【 ORIGINAL ARTICLE 】

Prognostic Factors in the Acute Exacerbation of Idiopathic Pulmonary Fibrosis: A Retrospective Single-center Study

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Abstract:

Objectives   Acute exacerbation of idiopathic pulmonary fibrosis (IPF-AE) has been recognized as a fatal pulmonary disorder, but the exact prognostic factors are unknown. The aim of the present study was to analyze the clinical characteristics of patients with IPF-AE and identify the prognostic factors.

Methods   The medical records of 59 cases of IPF-AE were retrospectively reviewed. Clinical data, laboratory data, radiographic findings, treatment, and time from the onset of symptoms to the initiation of corticosteroid pulse therapy, i.e. symptom duration, and outcome were analyzed.

Results   The IPF Stage, Gender-Age-Physiology (GAP) Index, symptom duration, and the high-resolution computed tomography (HRCT) score were significantly related to the prognosis in the univariate analysis. In the multivariate analysis, the symptom duration remained a significant prognostic factor (hazard ratio of 1-day increase, 1.11; 95% confidence interval, 1.01-1.15; p=0.0427). The area under the receiver operating characteristics curve of symptom duration was statistically significant for survivors versus non-survivors (area under the curve, 0.73; p=0.012). The survival period was significantly shorter in the late-treatment groups (≥5 days; n=30) than in the early-treatment groups (<5 days; n=29; log-rank test; p<0.0001).

Conclusion   The time interval between the onset of symptoms and the initiation of corticosteroid pulse therapy may be an independent prognostic factor in patients with IPF-AE.

Key words: idiopathic pulmonary fibrosis, acute exacerbation, prognostic factor, survival

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Introduction

Idiopathic interstitial pneumonia (IIP) is a progressive, fibrotic lung disease, characterized by hypoxia and diminishing lung volume with eventual respiratory failure (1). Idiopathic pulmonary fibrosis (IPF), histologically diagnosed as usual interstitial pneumonia (UIP), is the most common subtype of IIP (2). The etiology and pathogenesis of IPF are not fully understood, although the fibrotic process is generally considered to result from epithelial injury and activation followed by the formation of fibroblasts and the accumulation of extracellular matrix (3). The clinical course of IPF is quite variable, and the median survival time of IPF patients is estimated to be two to five years after the initial diagnosis (4, 5).

IPF usually progresses gradually, but acute exacerbation of IPF (IPF-AE) may occur at any stage in the clinical course. IPF-AE is defined by the rapid deterioration of disease in the absence of other causative diseases, such as infection, heart failure, or pulmonary embolism (6, 7). The prognosis of IPF-AE is poor, usually leading to death in a few weeks or months (8), with mortality between 60% and 80% (9). Although international guidelines recommend corticosteroids for the majority of patients with IPF-AE (5), no proven effective therapy has yet been found. Only a small

proportion of patients who received intensive treatment including high-dose intravenous corticosteroids have been reported to recover from IPF-AE.

The patient characteristics predictive of mortality have been studied (10-12), but the precise prognostic factors of IPF-AE remain unknown. The aim of this study was to analyze the clinical data of patients with IPF-AE and identify potential prognostic factors of IPF-AE.

Materials and Methods

Study population

The medical records of a consecutive series of inpatients with IPF-AE treated at Nippon Medical School Hospital between January 2008 and January 2017 were retrospectively reviewed. We registered only the first onset of IPF-AE. Fifty-nine cases of IPF-AE were included. All patients met the American Thoracic Society/European Respiratory Society (ATS/ERS) diagnostic criteria for IPF (2). IPF-AE was defined using the revised criteria (6, 7), in which the following three conditions must be satisfied during the course of IPF within 1 month: (1) increased dyspnea; (2) newly developed ground-glass opacities or consolidation on high-resolution computed tomography (HRCT); (3) decrease in arterial oxygen tension (PaO_2) of more than 10 mmHg under similar conditions; and (4) absence of infection, pneumothorax, cancer, pulmonary embolism, or congestive heart failure.

Patient variables obtained from medical records included age, sex, smoking history, baseline pulmonary function, treatment history, blood chemistry data, arterial blood gas data, status of oxygen inhalation, and therapeutic medicines (corticosteroid and immunosuppressants). The time from the onset of symptoms to the initiation of corticosteroid pulse therapy was calculated as the symptom duration. This study was approved by the ethics committee of Nippon Medical School Hospital (approval number: 27-02-559).

