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Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema

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Abstract

Objectives: To analyze the clinical characteristics and prognosis of acute exacerbation (AE) in patients with idiopathic pulmonary fibrosis (IPF) and pulmonary emphysema.

Design: A multicenter retrospective cohort study

Setting: Two university hospitals in Japan

Participants: Patients admitted to hospitals due to AE of IPF diagnosed based on a multidisciplinary discussion.

Interventions: None

Primary and secondary outcome measures: 90-day mortality rate

Methods: We retrospectively analyzed consecutive patients with AE of IPF, with or without pulmonary emphysema, admitted to two university hospitals between 2007 and 2018.

Results: Among 62 patients (median age, 75 years; 48 men) admitted for AE of IPF, 29 patients (46%) presented with concomitant pulmonary emphysema. There was no significant difference in the arterial partial oxygen pressure/fraction of inhaled oxygen (P/F) ratio or other laboratory and radiographic data between patients with and without emphysema. The 90-day mortality rate was significantly lower in patients with emphysema than in those with IPF alone (23% vs. 52%, $p = 0.03$). The median survival time was significantly longer in patients with emphysema than in those with IPF alone (405 vs. 242 days, $p = 0.02$).

Conclusion: Patients with IPF and emphysema had better short-term survival after AE than those with non-emphysematous IPF.

Strengths and limitations of this study

- We explored the prognosis of patients with combined pulmonary fibrosis and emphysema who developed acute exacerbations.
- The studied population was diagnosed based on a multidisciplinary discussion.
- We could not estimate the incidence of acute exacerbation among patients with idiopathic pulmonary fibrosis and emphysema because of the retrospective design of this study.

Background

Idiopathic pulmonary fibrosis (IPF) is characterized by chronic, progressive, fibrosing interstitial pneumonia of unknown etiology. The prognosis of IPF is poor, with a median survival time of 2–3 years. Acute exacerbation (AE) is the major cause of death in IPF patients, accounting for up to 40% of all deaths.[1] AE-IPF is defined as the worsening of respiratory failure with acute or subacute onset that cannot be explained by cardiac failure or fluid overload, which parallels the Berlin criteria for acute respiratory distress syndrome.[2]

Pulmonary emphysema is common in lungs with IPF, as the estimated prevalence of emphysema ranges between 25% and 50%.[3] Cottin et al. proposed the term combined pulmonary fibrosis and emphysema (CPFE), which comprises upper lobe-dominant emphysema and lower lobe-dominant fibrosis.[4] CPFE exhibits clinical characteristics, such as high prevalence in heavy smokers, relatively normal lung volumes accompanied by severely impaired gas exchange capacity, and a high risk for lung cancer and pulmonary arterial hypertension.[3-5] Data on the prognosis of IPF with emphysema are inconsistent among reports although recent studies have reported that the prognosis of CPFE is as poor as that of IPF alone.[6]

The incidence of AEs in patients with CPFE has been reported to be 9.4% per year [7], which is compatible with the annual rate of AEs in patients with IPF.[8] In contrast, AEs accounted for 31% of deaths in patients with IPF, but accounted for only 11.8% of deaths in patients with CPFE.[9] Other causes, such as lung cancer and pulmonary artery hypertension, may play a major role in the mortality of patients with IPF and emphysema.[3,4] Another possible explanation is that the prognosis of AE is better in patients with combined fibrosis and emphysema than in patients with IPF alone. Therefore, we analyzed the clinical characteristics and prognoses of patients with AE of IPF and pulmonary emphysema.

Methods

Patients

Consecutive patients admitted to two university hospitals for AE-IPF between January 2007 and August 2018 were retrospectively analyzed. IPF was diagnosed based on a multidisciplinary discussion (MDD) by two pulmonologists and a radiologist using the patients' clinical history, physical examination, laboratory test results, and radiographic data from high-resolution computed tomography (HRCT).

AE-IPF was diagnosed based on the following criteria:[2] 1) previous or concurrent diagnosis of IPF; (2) acute worsening or development of dyspnea typically of duration <1 month; 3) computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with the usual interstitial pneumonia pattern; and 4) deterioration not fully explained by cardiac failure or fluid overload. The patients with neoplasms undergoing active treatment, including radiation therapy, chemotherapy with cytotoxic or molecular-targeted drugs, or immunotherapy with immune checkpoint inhibitors, at the onset of AE were excluded.

AE-IPF was treated with an appropriate administration of oxygen and pharmacotherapy using prednisone (0.5–1 mg/kg per day) with or without preceding methylprednisolone pulse therapy (1 g/day for 3 days). The prednisone dose was tapered based on the response to therapy. In refractory cases, immunosuppressive therapy with intravenous cyclophosphamide (500 mg every 2–4 weeks) may have been added.

This study was approved by the Institutional Review Board of Tokai University Hospital (17R-198) and Tokai University Oiso Hospital (18R-241), and was conducted in compliance with the principles of the Declaration of Helsinki. Informed consent was obtained from the Tokai University Hospital website as an opt-out. Patients who rejected were excluded.

Clinical and laboratory parameters

The clinical and laboratory data within 12 months prior to and at the onset of AE were collected from medical charts. Spirometry was performed during stable disease using a

Super Spiro DISCOM-21FX III spirometer (CHEST Corp., Tokyo, Japan) by trained clinical technicians. The predicted values of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were calculated using a previously reported equation.[10] In patients without arterial blood gas data at the time of admission, the partial pressure of arterial oxygen (PaO_2) was calculated based on percutaneous arterial oxygen saturation (SpO_2) using the Hill formula.[11] The serum levels of Krebs von Lungen-6 (KL-6) were measured using an electrochemi-luminescence immunoassay and Lumipulse G1200 Analyzer (Rebio, Fuji, Japan). The surfactant protein D (SP-D) levels were measured using commercially available enzyme-linked immunosorbent assay kits (RayBiotech, Norcross, GA, USA).

Radiographic evaluation of thoracic CT and diagnosis IPF

Thoracic CT with 1.5-mm-thick axial sections was obtained at 1-cm intervals throughout the entire thorax in the inspiratory phase. Emphysema was defined as demarcated areas of decreased attenuation compared to contiguous normal lung tissue and marginated by a very thin or no wall, with upper-zone predominance. The existence of emphysema and diagnostic categories of usual interstitial pneumonia (UIP) based on CT patterns [12,13] were diagnosed based on a discussion between two pulmonologists and a radiologist.

Statistical analysis

The data are expressed as mean ± standard deviation or median and interquartile range for continuous variables, and number and percentage for categorical data. Group comparisons were made using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Kaplan–Meier survival curves and log-rank tests were used to evaluate the survival. Cox proportional hazards regression analysis of mortality within 90 days was performed using age, sex, and other factors with $p < 0.1$ in univariate analysis and data available in > 90% of the cases. A statistical analysis was performed using IBM SPSS

Statistics software ver. 21 (IBM, Chicago, IL, USA). The level of statistical significance was set at $p < 0.05$.

