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Clinical Features and Outcomes of Idiopathic Pulmonary Fibrosis Patients Hospitalized for Pneumonia

*Takamasa Wada and Hiromi Tomioka**

Department of Respiratory Medicine, Kobe City Medical Center West Hospital, Japan

Abstract

Objective: Considering the revised definition and new diagnostic criteria for acute exacerbations of Idiopathic Pulmonary Fibrosis (IPF), which proposed sub categorization of acute exacerbations as "triggered", it is important to evaluate the significance of pneumonia in managing IPF. This study aimed to describe the clinical features and outcomes of IPF patients hospitalized for pneumonia in the era of the new broader definition of acute exacerbations.

Methods: We conducted a retrospective cohort study of consecutive IPF patients admitted to Kobe City Medical Center West Hospital for pneumonia between 2008 and 2017. Baseline demographic and clinical data and outcomes were obtained from clinical records. Severity of pneumonia was evaluated using the A-DROP (Age, Dehydration, Respiratory failure, Orientation disturbance, and low blood Pressure) scoring system.

Results: Fifty-six cases (43 males, mean age 79.3±7.5 years) were considered to have pneumonia and 64 cases of acute exacerbation out of 321 cases with IPF were admitted during the study period. Most common pathogen was *Streptococcus pneumoniae*. Thirty-day and in-hospital mortality were 14.3% and 17.9%, respectively, values that were significantly lower than those for acute exacerbations of IPF (37.5% and 54.7%, respectively). In multiple logistic regression analysis only the A-DROP score was significantly associated with 30-day mortality due to pneumonia (odds ratio 65.0, 95% confidence interval 2.54-1657.47, p<0.0001).

Conclusion: Mortality of IPF patients hospitalized for pneumonia was significantly lower than for acute exacerbations of IPF. A-DROP score was significantly associated with 30-day mortality due to pneumonia.

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Correspondence:
Hiromi Tomioka, Department of Respiratory Medicine, Kobe City Medical Center West Hospital, 4, 2-chome, Ichibancho, Nagata-ku, Kobe 653-0013, Japan, Tel: 81-078-576-5251; Fax: 078-576-5358; E-mail: htomy@kcho.jp

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Introduction

Idiopathic Pulmonary Fibrosis (IPF) is defined as a specific form of chronic progressive fibrosing interstitial pneumonia of unknown cause [1]. Its clinical course is highly variable. Although some patients experience a steady progression of disease over time, many have an unpredictable disease course with periods of relative stability punctuated by episodes of acute and often fatal decline [2]. Acute exacerbation of IPF had been defined as an idiopathic acute worsening of dyspnea characterized radiologically by the presence of bilateral ground glass abnormality on high-resolution computed tomography scan of the chest [3]. However, distinguishing respiratory infections such as bacterial pneumonia from acute exacerbation is occasionally difficult in clinical practice. The 2016 International Working Group Report on acute exacerbation of IPF proposed sub categorization of acute exacerbations as either "triggered" or "idiopathic" [4], and acute exacerbation could be diagnosed even if a known trigger is present. Acute exacerbation can be triggered by pulmonary infection according to the 2016 diagnostic criteria, but clinical features of IPF patients hospitalized for pneumonia have not been established.

We retrospectively analyzed pneumonia cases among patients with IPF after we excluded cases of acute exacerbations according to the 2016 diagnostic criteria [4] admitted to a community teaching hospital in Japan over a 10-year period. The aim of this study was to describe the clinical features and outcomes of IPF patients hospitalized for pneumonia in the era of the new broader definition of acute exacerbations that included triggered acute exacerbations.

Materials and Methods

Study design and participants

We conducted a retrospective cohort study of consecutive IPF patients admitted to Kobe City

Table 1: Characteristics of study population with Idiopathic Pulmonary Fibrosis (IPF) and pneumonia and comparison between 30-day survivors and non-survivors.