IPF stage

We assumed that the baseline severity of IPF was critically important to compare the outcome of IPF-AE. According to the IPF severity classification of the Japanese Respiratory Society, the severity was classified as Stage 1 (PaO_2 ≥80 Torr at rest), Stage 2 (70-79 Torr), Stage 3 (60-69 Torr), or Stage 4 (<60 Torr at rest). Among patients with Stage 2/3 disease, the severity was increased by one stage if the lowest oxygen saturation by pulse oximetry was less than 90% during the 6-minute walk test.

Gender-Age-Physiology (GAP) index

We also used the GAP Index to assess the outcome based on the severity of IPF. The GAP Index includes gender, age, and physiology (forced vital capacity [FVC] and diffusing capacity of the lungs for carbon monoxide [DLco]). The GAP Index was calculated according to the total point score

(range, 0-8) (13).

HRCT score

All patients were evaluated by HRCT after the onset of IPF-AE, and the images were scored by two observers (K.A. and Y.S.) in a blinded manner without knowledge of the patient's clinical information. The HRCT score of the severity of lung lesions was calculated from the areas with (1) normal attenuation, (2) ground-glass attenuation, (3) consolidation, (4) ground-glass attenuation with traction bronchiectasis or bronchiolectasis, (5) consolidation with traction bronchiectasis or bronchiolectasis, and (6) honeycombing on HRCT according to previous reports (10). The overall HRCT score was obtained by adding the averages of each index.

Statistical analyses

In long-term observation, the outcomes are not accurate, as the patients may be treated at different hospitals. Patients were therefore stratified as survivors and non-survivors within 60 days of initiation of treatment. In each group, continuous variables were reported as the medians and 25th and 75th percentiles of the interquartile range. The significance of differences between survivors and non-survivors was tested with the Mann-Whitney U test for continuous variables. Fisher's exact test was used for categorical variables. Univariate and multivariate analyses using Cox proportional hazards regression models were used to assess the prognostic factors of the overall survival. We used receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) to determine the cut-off value of the independent prognostic factors for survivors and non-survivors that yielded the highest sensitivity and specificity, which was determined by the Youden index. Survival curves were drawn using Kaplan-Meier estimates according to appropriate cutoff value of the independent prognostic factors and compared with log-rank tests. Statistical analyses were performed using the JMP[®]11 software program (SAS Institute, Cary, USA). Statistical significance was defined as a p value <0.05.

Results

Patient characteristics

We identified 59 patients with IPF-AE who were treated at our institution between January 2008 and January 2017. The patient characteristics of age, sex, smoking history, IPF Stage, GAP Index, history of corticosteroid use, and history of antifibrotic therapy before the onset of IPF-AE are summarized in Table 1, while body temperature, blood chemistry, arterial blood gases, HRCT score, and treatment option at the onset of IPF-AE are summarized in Table 2. The IPF Stage was evaluated within 6 months before the onset of IPF-AE. GAP Index was evaluated from 6 to 12 months before the onset of IPF-AE. The proportion of patients with a

Table 1.   Clinical Characteristics of the Patient Series before the Onset of IPF-AE.

Variables	Overall (n=59)		Survivors (n=27)		Non-survivors (n=32)		p value*
Age (year)	74.0	(66.0-78.0)	73.0	(65.0-78.0)	75.0	(68.0-78.5)	0.377
Sex (male)	49		24		25		0.319
Brinkman Index[a]	800	(500-1,200)	870	(660-1,200)	800	(25-1,090)	0.131
IPF Stage[b]	2	(1-4)	2	(1-3)	3	(1.25-4)	0.111
GAP Index[c]	4	(3-5)	4	(3-5)	4	(3-5)	0.421
Regular use of steroid	9		3		6		0.488
Regular use of pirfenidone	13		6		7		1.000

Data expressed as median and the 25-75th percentiles of interquartile range

*Mann-Whitney U test or Fisher's exact test

[a]the number of cigarettes smoked per day multiplied by the number of years of smoking

[b]IPF Stage: classified by PaO_2 at rest and SpO_2 during the 6-minute walk test

[c]GAP Index: calculated from total score of gender, age, and two lung physiology variables (FVC and DLco) (13)

Table 2.   Clinical Characteristics of the Patient Series at the Onset of IPF-AE.