Patient and public involvement

This was a retrospective cohort study with no direct patient and public engagement.

Results

Clinical characteristics prior to AE

We identified 62 patients (median age, 75 years; 48 men and 14 women) admitted to hospitals due to AE-IPF during the study period. Notably, 29 patients (46.7%) had emphysema (IPF with emphysema group) and 33 patients had IPF without emphysema (IPF alone group).

The clinical characteristics at baseline (within 12 months before AE) are presented in Table 1. All the patients with emphysema were smokers, whereas 19 patients (58%) with IPF alone were never smokers. The total exposure to cigarette smoke (pack-years) was greater in the IPF with emphysema group than in the IPF alone group ($p < 0.001$). Age, sex, and proportion of patients with lung cancer, under long-term oxygen therapy, or on pharmacotherapy with prednisolone or antifibrotic agents were not significantly different between the groups. The data of pulmonary function tests within one year prior to AE were available in 20 cases in the IPF with emphysema group and 17 cases in the IPF alone group. The FVC, %FVC of the predicted value, and FEV_1 were significantly higher in the IPF with emphysema group (p = 0.045, 0.002, and 0.001, respectively), whereas the FEV_1/FVC was not significantly different between the groups. The diagnostic categories of UIP based on CT patterns were not significantly different between the groups. One case, which was categorized as an alternative pattern, was diagnosed as IPF upon autopsy.

Table 1. Baseline characteristics in patients with idiopathic pulmonary fibrosis with or without concomitant pulmonary emphysema

Characteristic	IPF with emphysema (n=29)	IPF alone (n=33)	P value
Age, years	74±6	76 ± 8	0.20
Male, n (%)	28 (97%)	20 (60%)	
Smoking status			
Smokers, n (%)	29 (100%)	14 (42%)	<0.001
Pack-years	59±68	12 ± 20	<0.001
Lung cancer, n (%)	2 (7%)	1 (3%)	0.59
KL-6 in serum (U/mL)	1266±697 (n=24)	1255 ± 817 (n=26)	0.741
Pulmonary functions	n=20	n=17	
FVC (L)	2.26±0.68	1.54 ± 0.61	0.045
FVC, %predicted	69.4±20.3	56.8 ± 22.4	0.002
FEV_1 (L)	1.9±0.5	1.3±0.4	0.001
FEV_1/FVC (%)	85.9±7.6	89.3 ± 9.2	0.110
Thoracic computed tomography			
CT pattern (2018 IPF guideline)			
Definite/Probable/Indeterminate/Alternative	21/7/0/1	14/19/0/0	0.08
Treatment, n (%)			
Prednisolone	7 (24%)	8 (24%)	0.99
Antifibrotic agents	6 (20%)	3 (9%)	0.13

IPF, interstitial pulmonary fibrosis; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; KL-6, Krebs von Lungen-6

Clinical characteristics upon admission due to AE

The laboratory data upon admission, such as leukocyte counts in peripheral blood and serum levels of lactate dehydrogenase, were not significantly different between the IPF with emphysema and IPF alone groups (Table 2). In addition, the fraction of inhaled oxygen (FIO_2) and the PaO_2/FIO_2 (P/F) ratio were not significantly different between the groups. The serum KL-6 and SP-D levels were higher in the IPF with emphysema group (p = 0.05 and 0.025, respectively).

Table 2. Clinical characteristics on admission due to acute exacerbation

	IPF with emphysema (n=29)	IPF alone (n=33)	P value
Respiratory rate (/min)	23±5	25±6	0.18
Laboratory data			
Leukocytes (×10^3 /μL)	10.1±3.1	11.0±5.1	0.27
Lactate dehydrogenase (U/L)	377±164	372±103	0.60
KL-6 (U/mL)	2109±1249	1644±1193	0.049
SP-D (U/mL) (n=46)	599±380 (n=24)	388±305 (n=22)	0.025
BNP (pg/mL) (n=47)	116±149 (n=24)	166±194 (n=23)	0.25
FIO_2	0.38±0.24	0.33±0.20	0.94
P/F ratio	233±105	221±80	0.51
Treatment, n (%)			
Drug			
High dose corticosteroids	29 (100%)	32 (97%)	-
Methylprednisolone pulse therapy	17 (58%)	22 (66%)	0.51
Immunosuppressive therapy	3 (10%)	4 (12%)	0.45
Oxygen therapy			
High flow nasal cannula	4 (13%)	8 (24%)	0.29
NIPPV	0 (0%)	2 (6%)	0.49
IPPV	0 (0%)	2 (6%)	0.49

AE, acute exacerbation; IPF, interstitial pulmonary fibrosis; KL-6, Krebs von Lungen-6; SP-D, surfactant protein D; P/F ratio, PaO_2/FIO_2 ratio; SIRS, systemic inflammatory response syndrome; NIPPV, non-invasive intermittent positive pressure ventilation; IPPV, intermittent positive pressure ventilation.

All the patients, except for one patient who was not treated with prednisolone, were treated with high-dose prednisolone and oxygen therapy. There was no difference in the proportion of patients treated with methylprednisolone pulse therapy and/or immunosuppressive therapy between the groups. Four patients with IPF and emphysema and 12 patients with IPF alone required a high-flow nasal cannula or positive-pressure ventilation for the treatment of respiratory failure.

Short-term prognosis within 90 days after admission

Nine (15%), 15 (24%), and 23 (38%) patients died within 7, 30, and 90 days of admission due to AE-IPF, respectively. The survivors were more likely to have emphysema (56%) than the deceased (30%), with an odds ratio of 0.27 (95% CI, 0.07–0.88; p = 0.02). FVC and P/F

ratio were lower (p = 0.02 and 0.06, respectively) in the deceased patients (Table 3). The survival rate was significantly higher in patients with emphysema than in those without emphysema (p = 0.03), and the 90-days survival rate was higher in patients with emphysema (76% and 50%, respectively; Figure 1). The age, sex, smoking history (pack-years), serum KL-6 levels, comorbidity of lung cancer, long-term oxygen therapy, and the proportion of patients using prednisolone and/or antifibrotic agents before AE were not significantly different between patients who died and those who survived for the first 90 days (Table 3). A Cox proportional hazards regression analysis revealed that the presence of emphysema (hazard ratio 0.33 [95%CI 0.14–0.82], p = 0.01) and P/F ratio (hazard ratio 0.99 [95%CI 0.98–0.99], p = 0.01) were predictors of mortality within 90 days after adjustment for age and sex (Table 4).