	Total (n=56)	Survivors (n=48)	Non-survivors (n=8)	P value
CAP/NHCAP	28/28	26/22	2/6	0.119
Male sex	43 (76.8)	37 (77.1)	6 (75.0)	0.900
Age, y	79.3 ± 7.5	78.9 ± 7.5	81.8 ± 7.4	0.328
Smoking status (current/ex/non)	5/41/10	5/36/7	0/5/3	0.190
Alcohol habit (yes/no)	14/42	9/39	5/3	0.027
Updated CCI, median	2	2	1.5	0.626
Home oxygen therapy	17 (30.4)	13 (27.1)	4 (50.0)	0.207
Treatments for IPF				
Corticosteroid	8 (14.3)	6 (12.5)	2 (25.0)	0.513
Immunosuppressive therapy	4 (7.1)	3 (6.3)	1 (12.5)	0.424
Anti-fibrotic agents	2 (3.6)	1 (2.1)	1 (12.5)	0.220
Body temperature, °C	37.9 ± 1.1	38.0 ± 1.1	37.8 ± 1.0	0.617
Pulse rate, /min	95.8 ± 13.8	95.0 ± 13.6	100.9 ± 15.3	0.270
Systolic blood pressure, mmHg	129.1 ± 21.0	130.5 ± 19.3	120.6 ± 29.2	0.221
Laboratory data on admission				
WBC count, × 10^2/mm^3	132.5 ± 4.9	133.5 ± 50.9	126.1 ± 38.0	0.697
RBC count, × 10^4/mm^3	398.8 ± 61.6	403.9 ± 62.2	367.8 ± 50.6	0.125
Platelets count, × 10^4/mm^3	22.5 ± 9.5	23.0 ± 9.4	19.3 ± 10.0	0.311
Total protein, g/dL	7.5 ± 0.8	7.6 ± 0.8	7.2 ± 0.6	0.191
Albumin, g/dL	2.9 ± 0.6 (n=52)	3.0 ± 0.6 (n=45)	2.2 ± 0.5 (n=7)	0.0006
Blood urea nitrogen, mg/dL	21.7 ± 11.9	20.1 ± 8.6	31.3 ± 22.3	0.013
Creatinine, mg/dL	0.8 ± 0.4	0.8 ± 0.3	0.9 ± 0.9	0.585
C-reactive protein, mg/dL	14.5 ± 10.2	13.5 ± 9.9	20.7 ± 10.9	0.062
KL-6, U/mL	930.3 ± 603.9 (n=36)	909.3 ± 573.6 (n=33)	1162.0 ± 1015.2 (n=3)	0.496
SP-D, (ng/mL)	176.2 ± 147.1 (n=26)	157.7 ± 129.9 (n=23)	318.1 ± 225.2 (n=3)	0.075
A-DROP score	2.2 ± 1.0	1.9 ± 0.8	3.6 ± 0.7	<0.0001

Data are presented as a number (%) or mean ± Standard Deviation (SD) unless otherwise specified.
CAP: Community-Acquired Pneumonia; NHCAP: Nursing- and Healthcare-Associated Pneumonia; CCI: Charlson Comorbidity Index

Medical Center West Hospital (a 358-bed community teaching hospital in Kobe City, Japan) due to pneumonia between January 2008 and December 2017. When the same patient was admitted more than once during the study period, all admissions were included in the analysis.

Patients with hospital-acquired pneumonia and those with acute exacerbations of IPF were excluded. This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kobe City Medical Center West Hospital with waiver of informed consent because of its retrospective nature (approval number 19-002, approval date July 13, 2019.).

Definitions

Diagnosis of IPF was based on the 2011 American Thoracic Society (ATS)/European Respiratory Society/Japanese Respiratory Society (JRS)/Latin American Thoracic Association guidelines [1]. Acute exacerbation of IPF was diagnosed according to the 2016 ATS criteria: Previous or concurrent diagnosis of IPF; acute worsening or development of dyspnea of typically <1 month duration; computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with a usual interstitial pneumonia pattern; and deterioration not fully explained by cardiac failure or fluid overload [4]. Pneumonia was defined as the presence of fever or a wet cough, an increased white blood cell count or C-Reactive Protein (CRP) level, and the presence of a newly developed focal infiltrate on chest imaging [5,6]. We categorized the pneumonia in these study patients into either a Community-Acquired Pneumonia (CAP) or Nursing and Healthcare-Associated Pneumonia (NHCAP) group. NHCAP is a Japanese variant of health care-associated pneumonia [7] that was modified for the healthcare system of Japan. CAP and NHCAP were defined according to the JRS guidelines [8,9]. NHCAP was determined based on any of the following conditions: Residence in an extended care facility or nursing home, discharge from hospital in the preceding 90 days, being elderly or physically disabled requiring healthcare, and continuously receiving endovascular therapy in an ambulatory setting [8]. Patients were classified into the CAP group if they did not meet the criteria for NHCAP.