Variables	Overall (n=59)		Survivors (n=27)		Non-survivors (n=32)		p value*	
Body temp (°C)	37.0	(36.6-37.7)	37.0	(36.6-38.0)	36.9	(36.6-37.4)	0.231	
LDH (U/L)	336	(287-413)	310	(266-382)	382	(311-437)	0.034	*
KL-6 (U/mL)	1,583	(1,007-2,288)	1,583	(798-2,288)	1,655	(1,133-2,399)	0.451	
SP-D (ng/mL)	281	(148-413)	308	(161-433)	274	(144-383)	0.589	
CRP (mg/dL)	9.7	(5.9-15.1)	9.2	(5.7-14.8)	9.9	(6.0-16.0)	0.612	
D-dimer (mg/mL)	2.7	(1.7-6.8)	3.3	(1.6-9.4)	2.6	(1.8-5.2)	0.654	
$PaCO_2$ (Torr)	34.4	(31.1-38.3)	35.0	(31.4-38.1)	33.9	(30.6-39.0)	0.731	
A-aDO_2 (Torr)	215	(88-436)	155	(84-431)	216	(103-451)	0.433	
P/F ratio (Torr)[a]	174	(97-253)	195	(97-268)	140	(96-238)	0.398	
HRCT score[b]	200	(181-216)	190	(180-209)	209	(185-229)	0.042	*
Treatment option								
Symptom duration (day)[c]	6.0	(3.0-9.0)	3.0	(2.0-6.0)	6.5	(5.0-10.0)	0.003	*
Mechanical ventilation[d]	24		5		19		0.002	*
PMX-DHP[e]	21		10		11		1.000	
Immunosuppressants[f]	28		12		16		0.798	

Data expressed as median and the 25-75th percentiles of interquartile range

*Mann-Whitney U test or Fisher's exact test

[a]P/F ratio: PaO_2/FiO_2 ratio

[b]HRCT score: calculated from the area of attenuation with traction bronchiolectasis or bronchiectasis on high-resolution computed tomography (10)

[c]Symptom duration: the time interval between onset of symptoms and initiation of corticosteroid pulse therapy

[d]Mechanical ventilation: use of invasive positive pressure ventilation or non-invasive positive pressure ventilation

[e]PMX-DHP: use of direct hemoperfusion using a polymyxin B immobilized fiber column

[f]Immunosuppressants: history of intravenous pulse therapy of cyclophosphamide or other oral immunosuppressive therapy other than corticosteroid pulse therapy

history of corticosteroid use was higher among non-survivors than survivors. The IPF Stage, A-aDO_2, and serum Krebs von den Lungen (KL)-6 levels were higher and the PaO_2/FiO_2 (P/F) ratio lower in non-survivors than in survivors. However, the differences were not statistically significant. In contrast, the serum lactate dehydrogenase (LDH), HRCT score, and symptom duration were significantly higher in non-survivors than in survivors.

All patients presented with a rapid deterioration of respiratory symptoms, including cough (n=27; 46%), increased dyspnea (n=55; 93%), and a fever (axillary temperature ≥ 37.5℃) (n=21; 36%). The median symptom duration was 3.0 days in survivors and 6.5 days in non-survivors. The median symptom duration was significantly shorter in survivors than in non-survivors (p=0.003, Table 2). The median HRCT score was 200 (range 160-255); there was a statistically significant but weak difference between survivors (median: 190) and non-survivors (median: 209) (p=0.042, Table 1).

Nine patients had been treated with oral corticosteroids before the onset of IPF-AE. Three patients had been treated with immunosuppressants, and 13 patients had been treated with pirfenidone as antifibrotic therapy. All patients received oxygen therapy and antibiotic treatment. Mechanical ventila-

Table 3.   Prognostic Factors of Acute Exacerbation of Idiopathic Pulmonary Fibrosis.