Table 3. Clinical characteristics of non-survivors and survivors at day 90

	Non-survivors at day 90 (n=23)	Survivors at day 90 (n=36)	P value
Baseline clinical characteristics			
Age, years	77±6	73±7	0.25
male, n (%)	17 (74%)	32 (89%)	0.18
Smoking status			
Smokers, n (%)	12 (52%)	26 (72%)	0.11
Pack-years	22±27	42.3±33.1	0.13
Pulmonary functions	n=13	n=23	
FVC (L)	1.56±0.72	2.23±0.67	0.02
FVC, %predicted	56.4±27.3	70.6±17.1	0.12
FEV_1/FVC (%)	89.5±9.5	86.3±7.6	0.24
Thoracic computed tomography			
Emphysema, n (%)	7 (30%)	20 (56%)	0.02
CT pattern (2018 IPF guideline)			
Definite/Probable/Indeterminate/Alternative	13/10/0/0	22/13/0/1	0.35
Treatment, n (%)			
Long-term oxygen therapy	5 (21%)	7 (19%)	0.83
Prednisolone	6 (26%)	8 (22%)	0.73
Antifibrotic agents	2 (7%)	6 (16%)	0.22
Clinical data on admission			
Respiratory rate (/min)	26±5	23±6	0.18
Laboratory data			
Leukocytes ($\times 10^3$ /μL)	11.2±3.5	11.0±5.1	0.34

Lactate dehydrogenase (U/L)	380±106	372±103	0.42
KL-6 (U/mL)	1926±1642	1644±1193	0.63
SP-D (U/mL)	352±147 (n=15)	388±305 (n=22)	0.23
FIO_2	0.40±0.29	0.34±0.20	0.3
P/F ratio	194±94	241±90	0.06
Treatments, n (%)			
Drugs			
Methylprednisolone pulse therapy	17 (74%)	22 (61%)	0.60
Immunosuppressive therapy	3 (13%)	4 (11%)	0.14
Oxygen therapy			
High flow nasal cannula	7 (30%)	5 (14%)	0.11
NPPV	2 (9%)	0 (0%)	0.16
IPPV	1 (4%)	1 (3%)	1.00

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IPPV, intermittent positive pressure ventilation; KL-6, Krebs von Lungen-6; NIPPV, non-invasive intermittent positive pressure ventilation; P/F ratio, PaO_2/FIO_2 ratio; SIRS, systemic inflammatory response syndrome; SP-D, surfactant protein D.

Table 4. Cox proportional hazards regression analysis of mortality within 90 days

	Hazard ratio	95% confidence interval	P value
Pulmonary emphysema	0.33	0.14-0.82	0.01
PaO_2/FIO_2 ratio	0.99	0.98-0.99	0.01

Adjusted for age and sex

In the multivariate analysis, FVC was not included because of the high rate of missing values. Therefore, we performed a sub-analysis by dividing the patients into four subgroups according to the presence or absence of emphysema and baseline FVC (≥60% or <60% of the predicted value). A Kaplan–Meier estimate according to this subgrouping revealed that the presence of emphysema tended to have a good prognosis regardless of the %FVC (Supplemental Figure 1). A Cox proportional hazards regression analysis including

the %FVC revealed that the presence of emphysema remained a predictor of mortality within 90 days (hazard ratio, 0.30 [95%CI 0.09–0.98], $p = 0.04$). (Supplemental Table 1)

Long-term prognosis

Notably, 49 patients, including 21 patients in the IPF with emphysema group and 28 patients in the IPF alone group, died during the observation period (median: 325 days, range: 2–1721 days). Although there was no difference in the total mortality between the groups, the median survival time was significantly longer in the IPF with emphysema group than in the IPF alone group (405 days vs. 254 days, $p = 0.02$, Table 5).

Table 5. Prognosis after acute exacerbation of IPF

	IPF with emphysema	IPF alone	P value
All patients	n = 29	n = 33	
Median survival time, days	405 (2-1544)	254 (2-1721)	0.02
Survivors at day 90	n = 22	n = 16	
Median survival time, days	573 (110-1544)	565 (106-1721)	0.96
Cause of death			
Acute exacerbation, n (%)	4 (20%)	6 (38%)	0.14
Chronic respiratory failure, n (%)	3 (14%)	4 (25%)	0.81
Pneumonia, n (%)	3 (14%)	0 (0%)	0.51
Unknown, n (%)	4 (20%)	1 (6%)	-

IPF, idiopathic pulmonary fibrosis

There were 38 patients who survived 90 days or more after admission due to AE-IPF, including 22 patients with emphysema and 16 patients without emphysema (Table 5). In these acute phase survivors, the long-term prognosis was not significantly different between patients with and without emphysema ($p = 0.8$) (Supplemental Figure 2). The median survival times for the IPF with emphysema and IPF alone groups were 573 and 565 days, respectively ($p = 0.96$). The leading cause of death in survivors was the exacerbation of IPF, regardless of the presence of emphysema (Table 5).

Discussion

We retrospectively analyzed 62 consecutive patients admitted for AE-IPF in two hospitals. Approximately half of the patients with AE-IPF exhibited pulmonary emphysema, who showed higher exposure to cigarette smoking, better FVC before AE, and higher levels of KL-6 and SP-D at AE. The patients with emphysema had better short-term survival than those without emphysema, although the long-term survival of the survivors was equivalent.

Several possibilities may explain why the presence of emphysema was associated with better short-term prognosis in patients with IPF. First, the higher baseline FVC observed in the IPF with emphysema group may have contributed to a better survival rate. However, several studies have demonstrated that higher FVC values were not associated with better prognosis in patients with AE of chronic fibrosing interstitial pneumonia (CFIP).[14,15] Furthermore, the co-presence of emphysema may have masked the decrease in FVC in the IPF with emphysema group and greater FVC does not suggest a better capacity for alveolar gas exchange, which is essential for favorable oxygenation. In fact, there was no difference in the P/F ratio at exacerbation, an essential factor associated with the poor prognosis of AE-IPF, between patients with and without emphysema. Ikuyama et al. also reported that patients with CPFE had better baseline %FVC and better prognosis after exacerbation than those with IPF alone;[16] however, there was no difference in the %DLCO or GAP score between the groups. Therefore, the higher baseline FVC observed in the IPF with emphysema group is unlikely to be the cause of the better short-term prognosis in these patients. Although substantial FVC data were lacking in the present study, pulmonary emphysema was an independent factor in determining the short-term prognosis even after adjustment for FVC values.

Ikuyama et al. reported that patients with CPFE exhibited significantly lower serum KL-6 levels on admission and postulated that lung damage was less extensive in these patients. [16] Another recent study also reported that higher serum KL-6 levels on admission were

associated with a poorer prognosis in patients with AE-IPF.[17] However, in our study, the serum KL-6 levels were higher in patients with IPF and emphysema. Therefore, patients with IPF and emphysema had better short-term survival, regardless of their serum KL-6 levels on admission.