Clinical evaluation

Baseline demographic and clinical data and outcomes were obtained from clinical records. Data included age, sex, lifestyle, comorbid diseases, and treatments for IPF before admission, vital signs, laboratory data, percutaneous oxygen saturation, bacteriological examinations, length of hospital stay, and 30-day or in-hospital death. Microbiological evaluations on admission included the following tests: Aerobic and anaerobic conventional cultures of

two blood samples, Gram stain and culture of sputum when available, and a rapid test (Binax NOW, Binax, Inc., Scarborough, ME, USA) for urinary antigen of *Streptococcus pneumoniae* or *Legionella pneumophila* serogroup 1. The severity of pneumonia was evaluated using the 6-point scale (0-5) of the A-DROP (Age, Dehydration, Respiratory failure, Orientation disturbance, and low blood Pressure) scoring system proposed by the JRS [9]. This is a modified version of the CURB-65 (Confusion, Uremia, Respiratory rate, Blood pressure, and age ≥ 65 years) clinical prediction rule [10]. Chronic comorbid conditions were reported using the updated Charlson comorbidity index [11,12]. The primary outcome was death within 30 days from the date of admission, which was expressed as 30-day mortality.

Statistical analysis

Continuous variables were compared using unpaired *t* and Mann-Whitney U tests. Categorical variables were compared using Chi-square and Fisher's exact tests. Baseline clinical characteristics were compared between 30-day survivors and non-survivors. Multiple logistic regression analysis was used to determine independent predictors of 30-day mortality and to obtain Odds Ratios (ORs) adjusted for possible confounding factors identified by the univariate analysis ($p<0.10$). In the mortality analyses, the A-DROP score (0-5) was treated as a continuous variable. The 95% Confidence Interval (CI) for each OR was calculated. Statistical significance was determined from the 95% CI, not including 1.00 for logistic analyses. We compared 30-day and in-hospital mortality between pneumonia patients with IPF and patients with acute exacerbations of IPF. Data on the latter were obtained from our previous retrospective study of consecutive patients with acute exacerbations of IPF admitted to our hospital during the same study period, which was from January 2008 to December 2017 [5]. All statistical analyses were performed using JMP software package version 13 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

We identified 321 cases with IPF admitted to our hospital during the study period. Of these, 56 cases (17.4%) (41 unique patients) had pneumonia and 64 cases (19.9%) (57 unique patients) had acute exacerbation of IPF. The former group consisted of 43 males (76.8%) and 13 females (23.2%) with a mean age of 79.3 years (range: 60-94 years) (Table 1). Nine patients were admitted more than once due to pneumonia: Six patients presented with two episodes and three patients presented with four episodes. Twenty-eight had CAP and 28 had NHCAP. Treatments for IPF before the occurrence of pneumonia included steroid (n=8, 2.5-20 mg prednisolone per day), immunosuppressive therapy (n=4, cyclosporine A), and anti-fibrotic agents (pirfenidone, nintedanib, n=1, respectively). Hospitalization due to pneumonia had a tendency to be more common in the winter and spring seasons: 20 in spring (March-May), 9 in summer (June-August), 10 in autumn (September-November), and 17 in winter (December-February).

Microbes identified on admission and first-line antimicrobials

Good-quality sputum data from samples with Geckler classifications [13] of 4 to 6 were obtained in 30 of the 41 cases evaluated and *Streptococcus pneumoniae, Moraxella catarrharis,* and *Haemophilus influenzae* were isolated in 3, respectively. *Streptococcus pneumoniae* was detected in 1 by blood cultures and in 5 by pneumococcal urine antigen tests (Table 2). Thus, the most common pathogen identified was *Streptococcus pneumoniae*. Penicillin was the most frequent first-line antibiotic used (Table 3).

Table 2: Microbes identified on hospital admission of 41 study cases with idiopathic pulmonary fibrosis and pneumonia.