	Per unit for HR[a]	HR	95% CI[b]	p value	
Univariate Cox analysis[c]					
Age	1 year	1.00	0.98-1.05	0.551	
Sex (Male)	Male	0.78	0.37-1.92	0.566	
Brinkman Index[d]	200	0.95	0.88-1.02	0.176	
IPF Stage[e]	1	1.50	1.17-1.94	0.0013	*
GAP Index[f]	1	1.45	1.10-1.93	0.0090	*
Regular use of steroid	Positive	1.23	0.50-2.58	0.630	
Regular use of pirfenidone	Positive	1.13	0.53-2.23	0.739	
LDH	10 IU/L	1.02	0.99-1.04	0.237	
KL-6	200 U/mL	1.03	0.97-1.07	0.340	
SP-D	20 ng/mL	0.99	0.96-1.03	0.761	
P/F ratio[g]	10 Torr	0.97	0.94-1.00	0.091	
HRCT score[h]	10	1.24	1.08-1.42	0.0021	*
Symptom duration[i]	1 day	1.11	1.05-1.17	0.0010	*
Immunosuppressants[j]	Positive	1.10	0.62-1.97	0.735	
Multivariate Cox analysis[k]					
IPF Stage	1	1.44	0.91-2.36	0.1211	
GAP Index	1	0.98	0.62-1.51	0.9108	
HRCT score	10	1.18	0.99-1.39	0.0532	
Symptom duration	1 day	1.11	1.01-1.15	0.0427	*

[a]HR: hazard ratio; HR is calculated with each per unit-increase.
[b]CI: confidence interval
[c]Univariate analysis with Cox proportional hazards regression models
[d]Brinkman Index: the number of cigarettes smoked per day multiplied by the number of years of smoking
[e]IPF Stage: classified by PaO_2 at rest and SpO_2 during the 6-minute walk test
[f]GAP Index: calculated from total score of gender, age, and lung physiology variables (FVC and DLco) (13)
[g]P/F ratio: PaO_2/FiO_2 ratio
[h]HRCT score: calculated from the area of attenuation with traction bronchiolectasis or bronchiectasis on high-resolution computed tomography (10)
[i]Symptom duration: the time interval between onset of symptoms and initiation of corticosteroid pulse therapy
[j]Immunosuppressants: history of intravenous pulse therapy of cyclophosphamide or other oral immunosuppressive therapy other than corticosteroid pulse therapy
[k]Multivariate analysis of Cox proportional hazards regression models

tion was used for the treatment of respiratory failure in 24 patients. Invasive positive pressure ventilation was used in 7 patients, and noninvasive positive pressure ventilation was used in 17. Direct hemoperfusion using a polymyxin B immobilized fiber column (PMX-DHP) was used for the treatment of IPF-AE in 21 patients. Corticosteroid pulse therapy (methylprednisolone, 500-1,000 mg/day for 3 days) was given to all patients. Twenty-eight patients were treated with an intravenous pulse of cyclophosphamide immediately after corticosteroid pulse therapy. Corticosteroid therapy was followed by a tapered dosage in all patients. Immunosuppressive therapy other than glucocorticoids was given to nine patients. The mean P/F ratio on the day after glucocorticoid pulse therapy was significantly lower in non-survivors than in survivors (p=0.0004).

An analysis of the survival after IPF-AE

At the time of follow-up, a total 49 patients were considered dead because of IPF progression, and 5 were considered dead due to other causes (1 sepsis; 1 lung cancer; 1 hemoptysis; 2 unknown causes). Four patients showed re-exacerbation of IPF, two of whom survived with corticosteroid pulse therapy. The survival rate was 55.9% at 30 days, 45.8% at 60 days, and 40.7% at 90 days after treatment with corticosteroid pulse therapy. The median survival from treatment was 45 days (range 1-1,710 days). Twenty-seven of the 59 patients that recovered were still alive at 60 days, while the remaining 32 had died from respiratory failure within 60 days. In non-survivors, the median survival time was 14 days (range 1-59).

Table 3 shows the results of univariate and multivariate Cox regression analyses. The IPF Stage, GAP Index, symptom duration, and HRCT score were significantly related to the prognosis in the univariate analysis. In the multivariate analysis, the symptom duration remained a significant prognostic factor [hazard ratio (HR) per 1-day increase, 1.11;
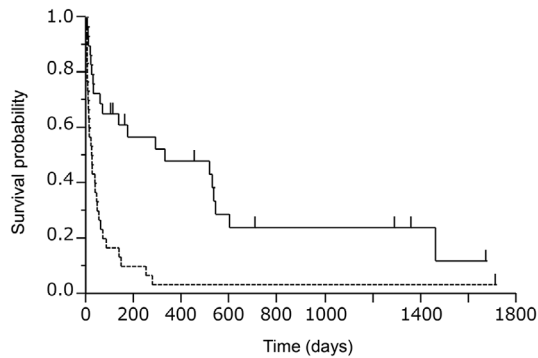
Figure. Kaplan-Meier survival curves show a difference in the overall survival. The survival was significantly shorter with late treatment (≥5 days; n=30, dotted line) than with early treatment (<5 days; n=29, solid line) (log-rank test; p<0.0001).