The heterogeneity of prognosis in patients with AE-IPF may be due to different pathological changes in the lungs during AE. Diffuse alveolar damage is the major pathological finding in the lungs with AE-IPF in autopsy cases, accounting for approximately 80% of cases, followed by alveolar hemorrhage.[18] In contrast, lung specimens obtained by surgical biopsy often show organizing pneumonia. Churg et al.[19] reported that 6 of 12 patients with AE-CFIP presented with organizing pneumonia and survived the acute phase, whereas half of the patients presenting with diffuse alveolar damage died. Currently, there is no histopathological information explaining the different prognoses of AE-IPF due to emphysema, and further studies are required.

The Kaplan–Meier estimate revealed significantly better short-term survival in the IPF with emphysema group than in the IPF alone group. However, in the survivors of acute phase, long-term prognosis was not significantly different between patients with and without emphysema. The major cause of death was AE-IPF, observed in 33 cases, comprising 11 patients (52%) with emphysema and 22 patients (81%) without emphysema. This observation may be consistent with a previous report which stated that patients with IPF who never smoked and developed AE had poorer prognoses than those with IPF who smoked.[17]

This study has several limitations. First, this was a retrospective study of cases in two clinical centers; therefore, the number of patients studied was limited. In addition, we could not estimate the incidence of AEs in patients with IPF and pulmonary emphysema because of the retrospective design of this study. Prospective multicenter studies, such as the Japan Idiopathic Interstitial Pneumonias Registry are currently ongoing in Japan and are warranted. Second, due to the real-world nature of the study, some clinical data, especially data on the

diffusion capacity and/or the six-minute walk test, which are used to calculate GAP scores to evaluate the IPF severity,[20,21] were missing in most cases. However, we propose that the presence or absence of emphysema on thoracic CT may be associated with the prognosis of AE, which is a leading cause of death in patients with IPF.

Conclusion

Patients with AE-IPF and concomitant pulmonary emphysema had better short-term prognoses than those without emphysema. Further studies are required to identify the histopathological characteristics of AE-IPF lungs with emphysema associated with better prognosis.

Abbreviations

AE, acute exacerbation; CFIP, chronic fibrosing interstitial pneumonia; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; FEV_1, forced expiratory volume in one second; FIO_2, fraction of inhaled oxygen; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von Lungen-6; PaO_2, arterial partial oxygen pressure; P/F ratio, PaO_2/FIO_2 ratio; SpO_2, oxygen saturation measured by pulse oximetry; SP-D, surfactant protein D

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Availability of data and material

The dataset used in this study is available from the corresponding author upon request.

Authors' contributions

YH, TT, and KA participated in the conception and design of the study, analyzed and interpreted the data, and wrote the manuscript. YH, TT, and KN evaluated radiological images. FT, KE, JT, KT, KN, ST, NH, YI, and TO collected and analyzed the clinical data. All authors read and approved the final draft.

Competing interests

The authors declare no competing interests regarding of this study.

Consent for publication

Informed consent was obtained from the Tokai University Hospital website as an opt-out. Patients who were rejected were excluded.

Ethics approval

This study was approved by the Institutional Review Board of Tokai University Hospital (17R-198) and Tokai University Oiso Hospital (18R-241).

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Figure legends

Figure1.

Kaplan–Meier survival curves for patients admitted to the hospital with AE-IPF with pulmonary emphysema (solid line, n = 29) and without emphysema (dashed line, n = 33).

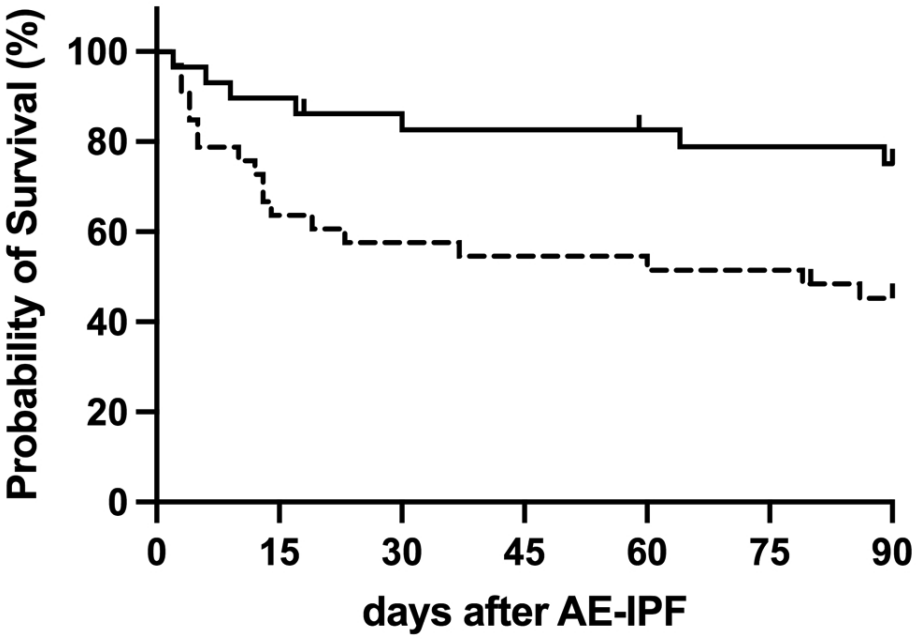

Figure 1

90x62mm (300 x 300 DPI)

Supplemental material

Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema

Yukihiro Horio[1], Takahisa Takihara[1], Fuminari Takahashi[3], Keito Enokida[1], Noriko Nakamura[2], Jun Tanaka[1], Katsuyoshi Tomomatsu[1], Kyoko Niimi[1], Sakurako Tajiri[3], Naoki Hayama[1], Yoko Ito[1] Tsuyoshi Oguma[1], and Koichiro Asano[1]

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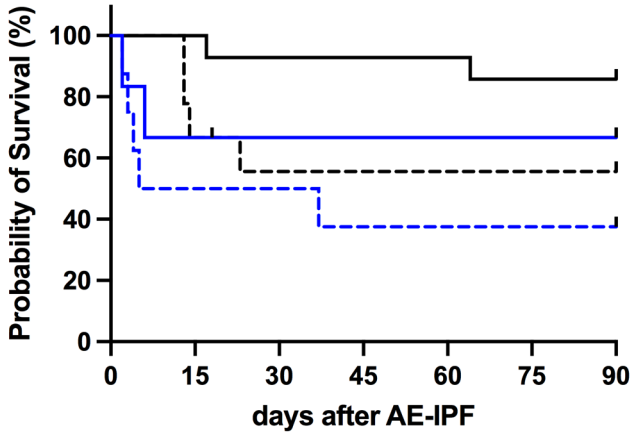
Supplemental Table 1. Cox proportional hazards regression analysis of mortality within 90 days including data of forced vital capacity (FVC)