Examination of sputum	n=41
Streptococcus pneumoniae	3
Moraxella catarrhalis	3
Heamophilus influenzae	3
Staphylococcus aureus	2
MSSA	2
MRSA	0
Klebsiella pneumoniae	1
Pseudomonas aeruginosa	1
Acinetobacter baumanii	1
Escherichia coli	0
Enterobactor spp.	0
Urine antigen test	
Streptococcus pneumoniae	5/46
Legionella pneumophila	0/38
Positive culture from blood	1*/44

Data are presented as number or number/total number evaluated.
MSSA: Methicillin-Sensitive *Staphylococcus aureus*; MRSA: Methicillin-Resistant *Staphylococcus aureus*
**Streptococcus pneumoniae*

Table 3: First-line antimicrobials and clinical outcomes in 56 hospitalized cases with idiopathic pulmonary fibrosis and pneumonia.

First-line antimicrobials	
Penicillin/beta-lactamase inhibitors	39 (69.6)
Cephalosporins	7 (12.5)
Carbapenems	6 (10.7)
Macrolides	5 (8.9)
Fluoroquinolone	4 (7.1)
Others*	2* (3.6)
Need for mechanical ventilation	6§ (10.7)
Length of hospital stay, days	16 (3-145)
30-day mortality	8 (14.3)
In-hospital mortality	10 (17.9)

Data are presented as number (%) or median (range).
*amikacin, minocycline, n=1, respectively § non invasive positive pressure ventilation, n=3; invasive mechanical ventilation, n=3

Outcomes

Among 56 cases, 44 were discharged, 2 were transferred to another hospital for recuperation, and 10 died in hospital (8 of these within 30 days. Causes of death were pneumonia in 7 cases, progression of chronic IPF in 2 cases, and pulmonary embolism in 1 case. Steroid therapy was newly initiated in 8 cases. Six cases needed mechanical ventilation (noninvasive ventilation in 3, intubation in 3). Thirty-day mortality and in-hospital mortality were 14.3% (95% CI; 7.4-25.7%) and 17.9% (95% CI; 10.0-29.8%), respectively. Figure 1 shows 30-day mortality and in-hospital mortality according to the A-DROP score. Both mortality rates tended to increase in accordance with severity.

When the baseline characteristics of 30-day survivors and non-survivors among the IPF patients with pneumonia were compared

Table 4: Logistic regression analysis for risk factors associated with 30-day mortality in hospitalized cases with idiopathic pulmonary fibrosis and pneumonia.

	Odds ratio	95% CI	P value
Alcohol habit	23.75	0.88-640.25	0.060
Blood urea nitrogen, mg/dL	0.97	0.88-1.05	0.439
C-reactive protein, mg/dL	1.10	0.93-1.31	0.217
A-DROP score	65.0	2.54-1657.47	<0.0001

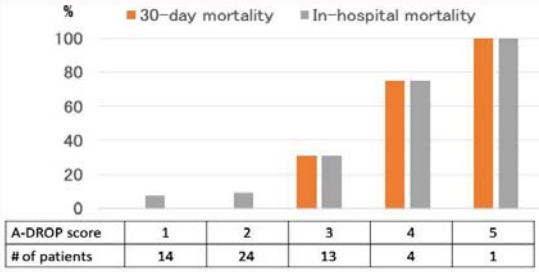

Figure 1: Thirty-day and in-hospital mortality according to the A-DROP score in patients with idiopathic pulmonary fibrosis hospitalized due to pneumonia.

(Table 1), alcohol habit, albumin, Blood Urea Nitrogen (BUN), and the A-DROP score were significantly different between the two groups.

Alcohol habit, BUN, CRP and A-DROP score were included in a multiple logistic regression analysis. Due to missing data, albumin and SP-D were not included in either of the analyses. Only the A-DROP score was significantly associated with 30-day mortality due to pneumonia (OR; 65.0, 95% CI; 2.54-1657.47, p<0.0001) (Table 4).

Thirty-day and in-hospital mortality were significantly lower in those with IPF with pneumonia (14.3% and 17.9%, respectively) than in those with acute exacerbations of IPF diagnosed based on the 2016 diagnostic criteria in our hospital (37.5% and 54.7%, respectively) [5] (Figure 2).

Discussion

Through our analyses, we found that pneumonia requiring hospitalization was associated with significant morbidity as was acute exacerbation of IPF in our IPF population but that the prognosis of the former was better than the latter. Considering the revised definition and new diagnostic criteria for acute exacerbation of IPF [4], which proposed sub categorization of acute exacerbations as "triggered", it is important to evaluate the significance of pneumonia in the management of IPF.