95% confidence interval (CI), 1.01-1.15; p=0.0427].

The area under the ROC curve for symptom duration was statistically significant in survivors versus non-survivors (AUC, 0.73 p=0.012). The optimal cut-off value of symptom duration for the prediction of the survival was 5 days, based on the Youden index, with a sensitivity of 78% and a specificity of 70%. A Kaplan-Meier analysis (Figure) revealed that the survival was significantly shorter in the late-treatment group (≥5 days; n=30) than in the early-treatment group (<5 days; n=29; log-rank test; p<0.0001).

Discussion

The prognosis of IPF-AE is poor, usually leading to death within a few weeks or months (6). A number of different treatments have been used, but the development of an effective therapy remains elusive. Recent international IPF guidelines recommend corticosteroids in the majority of patients with IPF-AE. However, only a small proportion of patients with steroid therapy have been reported to recover from respiratory failure. It is difficult to predict the effects of steroid therapy for IPF-AE. Therefore, an understanding of the prognostic factors would be helpful in the management of IPF-AE.

The interesting finding of this study is that the time from the onset of symptom to the initiation of corticosteroid pulse therapy, i.e. symptom duration, was an independent prognostic factor for the survival of IPF-AE. Our data suggest that symptom duration is a sensitive predictor of the survival of IPF-AE with a cut-off of 5 days. There are few reports describing early treatment with corticosteroid pulse therapy. Because a specific treatment for IPF-AE has not yet been established, we assume that the results of this study are of significance.

Previous studies have reported various prognostic factors in patients with IPF-AE, including age, sex, smoking history, FVC and DLco values (14-16), histopathologic findings, and radiologic findings (10). Akira et al. (11) found that the extent and pattern of HRCT and serum LDH levels

were predictors of the survival in IPF-AE. Patients with new parenchymal abnormalities, classified as a multifocal or diffuse pattern, have a worse prognosis than those with only peripheral involvement. Ohshimo et al. (17) found that the baseline KL-6 predicts an increased risk for IPF-AE, and Song et al. (12) found that the C-reactive protein (CRP) level was also a prognostic factor of IPF-AE.

As in previous studies, we found that the serum LDH was significantly higher in non-survivors than in survivors. However, this factor was not statistically significant in a univariate Cox regression analysis. Although a univariate analysis revealed that the IPF Stage, GAP Index, HRCT score, and symptom duration were significant prognostic factors, in a multivariate analysis, only symptom duration retained its significance as an independent factor. A few studies have reported several duration factors associated with the prognosis of IPF-AE. Simon-Blancal et al. (18) reported that the time between admission and the initiation of treatment might be a prognostic factor. In their report, the time between symptom onset and the initiation of steroid therapy was not associated with the prognosis. In our study, we detected no significant difference in the time between admission and the initiation of treatment (median duration of 1 day in survivors and 1 day in non-survivors; p=0.34). One possible reason for the difference in the results may be differences in patient characteristics between the two studies; for example, there were more mild cases of IPF-AE in Simon-Blancal's study than in our study. Usui et al. (19) conversely reported that symptom duration before admission was significantly shorter in non-survivors than in survivors of IPF-AE. However, they did not evaluate the time between the onset of symptoms and initiation of treatment as a prognostic factor for IPF-AE. We found a significant difference in the time between symptom onset and admission in our study (median duration of 2 days in survivors and 6 days in non-survivors; p=0.0104). This result supports the opposite conclusion, that the time from the onset of symptom to the initiation of corticosteroid pulse therapy, defined as the symptom duration, was a sensitive prognostic factor (p=0.003). In view of these analyses, we cannot explain why the duration of symptoms before admission was not significant in both reports. We hypothesize that the results may have been influenced by patient awareness of the disease.