	Hazard ratio	95% confidence interval	P value
Emphysema	0.30	0.09-0.98	0.04

adjusted for age, sex, and %FVC>60%

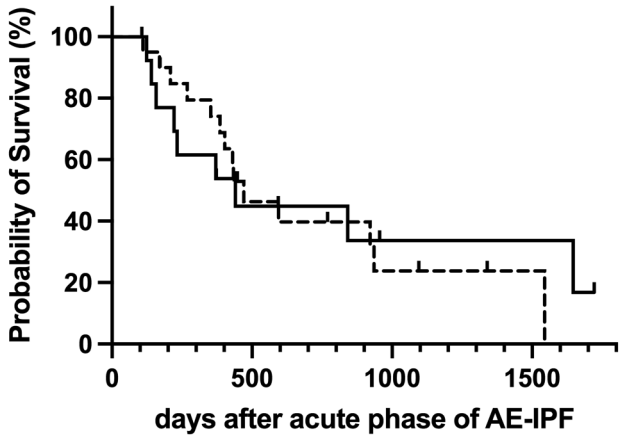
FVC; forced vital capacity

Supplemental Figure 1



Kaplan–Meier survival curves for patients admitted to hospitals due to acute exacerbation of idiopathic pulmonary fibrosis. The patients were divided into four subgroups according to the presence or absence of pulmonary emphysema and baseline forced vital capacity (FVC ≥60% or <60% of the predicted value): group 1 (black solid line, n = 14, with emphysema and baseline FVC ≥ 60%), group 2 (black dashed line, n = 9, without emphysema and baseline FVC ≥ 60%), group 3 (blue solid line, n = 6, with emphysema and baseline FVC < 60%), and group 4 (blue dashed line, n = 8, without emphysema and baseline FVC < 60%).

Supplemental Figure 2



Kaplan-Meier survival curves for acute phase survivors (90 days) after acute exacerbation of idiopathic pulmonary fibrosis with pulmonary emphysema (solid line, n = 22) and without emphysema (dashed line, n = 16).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1.2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10

		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema: a retrospective cohort study in Japan

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Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema: a retrospective cohort study in Japan

Yukihiro Horio[1], Takahisa Takihara[1], Fuminari Takahashi[3], Keito Enokida[1], Noriko Nakamura[2], Jun Tanaka[1], Katsuyoshi Tomomatsu[1], Kyoko Niimi[1], Sakurako Tajiri[3], Naoki Hayama[1], Yoko Ito[1] Tsuyoshi Oguma[1], and Koichiro Asano[1]

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Abstract

Objectives: To analyze the clinical characteristics and prognosis of acute exacerbation (AE) in patients with idiopathic pulmonary fibrosis (IPF) and pulmonary emphysema.

Design: A multicenter retrospective cohort study

Setting: Two university hospitals in Japan

Participants: Patients admitted to hospitals due to AE of IPF diagnosed based on a multidisciplinary discussion.

Interventions: None

Primary and secondary outcome measures: 90-day mortality rate

Methods: We retrospectively analyzed consecutive patients with AE of IPF, with or without pulmonary emphysema, admitted to two university hospitals between 2007 and 2018.

Results: Among 62 patients (median age, 75 years; 48 men) admitted for AE of IPF, 29 patients (46%) presented with concomitant pulmonary emphysema. There was no significant difference in the arterial partial oxygen pressure/fraction of inhaled oxygen (P/F) ratio or other laboratory and radiographic data between patients with and without emphysema. The 90-day mortality rate was significantly lower in patients with emphysema than in those with IPF alone (23% vs. 52%, $p = 0.03$). The median survival time was significantly longer in patients with emphysema than in those with IPF alone (405 vs. 242 days, $p = 0.02$).

Conclusion: Patients with IPF and emphysema had better short-term survival after AE than those with non-emphysematous IPF.

Strengths and limitations of this study

- The studied population was patients with idiopathic pulmonary fibrosis (IPF) who developed acute exacerbations.
- The diagnosis of IPF, emphysema, and acute exacerbation was based on a multidisciplinary discussion by pulmonary physicians and a radiologist.
- The number of patients studied was limited as a retrospective study in two clinical centers.
- The incidence of acute exacerbation among patients with IPF with or without emphysema could not be analuzed because of the retrospective design of this study.
- Some data such as pulmonary function tests prior to acute exacerbation were not available.

Background

Idiopathic pulmonary fibrosis (IPF) is characterized by chronic, progressive, fibrosing interstitial pneumonia of unknown etiology. The prognosis of IPF is poor, with a median survival time of 2–3 years. Acute exacerbation (AE) is the major cause of death in IPF patients, accounting for up to 40% of all deaths.[1] AE-IPF is defined as the worsening of respiratory failure with acute or subacute onset that cannot be explained by cardiac failure or fluid overload, which parallels the Berlin criteria for acute respiratory distress syndrome.[2]

Pulmonary emphysema is common in lungs with IPF, as the estimated prevalence of emphysema ranges between 25% and 50%.[3] Cottin et al. proposed the term combined pulmonary fibrosis and emphysema (CPFE), which comprises upper lobe-dominant emphysema and lower lobe-dominant fibrosis.[4] CPFE exhibits clinical characteristics, such as high prevalence in heavy smokers, relatively normal lung volumes accompanied by severely impaired gas exchange capacity, and a high risk for lung cancer and pulmonary arterial hypertension.[3-5] Data on the prognosis of IPF with emphysema are inconsistent among reports although recent studies have reported that the prognosis of CPFE is as poor as that of IPF alone.[6]

The incidence of AEs in patients with CPFE has been reported to be 9.4% per year [7], which is compatible with the annual rate of AEs in patients with IPF.[8] In contrast, AEs accounted for 31% of deaths in patients with IPF, but accounted for only 11.8% of deaths in patients with CPFE.[9] Other causes, such as lung cancer and pulmonary artery hypertension, may play a major role in the mortality of patients with IPF and emphysema.[3,4] Another possible explanation is that the prognosis of AE is better in patients with combined fibrosis and emphysema than in patients with IPF alone. Therefore, we analyzed the clinical characteristics and prognoses of patients with AE of IPF and pulmonary emphysema.

Methods

Patients

Consecutive patients admitted to two university hospitals for AE-IPF between January 2007 and August 2018 were retrospectively analyzed. IPF was diagnosed based on a multidisciplinary discussion (MDD) by two pulmonologists and a radiologist using the patients' clinical history, physical examination, laboratory test results, and radiographic data from high-resolution computed tomography (HRCT).

AE-IPF was diagnosed based on the following criteria:[2] 1) previous or concurrent diagnosis of IPF; (2) acute worsening or development of dyspnea typically of duration <1 month; 3) computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with the usual interstitial pneumonia pattern; and 4) deterioration not fully explained by cardiac failure or fluid overload. The patients with neoplasms undergoing active treatment, including radiation therapy, chemotherapy with cytotoxic or molecular-targeted drugs, or immunotherapy with immune checkpoint inhibitors, at the onset of AE were excluded.

