Taiwan National Health Insurance Research Database (NHIRD) and a national medical centre (NMC). This study aimed to determine the impact of respiratory hospitalisation on patient outcomes and to identify the independent prognostic factors for hospital mortality in patients with IPF.

Methods

Ethics statement

We consulted with the institutional review board of Taipei Veterans General Hospital (approval number: IRB2016-06-004CC) and waived informed consent for our retrospective observational cohort study.

Part I: Taiwanese National Health Insurance Research Database

Data source

The patient data were obtained from the NHIRD which enrolls 99.8% of the entire 23 million population. The accuracy of insurance claims data in Taiwan are validated and have 92.4% accuracy for patients with ≥ 1 hospitalisation per year[18]. Data between January 1, 2001 and December 31, 2011 (study period) were analysed, and health plan enrollees aged 18–100 years old during the study period were included in the analyses.

Study sample

IPF was defined based on the 2011 American Thoracic Society/European Respiratory Society criteria[19] which included the four following conditions: (1). at least one NHI claim with IPF diagnosis (ICD-9-CM code: 516.3) between January 1, 2001 and December 31, 2011; (2). no NHI claim with diagnosis for any other interstitial lung diseases “see Supplementary Appendix S1, Additional File 1 “since the day of IPF diagnosis;(3). patient’s age of ≥ 18 years old at the time of IPF diagnosis and (4). at least one NHI procedure for surgical lung biopsy or computed tomography of the thorax “see Supplementary Appendix S1, Additional File 1 “ before or on the day of IPF diagnosis. Hospitalisations of at least 1 day in duration subsequent to the IPF diagnosis were categorised as respiratory or non-respiratory in nature“see Supplementary Appendix S2, Additional File 1”, “see Supplementary Figure S1, Additional File 2”.

Part II: Electronic medical records from a national medical centre

Study sample

We retrospectively examined the electronic medical charts of all patients with IPF who were admitted to our institution for ICD-9-CM code 516.3 between January 2001 and January 2015. Each admission was reassessed by two independent pulmonologists for IPF diagnosis as defined by the 2011 American Thoracic Society/European Respiratory Society criteria[19]. Of them, radiological confirmed to have usual interstitial pneumonia on high-resolution computed tomography (HRCT) by two independent radiologists “see Supplementary Figure S2, Additional File 2”.

Data collection

Demographic and pulmonary function test data were collected during IPF diagnosis. The gender, age, physiology index for IPF (GAP index) was calculated for each patient[20]. The clinical characteristics that were collected within 24 h at the first hospitalisation were considered as physical and laboratory findings, such as the use of steroids or long-term oxygen therapy prior to hospitalisation, HRCT scan and bronchoalveolar lavage. Hospitalisations of at least 24 h following IPF diagnosis were categorised as ARD and non-ARD ones for survival analysis. The primary outcome was the survival status after the first hospitalisation. The secondary outcome was to identify the predictor of in-hospital and within 1-year follow-up mortality. Survival status that was obtained from electronic medical records and telephone were reviewed by the investigator.

Definition

Hospitalisation forward was defined, as shown in “Supplementary Table S1, Additional File 3”. ARD was further categorised as AE-IPF, parenchymal cause of ARD other than AE (e.g., pneumonia and subacute progression), or extra-parenchymal cause of ARD (e.g., pneumothorax and pleural effusion)[21] “see Supplementary Figure S2, Additional File 2”. AE-IPF was diagnosed according the revised diagnostic criteria[22]. Radiation pattern on HRCT was classified as peripheral, multifocal and diffuse types by one radiologist and one pulmonologist.

Statistical Analysis

On the basis of Taiwanese NHIRD, we counted the number of patients diagnosed with IPF and calculated the incidence rate as the number of newly diagnosed patients per 100,000 persons in the NHI system in each year from 2001 to 2011. Survival time was calculated from diagnosis to death or the end of 2011. We estimated the median time on the basis of a Kaplan–Meier survival estimator. Survival time for patients with respiratory or non-respiratory hospitalisation was calculated with Kaplan–Meier survival curves and compared by the log-rank test.