When patients with IPF-AE failed to notice a worsening of their symptoms, then the severity of IPF-AE usually become intensified at admission. However, there was no significant relationship between the symptom duration and the severity of IPF-AE at admission, as indicated by A-aDO2 (p=0.674) or P/F ratio (p=0.679). The HRCT score was considerably higher for longer symptom durations, although this relationship was not statistically significant (p=0.070). As a potential explanation for why early treatment was associated with the prognosis, a delay in receiving corticosteroid therapy might lead to irreversible progression of alveolar damage and fibrosis, resulting in a worse outcome. It is therefore critical to improve the clinical status as soon as possi-

ble. The differential diagnosis includes diseases such as congestive heart failure and pulmonary infectious diseases, which underscores the need for a quick, standardized diagnostic approach.

In this study, we did detected no significant differences in the IPF Stage and GAP Index between survivors and non-survivors. Furthermore, these factors were significant in a univariate Cox regression analysis but were not in a multivariate analysis. These factors are commonly used to predict the mortality in patients with IPF aside from IPF-AE. Homma et al. (20) reported that the outcome in patients with IPF was significantly associated with the severity of the IPF Stage. Because our study included patients diagnosed with IPF-AE, the baseline characteristic was a severe disease state. Therefore, we assume that these factors did not differ significantly between survivors and non-survivors. Regarding the GAP Index, some missing pulmonary function data may have limited the statistical analysis.

The HRCT score was related to the prognosis in the univariate Cox regression analysis but not in the multivariate analysis. The HRCT score has been shown to be an independent prognostic factor for patients with acute respiratory distress syndrome and acute interstitial pneumonia other than IPF-AE (21). The HRCT score showed a high score for the lungs, which is often associated with honeycomb lung (or emphysema which is difficult to distinguish from honeycombing). Therefore, these measurement errors may have influenced the statistical analysis.

PMX-DHP did not induce any significant improvement in the prognosis of IPF-AE (p=1.000). This finding is because PMX-DHP is used for severe cases. The P/F ratio was lower in the PMX-DHP group (mean, 151) than in the non-PMX-DHP group (mean, 192) (p=0.088).

Several limitations associated with the present study warrant mention. First, our study included only 59 patients at a single study center. In addition, it was a retrospective analysis; thus, the clinical information obtained from medical records was limited. The symptom duration was not necessarily objective. Many elderly patients (median age, 74.0 years) were included. Elderly patients tend to be inaccurate in their complaints of symptoms. A strict evaluation, such as scoring subjective symptoms and having patients keep diaries, is necessary. To resolve these problems, the effectiveness of early treatment intervention should be investigated further in a prospective study with a larger sample size. Second, the clinical profiles of patients with IPF are generally heterogeneous. Furthermore, in the present study, the diagnosis of IPF was dependent on the HRCT findings. Almost no patients had undergone transbronchial lung biopsies or surgical lung biopsies. As such, the baseline characteristics of patients clinically diagnosed with IPF cannot be unified accurately. Third, determining complication with an infection is the most important factor in the diagnosis of IPF-AE. Few patients underwent bronchoalveolar lavage; therefore, we cannot completely rule out the possibility of infection. However, significant efforts were made to exclude infection using sputum or blood cultures, serum antigen or antibody for pathogenic organisms, and serum β-D-glucan. Patients with obvious infections were excluded from this study. Finally, the dose of corticosteroids and the choice of immunosuppressive therapy for IPF-AE were not prescribed at our institute. Therefore, it was difficult to evaluate the maintenance dose of corticosteroid therapy and the choice of antifibrotic therapy as prognostic factors. However, the dose of corticosteroid pulse therapy had no significant effect on the prognosis. We cannot rule out that these above factors might have affected the outcome of the analyses. To clarify the accurate prognostic factors, it will be necessary to conduct a clinical trial with a protocol prescribing the usage of corticosteroids, immunosuppressants, and anti-fibrotic drugs.

Evidence of the benefits of early intervention has not yet been included in the treatment guidelines for interstitial pneumonia. Our study results raise the important question of whether or not early intervention for IPF-AE patients with corticosteroid pulse therapy affects the prognosis. Our findings also highlight the importance of the early diagnosis of IPF-AE. It may be beneficial to advise patients with IPF to be attentive to their health status and to visit the hospital as soon as possible if they become aware of the worsening of symptoms such as cough, dyspnea, or a fever.

In summary, we have shown an association between an increased delay in treatment and an increased risk of death in IPF-AE patients. We conclude that the time interval between the onset of symptoms and initiation of corticosteroid pulse therapy is an independent prognostic factor in patients with IPF-AE. Further study is needed to validate our results.

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