AE-IPF was treated with an appropriate administration of oxygen and pharmacotherapy using prednisone (0.5–1 mg/kg per day) with or without preceding methylprednisolone pulse therapy (1 g/day for 3 days). The prednisone dose was tapered based on the response to therapy. In refractory cases, immunosuppressive therapy with intravenous cyclophosphamide (500 mg every 2–4 weeks) may have been added.

This study was approved by the Institutional Review Board of Tokai University Hospital (17R-198) and Tokai University Oiso Hospital (18R-241), and was conducted in compliance with the principles of the Declaration of Helsinki. Informed consent was obtained from the Tokai University Hospital website as an opt-out. Patients who rejected were excluded.

Clinical and laboratory parameters

The clinical and laboratory data within 12 months prior to and at the onset of AE were collected from medical charts. Spirometry was performed during stable disease using a

Super Spiro DISCOM-21FX III spirometer (CHEST Corp., Tokyo, Japan) by trained clinical technicians. The predicted values of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were calculated using a previously reported equation.[10] In patients without arterial blood gas data at the time of admission, the partial pressure of arterial oxygen (PaO_2) was calculated based on percutaneous arterial oxygen saturation (SpO_2) using the Hill formula.[11] The serum levels of Krebs von Lungen-6 (KL-6) were measured using an electrochemi-luminescence immunoassay and Lumipulse G1200 Analyzer (Rebio, Fuji, Japan). The surfactant protein D (SP-D) levels were measured using commercially available enzyme-linked immunosorbent assay kits (RayBiotech, Norcross, GA, USA).

Radiographic evaluation of thoracic CT and diagnosis IPF

Thoracic CT with 1.5-mm-thick axial sections was obtained at 1-cm intervals throughout the entire thorax in the inspiratory phase. Emphysema was defined as demarcated areas of decreased attenuation compared to contiguous normal lung tissue and marginated by a very thin or no wall, with upper-zone predominance. The extent of emphysema was evaluated by low attenuation area (LAA) score in chest CT according to the method proposed by Goddard et al. [12] The cases with LAA score > 0 was classified in the emphysema group. The existence of emphysema and diagnostic categories of usual interstitial pneumonia (UIP) based on CT patterns [12,13] were diagnosed based on a discussion between two pulmonologists and a radiologist.

Statistical analysis

The data are expressed as mean ± standard deviation or median and interquartile range for continuous variables, and number and percentage for categorical data. Group comparisons were made using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Kaplan–Meier survival curves and log-rank tests were used to evaluate the survival. Cox proportional hazards regression analysis of mortality within 90

days was performed using age, sex, and other factors with $p < 0.1$ in univariate analysis and data available in > 90% of the cases. A statistical analysis was performed using IBM SPSS Statistics software ver. 21 (IBM, Chicago, IL, USA). The level of statistical significance was set at $p < 0.05$.

Patient and public involvement

This was a retrospective cohort study with no direct patient and public engagement.

Results

Clinical characteristics prior to AE

Among 103 patients admitted to hospitals due to acute respiratory failure of idiopathic interstitial pneumonia during the study period, we identified 62 patients with AE-IPF (median age, 75 years; 48 men and 14 women, Supplemental Figure 1). Notably, 29 patients (46.7%) had emphysema (IPF with emphysema group) and 33 patients had IPF without emphysema (IPF alone group).

The clinical characteristics at baseline (within 12 months before AE) are presented in Table 1. All the patients with emphysema were smokers, whereas 19 patients (58%) with IPF alone were never smokers. The total exposure to cigarette smoke (pack-years) was greater in the IPF with emphysema group than in the IPF alone group ($p < 0.001$). Age, sex, body mass index, proportion of patients with co-morbidities, under long-term oxygen therapy, or on pharmacotherapy with prednisolone or antifibrotic agents were not significantly different between the groups. The data of pulmonary function tests within one year prior to AE were available in 20 cases in the IPF with emphysema group and 17 cases in the IPF alone group. The FVC, %FVC of the predicted value, and FEV_1 were significantly higher in the IPF with emphysema group ($p = 0.045$, 0.002, and 0.001, respectively), whereas the FEV_1/FVC was not significantly different between the groups. The diagnostic categories of UIP based on CT

patterns were not significantly different between the groups. One case, which was categorized as an alternative pattern, was diagnosed as IPF upon autopsy.

Table 1. Baseline characteristics in patients with idiopathic pulmonary fibrosis with or without concomitant pulmonary emphysema

Characteristic	IPF with emphysema (n=29)	IPF alone (n=33)	P value
Age, years	74±6	76 ± 8	0.20
Male, n (%)	28 (97%)	20 (60%)	
Body mass index	21.9 ± 3.2 (n=25)	22.7 ± 4.3 (n=29)	0.40
Smoking status			
Smokers, n (%)	29 (100%)	14 (42%)	<0.001
Pack-years	59±68	12 ± 20	<0.001
Co-morbidity			
Lung cancer, n (%)	2 (7%)	1 (3%)	0.59
Any cancer, n (%)	5 (17%)	3 (9%)	0.33
Diabetes mellitus, n (%)	6 (21%)	10 (30%)	0.38
Chronic heart failure, n (%)	6 (21%)	13 (39%)	0.11
Chronic renal failure, n (%)	0 (0%)	2 (6%)	0.59
Chronic respiratory infection, n (%)	1 (3%)	1 (3%)	0.93
Laboratory data			
KL-6 in serum (U/mL)	1266±697 (n=24)	1255 ± 817 (n=26)	0.74
Albumin in serum (g/mL)	3.7 ± 0.5 (n=20)	3.7 ± 0.3 (n=23)	0.64
Pulmonary functions	n=20	n=17	
FVC (L)	2.26±0.68	1.54 ± 0.61	0.045
FVC, %predicted	69.4±20.3	56.8 ± 22.4	0.002
FEV_1 (L)	1.9±0.5	1.3±0.4	0.001
FEV_1/FVC (%)	85.9±7.6	89.3 ± 9.2	0.11
Thoracic computed tomography			
CT pattern (2018 IPF guideline)			
Definite/Probable/Indeterminate/Alternative	21/7/0/1	14/19/0/0	0.08
Low-attenuation area score	5.8 ± 2.0	0.0 ± 0.0	#
Treatment, n (%)			
Prednisolone	7 (24%)	8 (24%)	0.99
Antifibrotic agents	6 (20%)	3 (9%)	0.13

IPF, interstitial pulmonary fibrosis; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; KL-6, Krebs von Lungen-6

Clinical characteristics upon admission due to AE

168 The laboratory data upon admission, such as leukocyte counts in peripheral blood and serum
169 levels of lactate dehydrogenase, were not significantly different between the IPF with
170 emphysema and IPF alone groups (Table 2). In addition, the fraction of inhaled oxygen (FIO_2)
171 and the PaO_2/FIO_2 (P/F) ratio were not significantly different between the groups. The serum
172 KL-6 and SP-D levels were higher in the IPF with emphysema group (p = 0.05 and 0.025,
173 respectively).