For data from the NMC, Chi-squared test or Fisher’s exact test was used for categorical variables, and t-test or Mann–Whitney U test was used for continuous variables. Median survival time was analysed from initial consultation until death or the end of 2015. Survival time for patients with ARD or non-ARD hospitalisation was analysed based on the Kaplan–Meier estimator and the log-rank test. A multivariate Cox regression model performed by the method of enter technique was applied using the variables

associated with in-hospital mortality and 1-year mortality as a univariate analysis. A two-sided $p \leq 0.05$ was considered statistically significant. All data were analysed using IBM SPSS 19 statistical package.

Results

Impact of hospitalisation for respiratory causes on survival in patients with IPF from NHIRD

A total of 348 patients with ICD-9 code 516.3 were evaluated between 2001 and 2011. Among these patients, 122 were confirmed to have IPF (Figure S1). The mean age was 65.0 ± 16.7 years old, and the male-to-female ratio was 2.5:1. The median survival from diagnosis to death was 5.2 years. A total of 84 patients underwent hospitalisation after diagnosis and 29.8% (25/84) were admitted due to respiratory cause. The median survival was lower in patients with respiratory hospitalisation than those admitted due to non-respiratory hospitalization ($n=59$) (2.3 years vs 9 years, $p=0.007$; Figure 1a).

Impact of ARD hospitalisation on survival of patients with IPF in cohort from a NMC

A total of 129 hospitalised patients with ICD-9 code 516.3 were evaluated between 2001 and 2015. Among these patients, 53 patients with definite IPF were enrolled, including ARD hospitalisation ($n=30$), extra-parenchymal causes ($n=6$) and non-ARD hospitalisation ($n=17$). The median survival from initial diagnosis to death was 27 months. The median survival was lower in patients with ARD hospitalisation than those in non-ARD hospitalisation (0.9 months vs. 29.6 months, $p<0.001$; Fig. 1b). For ARD hospitalisation, 60 % of them died on their first hospitalisation compared with 0% of non-ARD hospitalized patients ($p<0.001$) (Table 1). Particularly, AE-IPF accounts for 53.3 % (16/30) of ARD hospitalization (Figure S2). 9 of the 16 AE-IPF patients needed ICU care with mechanical ventilation. Furthermore, the hospital mortality for patients in ICU with MV was 84.6% (11/13) with median survival time was 23 days. The median survival for AE-IPF was much lower than hospitalization for parenchymal cause (0.8 months vs 12.0 months; $p=0.006$). Mortality at 1yr after hospitalisation for ARD was significantly worse than in non-ARD (73.3 % vs 5.9%, $p<0.001$) (Table 1). 29 patients survived from ARD hospitalization were followed and median time to death after discharge was 5.7 months.

Comparison of characteristics of two cohorts

Patients in NMC cohort were statistically older at diagnosis (74.2 vs 67.0, $p<0.002$) with lower median survival (27 months vs 62.4 months) and higher in-hospital and 1-year mortality rate than those in NHIRD. (38.3% vs 4.8%, $P<0.001$; 49% vs 15.4%, $p<0.001$, respectively). The incidence of respiratory hospitalisation, mechanical ventilation, and co-existing comorbidity in gastroesophageal reflux, diabetes mellitus, chronic kidney disease, pulmonary hypertension or emphysema were statistically higher for patients in NMC compared to those in NHIRD (Table 3).

Independent factors associated with in-hospital and 1 year mortality for ARD hospitalisation

The patients hospitalised for ARD had statistically higher GAP score (Table 2), lower oxygenation (P/F ratio; partial pressure of oxygen/fraction of inspired oxygen), higher C-reactive protein (CRP) levels, higher

neutrophil counts and lower serum albumin levels compared to those non-ARD hospitalisation (Table 1). The predictors of in-hospital mortality (Table 4) and 1 year mortality (Table 5) for patients with IPF are presented. For both in-hospital and 1 year mortality, multivariate analysis adjusting for patient characteristics confirmed the independent predictive factors were steroid pulse therapy, AE-IPF and ICU admission with MV.