We identified 56 cases (17.4%) of pneumonia out of 321 cases of IPF admitted to our hospital over a 10-year period. Respiratory-related hospitalizations including those for pneumonia are considered important events because these have been proposed as predictive of survival of patients with IPF [14-16]. Song et al. [17] reported that acute exacerbation of IPF was the most frequent cause of respiratory-related hospitalizations (55.2%), followed by infection (31.3%) in 163 IPF patients presenting with an acute (within 30 days) worsening of dyspnea requiring hospitalization. Teramachi et al. [18] reported that among 122 patients with a hospitalization for acute respiratory deterioration 29% were diagnosed with acute exacerbation of IPF followed by pneumonia (23%). On the other hand, Nishiyama et al. [16] reported that pneumonia was the most common cause (47%) of respiratory-related hospitalizations in IPF,

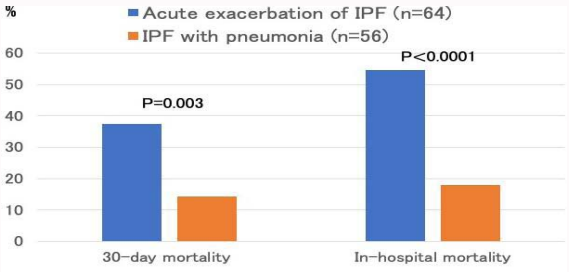

Figure 2: Comparison of outcomes between acute exacerbation of Idiopathic Pulmonary Fibrosis (IPF) and IPF with pneumonia.

followed by acute exacerbation of IPF (29.4%) among 106 patients. Although frequency varied by study design and indications for hospitalization, the frequency of respiratory-related hospitalization due to pneumonia in IPF patients was shown to be almost equal to that of acute exacerbation.

Hospitalized cases of IPF due to pneumonia were more likely to be male, older, or smokers. These characteristics reflected the clinical background of the IPF population. IPF predominantly affects the elderly population and is assumed to be a disease of aging [19]. Pneumonia is also an age-related disease causing an enormous burden in the aging population [20,21]. Aspiration is considered a major cause of pneumonia in the elderly [21-23]. Since diffuse alveolar damage caused by gastro-esophageal reflux has been suggested to explain acute exacerbation of IPF [24,25], aspiration is also one of the known triggers of acute exacerbations of IPF [4]. In addition, these two events, pneumonia and acute exacerbation [5,26,27], are common mainly in winter and spring. This similar seasonality supports an infectious etiology of acute exacerbation of IPF such as respiratory viral infection [28-30] or atypical pathogens [31]. In fact, we [5] and Teramachi et al. [18] have experienced "triggered" acute exacerbation of IPF followed by pneumonia. In such cases, although patients were diagnosed with focal pneumonia at admission, newly developing bilateral infiltrates appeared in the normal area during their clinical course and they were subsequently diagnosed with "triggered" acute exacerbation.

In our study population of patients hospitalized with community-onset pneumonia with IPF, percentages of NHCAP, derived from the concept of health-care associated pneumonia as defined in the United States [7], reached 50%. According to the reported percentages of patients with NHCAP in Japan, ranging from 33.8% to 41.4% [32-37], the ratio of NHCAP among our study patients seemed to be high. Since IPF is a chronically progressive interstitial lung disease that results in severe disability and affects the quality of life [38,39], IPF patients would meet the conditions for the acquisition of NHCAP.

In our study *Streptococcus pneumoniae* was found to be the most common bacterial pathogen. There are few data on causative organisms in IPF patients with bacterial pneumonia. Oda et al. [40] studied 541 IPF patients hospitalized with bacterial pneumonia using a nationwide Japanese clinical database. They found that the four most common pathogens were *Streptococcus pneumoniae* (31.6%), methicillin-resistant *Staphylococcus aureus* (18.4%), *Klebsiella pneumoniae* (9.2%), and *Pseudomonas aeruginosa* (9.2%). The appropriate use of antimicrobials targeting *Streptococcus pneumoniae* should be considered in IPF patients with bacterial pneumonia, and pneumococcal vaccination at the earliest opportunity after the diagnosis of IPF may be an important strategy