Table 2. Clinical characteristics on admission due to acute exacerbation

	IPF with emphysema (n=29)	IPF alone (n=33)	P value
Respiratory rate (/min)	23±5	25±6	0.18
Laboratory data			
Leukocytes (×10^3 /μL)	10.1±3.1	11.0±5.1	0.27
Lactate dehydrogenase (U/L)	377±164	372±103	0.60
KL-6 (U/mL)	2109±1249	1644±1193	0.049
SP-D (U/mL) (n=46)	599±380 (n=24)	388±305 (n=22)	0.025
BNP (pg/mL) (n=47)	116±149 (n=24)	166±194 (n=23)	0.25
FIO_2	0.38±0.24	0.33±0.20	0.94
P/F ratio	233±105	221±80	0.51
Treatment, n (%)			
Drug			
High dose corticosteroids	29 (100%)	32 (97%)	-
Methylprednisolone pulse therapy	17 (58%)	22 (66%)	0.51
Immunosuppressive therapy	3 (10%)	4 (12%)	0.45
Oxygen therapy			
High flow nasal cannula	4 (13%)	8 (24%)	0.29
NIPPV	0 (0%)	2 (6%)	0.49
IPPV	0 (0%)	2 (6%)	0.49
Do-not-resuscitation order, n (%)	29 (100%)	31 (94%)	0.92

AE, acute exacerbation; IPF, interstitial pulmonary fibrosis; KL-6, Krebs von Lungen-6; SP-D, surfactant protein D; P/F ratio, PaO_2/FIO_2 ratio; SIRS, systemic inflammatory response syndrome; NIPPV, non-invasive intermittent positive pressure ventilation; IPPV, intermittent positive pressure ventilation.

174 All the patients, except for one patient who was not treated with prednisolone, were treated
175 with high-dose prednisolone and oxygen therapy. There was no difference in the proportion
176 of patients treated with methylprednisolone pulse therapy and/or immunosuppressive

therapy between the groups. Four patients with IPF and emphysema and 12 patients with IPF alone required a high-flow nasal cannula or positive-pressure ventilation for the treatment of respiratory failure.

Short-term prognosis within 90 days after admission

Nine (15%), 15 (24%), and 23 (38%) patients died within 7, 30, and 90 days of admission due to AE-IPF, respectively. The survivors were more likely to have emphysema (56%) than the deceased (30%), with an odds ratio of 0.27 (95% CI, 0.07–0.88; $p = 0.02$). FVC and P/F ratio were lower ($p = 0.02$ and 0.06, respectively) in the deceased patients (Table 3). The survival rate was significantly higher in patients with emphysema than in those without emphysema ($p = 0.03$), and the 90-days survival rate was higher in patients with emphysema (76% and 50%, respectively; Figure 1). The age, sex, smoking history (pack-years), serum KL-6 levels, comorbidity of lung cancer, long-term oxygen therapy, and the proportion of patients using prednisolone and/or antifibrotic agents before AE were not significantly different between patients who died and those who survived for the first 90 days (Table 3). A Cox proportional hazards regression analysis revealed that the presence of emphysema (hazard ratio 0.33 [95%CI 0.14–0.82], $p = 0.01$) and P/F ratio (hazard ratio 0.99 [95%CI 0.98–0.99], $p = 0.01$) were predictors of mortality within 90 days after adjustment for age and sex (Table 4).

Table 3. Clinical characteristics of non-survivors and survivors at day 90

	Non-survivors at day 90 (n=23)	Survivors at day 90 (n=36)	P value
Baseline clinical characteristics			
Age, years	77±6	73±7	0.25
male, n (%)	17 (74%)	32 (89%)	0.18
Smoking status			
Smokers, n (%)	12 (52%)	26 (72%)	0.11
Pack-years	22±27	42.3±33.1	0.13
Pulmonary functions	n=13	n=23	
FVC (L)	1.56±0.72	2.23±0.67	0.02

FVC, %predicted	56.4±27.3	70.6±17.1	0.12
FEV_1/FVC (%)	89.5±9.5	86.3±7.6	0.24
Thoracic computed tomography			
Emphysema, n (%)	7 (30%)	20 (56%)	0.02
CT pattern (2018 IPF guideline)			
Definite/Probable/Indeterminate/Alternative	13/10/0/0	22/13/0/1	0.35
Treatment, n (%)			
Long-term oxygen therapy	5 (21%)	7 (19%)	0.83
Prednisolone	6 (26%)	8 (22%)	0.73
Antifibrotic agents	2 (7%)	6 (16%)	0.22
Clinical data on admission			
Respiratory rate (/min)	26±5	23±6	0.18
Laboratory data			
Leukocytes ($\times 10^3$ /μL)	11.2±3.5	11.0±5.1	0.34
Lactate dehydrogenase (U/L)	380±106	372±103	0.42
KL-6 (U/mL)	1926±1642	1644±1193	0.63
SP-D (U/mL)	352±147 (n=15)	388±305 (n=22)	0.23
FIO_2	0.40±0.29	0.34±0.20	0.3
P/F ratio	194±94	241±90	0.06
Treatments, n (%)			
Drugs			
Methylprednisolone pulse therapy	17 (74%)	22 (61%)	0.60
Immunosuppressive therapy	3 (13%)	4 (11%)	0.14
Oxygen therapy			
High flow nasal cannula	7 (30%)	5 (14%)	0.11
NPPV	2 (9%)	0 (0%)	0.16
IPPV	1 (4%)	1 (3%)	1.00

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IPPV, intermittent positive pressure ventilation; KL-6, Krebs von Lungen-6; NIPPV, non-invasive intermittent positive pressure ventilation; P/F ratio, PaO_2/FIO_2 ratio; SIRS, systemic inflammatory response syndrome; SP-D, surfactant protein D.

Table 4. Cox proportional hazards regression analysis of mortality within 90 days

	Hazard ratio	95% confidence interval	P value
Pulmonary emphysema	0.33	0.14-0.82	0.01
PaO_2/FIO_2 ratio	0.99	0.98-0.99	0.01

Adjusted for age and sex

In the multivariate analysis, FVC was not included because of the high rate of missing values. Therefore, we performed a sub-analysis by dividing the patients into four subgroups according to the presence or absence of emphysema and baseline FVC (≥60% or <60% of the predicted value). A Kaplan–Meier estimate according to this subgrouping revealed that the presence of emphysema tended to have a good prognosis regardless of the %FVC (Supplemental Figure 2). A Cox proportional hazards regression analysis including the %FVC revealed that the presence of emphysema remained a predictor of mortality within 90 days (hazard ratio, 0.30 [95%CI 0.09–0.98], $p = 0.04$). (Supplemental Table 1)

Long-term prognosis

Notably, 48 patients, including 21 patients in the IPF with emphysema group and 27 patients in the IPF alone group, died during the observation period (median: 325 days, range: 2–1721 days). Although there was no difference in the total mortality between the groups, the median survival time was significantly longer in the IPF with emphysema group than in the IPF alone group (405 days vs. 254 days, $p = 0.02$, Table 5).