Discussion

The current study confirmed the impact of respiratory hospitalisation on patient outcomes and identify the prognostic factors for mortality in patients with IPF. In the NHIRD cohort, the median survival was lower in patients with respiratory hospitalisation compared with non-respiratory hospitalisation. The finding was also observed in the NMC cohort for patients with ARD hospitalisation. The median survival from IPF diagnosis to death was 5.2 and 2.3 years for NHIRD and NMC cohorts respectively. The differences in survival between these two cohorts were associated with age of diagnosis, causes of hospitalisation, mechanical ventilation and comorbidities. The patients hospitalised for ARD had statistically higher GAP score, lower oxygenation, higher C-reactive protein levels, higher neutrophil counts and lower serum albumin levels compared to those non-ARD hospitalisation. For both in-hospital and 1 year mortality, multivariate analysis adjusting for patient characteristics revealed that steroid pulse therapy, acute exacerbation and mechanical ventilation are the independent predictive factors. The respiratory hospitalisation negatively impacted patient outcomes and the independent prognostic factors may be utilised to refine the management in patients with IPF.

ARD hospitalisation is commonly due to AE-IPF which has extremely poor outcome and high mortality rate reported in some studies [4–6]. Teramachi et al. [21] showed ARD hospitalisation was observed in 54.2% (122/225) of IPF hospitalisation, whilst AE-IPF accounted for 28.7% (35/122) of ARD. Brown et al. analysed 150 IPF hospitalisation and 77.3% (116/150) were admitted for respiratory cause [7]. The results were similar to our findings, 29.8% and 63.8% for respiratory hospitalisation in NHIRD and NMC cohorts. AE-IPF was still the major cause of respiratory hospitalisation (53.3%). The findings above indicated the importance of understanding the mechanisms of pathophysiology related to respiratory deterioration in patients with IPF.

AE-IPF is most likely triggered by an acute event that leads to respiratory deterioration. Evidence suggests that pathobiology of AE-IPF involves both chronic (underlying epithelial cell dysfunction and fibroblast accumulation and activation) and acute disease process [22]. The major histological findings in AE-IPF were a diffusing alveolar damage (DAD) pattern superimposed on a usual interstitial pneumonia pattern [23, 24]. DAD is similar to the pathological finding of acute respiratory distress syndrome (ARDS) that can occur in patients without chronic lung disease following a large number of triggers [25]. The key driver of the pathogenesis was dysregulated inflammation both in the epithelial and endothelial sites, recruiting activated macrophages and neutrophils which release a variety of inflammatory mediators [26]. Acute worsening of IPF may result from various viral infections in an immune-mediated manner [27, 28], or an increased bacterial burden in the alveoli [29]. By contrast, significantly increased

inflammatory cytokines in AE-IPF with or without undiagnosed infection has been reported. CRP level and neutrophil count[30] could be prognostic factors for AE-IPF [31, 32] and these are consistent with our findings.

Corticosteroids may have some beneficial effects on AE-IPF and high-dose corticosteroids are commonly applied for the treatment of AE-IPF[24, 33, 34]. However, there were no controlled trials on which to judge efficacy. In our observation, steroids pulse therapy for AE-IPF was associated with the increased hospital mortality which may suggest progressive alveolar damage superimposed on interstitial fibrosis and the necessity of oxygen supplement and even MV support. This could explain why steroid pulse therapy and ICU admission with MV predict poor outcome.

Our study has several limitations. Firstly, the NHIRD database lacks detailed clinical information. Therefore, we cannot investigate the impact of other factors on patient survival, given that we use NMC clinical record to identify the clinical characteristics in patients with IPF. Secondly, NMC cohort was a retrospective study based on clinical records, and there were some items with missing values included in the statistical analysis. Third, this study included the period when antifibrotics were not approved in Taiwan. It is possible that differences in treatment plan influenced the incidence of AE-IPF. Fourth, we were limited in our ability to collect complete information on hospitalizations that may have occurred outside of NMC.

Conclusion

In summary, hospitalisation for ARD is an ominous predictor of subsequent mortality in patients with IPF. Clinical independent predictors for mortality would be useful in counselling patients, making treatment decisions and considering lung transplantation promptly.

Declarations

Acknowledgement

The authors are grateful to the KGSupport-Academic Submission Services for editing the manuscript.

Author Contributions

SN.Y.,HK. K and DW. P. were responsible for the study design and were involved in data analysis. SN.Y., PC. L. and CC. H.were responsible for data collection and interpretation. SN.Y and HY. H. performed the statistical analyses. SN.Y.,HK. K and YL. C wrote the first draft of the manuscript, which was revised by all authors. MI. C. and DW. P. are the guarantors of the paper, and they take responsibility for the integrity of the work as a whole, from inception to the published article.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by IRB of Taipei Veterans General Hospital, Taipei, Taiwan - approval: 2016-06-004CC. Adult participant consent was not required for our observational cohort study.