for preventing pneumococcal pneumonia in patients with IPF [40]. Fibrosis progression in response to *Streptococcus pneumoniae* has been reported in mouse models of pulmonary fibrosis [41]. On the other hand, Yamazaki et al. [6] studied 48 IPF patients hospitalized due to pulmonary infection including pneumonia and bronchitis and found that the causative pathogens mainly consisted of gram-negative bacteria such as *Haemophilus in luenzae* (14.5%) followed by *Pseudomonas aeruginosa* (4.1%), and *Klebsiella pneumoniae* (4.1%). They included causative pathogens in bronchitis, which may account for the different results from ours and Oda et al. [40]. The discovery of the lung microbiome has prompted the exploration of its role in IPF. Molyneaux et al. [42] demonstrated that the lower airways of patients with IPF were not sterile and indeed were more likely to harbor potentially pathogenic *Haemophilus*, *Neisseria*, and *Streptococcus* species than healthy controls.

In our study population 30-day mortality and in-hospital mortality was 14.3% and 17.9%, respectively. These figures are similar to those of Yamazaki et al. [6] showing that the 30-day and hospital mortality rates were 14.5% and 18.7%, respectively, in 48 IPF patients hospitalized due to pulmonary infection. Since the mortality rate of CAP requiring hospitalization has been reported as 2% ~ 8% [43,44], these figures are approximately double that. Prognosis of IPF with pneumonia was, however, better than that of acute exacerbation of IPF. Thirty-day and in-hospital mortality were significantly lower than for acute exacerbations of IPF diagnosed based on the 2016 diagnostic criteria in the same period in our hospital (Figure 2). Acute exacerbations of IPF are associated with high short-term mortality. Respiratory failure from acute exacerbation of IPF was associated with high in-hospital mortality, in most case series upward of 50% [4]. It is important to distinguish acute exacerbation of IPF from acute respiratory deterioration of other parenchymal causes such as pneumonia from both the therapeutic and prognostic points of view [18].

With regard to prognostic factors we found that only the A-DROP score was significantly associated with 30-day mortality ($p<0.0001$). Proper severity scoring is crucial in determining the therapeutic strategy for adult pneumonia. The Pneumonia Severity Index (PSI) has been proposed as a system for assessing pneumonia severity based on the results of the PORT study [45]. However, this system is very complex and inconvenient for determining the initial treatment. Yamazaki et al. [6] used the PSI as a clinical prediction score in their cohort of IPF patients hospitalized due to pulmonary infection; however, no significant predictors including the PSI for 30-day mortality were identified in multivariate logistic regression analyses. Koizumi et al. [37] reported that A-DROP was not inferior to PSI and CURB-65 in usefulness in CAP and NHCAP. Therefore, this simple and easy severity scoring system also may be useful to predict mortality in IPF patients hospitalized for pneumonia.

This study has several limitations. First, it was retrospective and therefore it is possible that unmeasured variables affected outcomes. In spite of the results of the univariate analysis, albumin and SP-D were not included in either of the analyses of mortality due to missing data. Especially, albumin showed significant differences between 30-day survivors and non-survivors. Serum albumin was shown to be a significant prognostic factor in CAP [46,47] and community-onset pneumonia including NHCAP [48]. Therefore, albumin should be considered as a possible candidate for a prognostic factor in IPF patients hospitalized for pneumonia. Second, the study was performed at a single center and consisted of a small sample size. In our study population of IPF patients hospitalized with pneumonia, the rate of patients received anti-fibrotic therapy was low. Although pirfenidone is available from 2008 and nintedanib is available from 2015 in Japan, these two antifibrotic drugs are internationally approved and recommended for patients with IPF in 2015 [49]. Therefore, the results may not be applicable to populations in other areas and in more recent IPF population. Third, the proportion of patients with the etiology of pneumonia identified was low. Although protected respiratory sampling using bronchoscopy may be recommended, we have encountered difficulty in obtaining samples especially in the elderly population. In addition, a PCR analysis was not performed to detect causative pathogens. Viruses, anaerobes, and some atypical pathogens such as *Mycoplasma pneumoniae* might have been overlooked.

In conclusion, 30-day and in-hospital mortality among IPF patients hospitalized for pneumonia were significantly lower than those of acute exacerbations diagnosed based on the 2016 diagnostic criteria. The A-DROP score was significantly associated with 30-day mortality due to pneumonia. It is important to distinguish pneumonia from acute exacerbation in the era of a new broader definition of acute exacerbations. Further multicenter prospective studies are needed to identify other prognostic factors and the responsible lung microbiome.

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