Competing interests

The authors declare no conflict of interest concerning this article

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Abbreviations

ARD, acute respiratory deterioration; AE, acute exacerbation; BAL, bronchoalveolar lavage; BMI, body mass index; CHF, congestive heart failure; CRP, C-reactive protein; CVA, cerebrovascular accident; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease, DLCO, diffusing capacity of lung for CO; FVC, forced vital capacity; GAP index, gender, age, physiology index for idiopathic pulmonary fibrosis; GERD, gastroesophageal reflux; HRCT, high-resolution computed tomography; ICU, intensive care unit; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MV, mechanical ventilator; NHIRD, National Health Insurance Research Database; P/F, partial pressure of oxygen/fraction of inspired oxygen; TLC, total lung capacity; UIP, usual interstitial pneumonia

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Tables

Table 1 Clinical characteristics in patients with IPF according to hospitalization for ARD and non- ARD

Laboratory data 24 hours after hospitalization	Total cohort (n=47)	Non-ARD (n=17)	ARD (n=30)*	p-value
P/F ratio	218.3 ± 111.3	306.4 ± 102.8	181.1 ± 93.6	0.001
LDH	347.6 ± 285.7	268.2 ± 103.1	403.7 ± 357.4	0.215
CRP	4.9 ± 6.8	0.8 ± 0.6	6.0 ± 7.2	0.001
Hgb	12.7 ± 2.3	13.5 ± 2.5	12.3 ± 2.0	0.077
WBC(X10 ³)	1.2 ± 3.9	9.1 ± 2.7	12.3 ± 4.1	0.003
Neutrophil (%)	76.0 ± 12.3	67.5 ± 11.1	80.5 ± 10.4	<0.001
Lymphocyte (%)	15.8 ± 10.1	20.7 ± 10.7	13.1 ± 8.8	0.013
Eosinophil (%)	1.8 ± 2.6	3.2 ± 3.5	1.1 ± 1.6	0.036
Albumin	3.4 ± 0.7	3.8 ± 0.6	3.1 ± 0.6	0.003
Scr	1.5 ± 1.1	1.6 ± 1.0	1.4 ± 1.2	0.71
Admission for AE-IPF	16(34)	0	16(53.3)	<0.001
Pulse therapy	6(12.8)	0	6(20)	0.074
Radiation pattern with diffuse type on HRCT	28(59.6)	3(17.6)	25(83.3)	<0.001
ICU admission	14(29.8)	0	14(46.7)	0.001
MV support	13(27.7)	0	13(43.3)	0.001
NIV support	8(17)	2(6)	6(20)	0.692
Hospital days	14.6 ± 19.7	6.7 ± 5.9	19.0 ± 23.2	0.009
Died during first hospitalization	18(38.3)	0(0)	18(60)	<0.001
Died within a year of first hospitalization	23(49)	1(5.9)	22(73.3)	<0.001

Data are presented as mean ± SD or number (%). *excluding IPF patients with hospitalization for extra-parenchymal cause (n = 6), abbreviation: P/F, partial pressure of oxygen/fraction of inspired oxygen; LDH, *lactate dehydrogenase*; CRP, C-reactive protein; *Hgb*, *hemoglobin*; WBC, white blood cell; Scr, serum

creatinine;AE-IPF, acute exacerbation; ICU, intensive care unit ;MV, mechanical ventilator; NIV, non-invasive ventilator

Table 2 Baseline characteristics of patients with IPF according to hospitalization for ARD and non-ARD

	Total (n=47)	Non-ARD (n=17)	ARD (n=30) *	P- value
Age	74.2 ± 9.8	75.0 ± 10.9	73.7 ± 9.3	0.688
BMI (N=38)	22.9 ± 3.9	24.3 ± 3.8	22.0 ± 3.7	0.092
GAP Index (N=45)	5.2 ± 1.5	4.4 ± 1.2	5.7 ± 1.5	0.007
FVC (% Pred.,N=46)	66.5 ± 15.9	73.2 ± 12.1	62.0 ± 16.8	0.028
DLco (% Pred.,N=41)	37.5 ± 13.4	36.9 ± 16.2	38.0 ± 11.0	0.819
TLC (mL, N=38)	3.6 ± 0.8	3.9 ± 0.8	3.3 ± 0.8	0.035
Male, Sex (n,%)	40(85)	16(94.1)	24(80)	0.396
Smoking status				0.073
Nonsmoker(n,%)	21(44.7)	5(29.4)	16(53.3)	
Exsmoker(n, %)	24(51.1)	10(58.8)	14(46.7)	
Current smoker(n, %)	2(4.3)	2(11.8)	0	
GERD	8(17)	1(5.9)	7(23.3)	0.228
GERD after treatment	7(14.9)	1(5.9)	6(20)	0.396
Diabetes mellitus	10(21.3)	4(23.5)	7(19.4)	0.730
Coronary artery disease	23(49)	8(47.1)	15(50)	1.00
CHF	3(6.4)	2(11.8)	1(3.3)	0.544
CVA	2(4.3)	2(11.8)	0	0.126
CKD	9(19.1)	4(23.5)	5(16.7)	0.704
Cancer history	5(10.6)	5(29.4)	0	0.010
Pulmonary hypertension	8(17)	1(5.9)	7(23.3)	0.228
COPD	9(16.9)	4(23.5)	4(13.3)	0.425
Bronchiectasis	7(17.9)	1(5.9)	6(30)	0.396
Emphysema	3(6.4)	2(11.8)	1(3.3)	0.586
Clubbed finger	5(10.6)	2(11.8)	3(10)	1.000
Surgical lung biopsy	7(14.9)	4 (23.5)	3(10)	0.235
Long term O ₂ therapy	7(14.9)	1(5.9)	6(20)	0.398
Steroid use before admission	11(23.4)	3(17.6)	8(26.7)	0.722

Data are presented as mean ± SD or number (%),*excluding IPF patients with hospitalization for extra-parenchymal cause (n = 6); BMI, *body mass index*; GAP Index, (Gender, Age, Physiology Index for

Idiopathic Pulmonary Fibrosis); FVC,forced vital capacity; DLco,diffusing capacity of lung for carbon monoxide;TLC, total lung capacity; GERD, gastroesophageal reflux; CHF,congestive heart failure; CVA,cerebrovascular accident ;CKD,chronic kidney disease ; COPD,chronic obstructive pulmonary disease

Table 3.Characteristics of patients with hospitalization according to data source

	NHIR (n=84)	NMC (n=47)	<i>P</i> -value
Median survival [‡]	62.4 months	27 months	
Age	67±16	74.2±9.8	0.002
Sex(male)	58(69)	40(85)	0.042
Respiratory hospitalization	25(29.8)	30(63.8)	<0.001
Died during first hospitalization	4(4.8)	18(38.3)	<0.001
Died within a year of first hospitalization ccause)cause)	13(15.4)	23(49)	<0.001
Mechanical ventilator support	5(5.9)	13(27.6)	0.0005
Comorbidity			
GERD	2(2.4)	8(17)	0.0025
Diabetes mellitus	6(7.1)	10(21.3)	0.0172
Coronary artery disease	30(35.7)	23(49)	0.1369
CHF	3(3.6)	3(6.4)	0.4633
CVA	0(0)	2(4.3)	0.0554
CKD	1(1.2)	9(19.1)	0.0002
Cancer history	3(3.6)	5(10.6)	0.1087
Pulmonary hypertension	0(0)	8(17)	0.0001
COPD	4(4.8)	9(19.1)	0.0087

Data are presented as mean ± SD or number (%)[‡],Fromfirst hospitalization to death; NHIR, national health insurance research database;NMC, national medical center;GERD, gastroesophageal reflux;

CHF,congestive heart failure; CVA, cerebrovascular accident ;CKD, chronic kidney disease ; COPD, chronic obstructive pulmonary disease

Table 4 Predictors of in-hospital mortality at first hospitalization in patients with IPF (n=47)

Covariable	Univariable (HR, CI)	<i>P</i> value	Multivariable ^a (HR, CI)	<i>P</i> value
AE-IPF on admission	10.44(3.38-32.22)	<0.001	14.56(2.90-73.10)	0.001
MV support.	6.25(2.38-16.34)	<0.001	15.02(3.02-74.73)	0.001
ICU admission	5.20(1.99-15.53)	0.001	8.71(1.91-39.67)	0.005
Diffuse type on HRCT	4.03(1.16-13.94)	0.028	3.76(0.70-20.35)	0.124
P/F ratio	0.99(0.99-0.99)	0.005	0.98(0.98-0.99)	0.013
Steroid pulse therapy	4.84(1.79-13.12)	0.002	19.26(3.75-100.0)	<0.001
CRP, mg/dL	1.12(1.05-1.19)	<0.001	1.19(1.06-1.34)	0.003
Hemoglobin, g/dL	0.81(0.67-0.98)	0.027	0.76(0.49-1.20)	0.244
WBC,10 ³ /ul	1.00(1.00-1.00)	0.006	1.00(1.00-1.00)	0.058
Neutrophil, %	1.09(1.04-1.15)	0.001	1.09(1.01-1.17)	0.025
Lymphocyte, %	0.90(0.84-0.96)	0.002	0.90(0.81-0.99)	0.049
Eosinophil. %	0.67(0.45-0.99)	0.047	0.67(0.40-1.14)	0.137
Albumin, g/dL	0.14 (0.05-0.36)	<0.001	0.04(0.003-0.39)	0.006

a ; correcting for a prior covariates of age, BMI, GAP index.

abbreviation: BMI, *body mass index*; GAP Index, (Gender, Age, Physiology Index for Idiopathic Pulmonary Fibrosis) AE-IPF, acute exacerbation; MV, mechanical ventilator; ICU, intensive care unit ;HRCT, High Resolution Computed Tomography; P/F, partial pressure of oxygen/fraction of inspired oxygen; CRP, C-reactive protein; WBC, white blood cell

Table 5 Predictors of 1-year mortality after first hospitalization in patients with IPF (n=47)

Covariable	Univariable (HR, CI)	<i>P</i> value	Multivariable ^a (HR, CI)	<i>P</i> value
AE-IPF on admission	8.65(3.37-22.25)	<0.001	10.70(2.77-41.30)	0.001
MV support.	5.14(2.22-11.90)	<0.001	6.46(1.98-21.06)	0.002
ICU admission	5.04(2.18-11.68)	<0.001	5.28(1.57-17.76)	0.007
Diffuse type on HRCT	4.07(1.38-12.02)	0.011	3.30(0.79-13.82)	0.103
P/F ratio	0.99(0.99-0.99)	0.004	0.98(0.98-0.99)	0.01
Steroid pulse therapy	4.91(1.81-13.31)	0.002	20.30(4.39-93.75)	<0.001
CRP, mg/dL	1.12(1.05-1.19)	<0.001	1.16(1.05-1.27)	0.003
Hemoglobin, g/dL	0.84(0.70-1.01)	0.057	0.93(0.65-1.33)	0.682
WBC, 10 ³ /ul	1.00(1.00-1.00)	0.006	1.00(1.00-1.00)	0.08
Neutrophil, %	1.08(1.04-1.13)	<0.001	1.08(1.02-1.15)	0.013
Lymphocyte, %	0.91(0.86-0.96)	0.001	0.91(0.83-0.99)	0.023
Eosinophil, %	0.63(0.43-0.91)	0.015	0.64(0.40-1.02)	0.06
Albumin, g/dL	0.11(0.04-0.29)	<0.001	0.04(0.004-0.34)	0.004

a ; correcting for a prior covariates of age, BMI, GAP. abbreviation: BMI, *body mass index*; GAP Index, (Gender, Age, Physiology Index for Idiopathic Pulmonary Fibrosis); AE-IPF, acute exacerbation; MV, mechanical ventilator; ICU, intensive care unit ;HRCT, High Resolution Computed Tomography; P/F, partial pressure of oxygen/fraction of inspired oxygen; CRP, C-reactive protein; WBC, white blood cell

Figures

Figure 1

1A: Survival curve according to hospitalisation for respiratory and nonrespiratory causes in IPF cohort from Taiwanese NHIRD. IPF, idiopathic pulmonary fibrosis; NHIRD, National Health Insurance Research database. 1B: Survival curve according to hospitalisation due to ARD and non-ARD in IPF cohort from a tertiary centre. ARD, acute respiratory deterioration; IPF, idiopathic pulmonary fibrosis.