Table 5. Prognosis after acute exacerbation of IPF

	IPF with emphysema	IPF alone	P value
All patients	n = 29	n = 33	
Median survival time, days	405 (2-1544)	254 (2-1721)	0.02
Survivors at day 90	n = 22	n = 16	
Median survival time, days	573 (110-1544)	565 (106-1721)	0.96
Cause of death	n = 14	n = 11	
Acute exacerbation, n (%)	4 (28%)	6 (55%)	0.24
Chronic respiratory failure, n (%)	3 (22%)	4 (36%)	0.66
Pneumonia, n (%)	3 (22%)	0 (0%)	0.23
Unknown, n (%)	4 (28%)	1 (9%)	-

IPF, idiopathic pulmonary fibrosis

There were 38 patients who survived 90 days or more after admission due to AE-IPF, including 22 patients with emphysema and 16 patients without emphysema (Table 5). In

these acute phase survivors, the long-term prognosis and cause of death was not significantly different between patients with and without emphysema (p = 0.8) (Supplemental Figure 3, Table 5). The median survival times for the IPF with emphysema and IPF alone groups were 573 and 565 days, respectively (p = 0.96). The leading cause of death in survivors was the exacerbation of IPF, regardless of the presence of emphysema (Table 5).

Discussion

We retrospectively analyzed 62 consecutive patients admitted for AE-IPF in two hospitals. Approximately half of the patients with AE-IPF exhibited pulmonary emphysema, who showed higher exposure to cigarette smoking, better FVC before AE, and higher levels of KL-6 and SP-D at AE. The patients with emphysema had better short-term survival than those without emphysema, although the long-term survival of the survivors was equivalent.

Several possibilities may explain why the presence of emphysema was associated with better short-term prognosis in patients with IPF. First, the higher baseline FVC observed in the IPF with emphysema group may have contributed to a better survival rate. However, several studies have demonstrated that higher FVC values were not associated with better prognosis in patients with AE of chronic fibrosing interstitial pneumonia (CFIP).[14,15] Furthermore, the co-presence of emphysema may have masked the decrease in FVC in the IPF with emphysema group and greater FVC does not suggest a better capacity for alveolar gas exchange, which is essential for favorable oxygenation. In fact, there was no difference in the P/F ratio at exacerbation, an essential factor associated with the poor prognosis of AE-IPF, between patients with and without emphysema. Ikuyama et al. also reported that patients with CPFE had better baseline %FVC and better prognosis after exacerbation than those with IPF alone;[16] however, there was no difference in the %DLCO or GAP score between the groups. Therefore, the higher baseline FVC observed in the IPF with emphysema group is unlikely to be the cause of the better short-term prognosis in these patients. Although substantial FVC data were lacking in the present study, pulmonary

emphysema was an independent factor in determining the short-term prognosis even after adjustment for FVC values.

Ikuyama et al. reported that patients with CPFE exhibited significantly lower serum KL-6 levels on admission and postulated that lung damage was less extensive in these patients. [16] Another recent study also reported that higher serum KL-6 levels on admission were associated with a poorer prognosis in patients with AE-IPF.[17] However, in our study, the serum KL-6 levels were higher in patients with IPF and emphysema. Therefore, patients with IPF and emphysema had better short-term survival, regardless of their serum KL-6 levels on admission.

The heterogeneity of prognosis in patients with AE-IPF may be due to different pathological changes in the lungs during AE. Diffuse alveolar damage is the major pathological finding in the lungs with AE-IPF in autopsy cases, accounting for approximately 80% of cases, followed by alveolar hemorrhage.[18] In contrast, lung specimens obtained by surgical biopsy often show organizing pneumonia. Churg et al.[19] reported that 6 of 12 patients with AE-CFIP presented with organizing pneumonia and survived the acute phase, whereas half of the patients presenting with diffuse alveolar damage died. Currently, there is no histopathological information explaining the different prognoses of AE-IPF due to emphysema, and further studies are required.

The Kaplan–Meier estimate revealed significantly better short-term survival in the IPF with emphysema group than in the IPF alone group. However, in the survivors of acute phase, long-term prognosis was not significantly different between patients with and without emphysema. The major cause of death was AE-IPF, observed in 33 cases, comprising 11 patients (52%) with emphysema and 22 patients (81%) without emphysema. This observation may be consistent with a previous report which stated that patients with IPF who never smoked and developed AE had poorer prognoses than those with IPF who smoked.[17]

This study has several limitations. First, this was a retrospective study of cases in two clinical centers; therefore, the number of patients studied was limited. In addition, we could not estimate the incidence of AEs in patients with IPF and pulmonary emphysema because of the retrospective design of this study. Prospective multicenter studies, such as the Japan Idiopathic Interstitial Pneumonias Registry are currently ongoing in Japan and are warranted. Second, due to the real-world nature of the study, some clinical data, especially data on the diffusion capacity and/or the six-minute walk test, which are used to calculate GAP scores to evaluate the IPF severity,[20,21] were missing in most cases. However, we propose that the presence or absence of emphysema on thoracic CT may be associated with the prognosis of AE, which is a leading cause of death in patients with IPF.

Conclusion

Patients with AE-IPF and concomitant pulmonary emphysema had better short-term prognoses than those without emphysema. Further studies are required to identify the histopathological characteristics of AE-IPF lungs with emphysema associated with better prognosis.

Abbreviations

AE, acute exacerbation; CFIP, chronic fibrosing interstitial pneumonia; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; FEV_1, forced expiratory volume in one second; FIO_2, fraction of inhaled oxygen; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von Lungen-6; PaO_2, arterial partial oxygen pressure; P/F ratio, PaO_2/FIO_2 ratio; SpO_2, oxygen saturation measured by pulse oximetry; SP-D, surfactant protein D

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Availability of data and material

The dataset used in this study is available from the corresponding author upon request.

Authors' contributions

Yukihiro Horio contributed to the conception and design of the study, analyzed and interpreted the data, and wrote the first version of the draft. Takahisa Takihara contributed to the conception and design of the study, analyzed the data (radiological images), and wrote the first version of the draft. Fuminari Takahashi contributed to the acquisition of data and revised the manuscript critically for important intellectual content. Keito Enokida contributed to the acquisition of data, analyzed the data (radiological images), and revised the manuscript critically for important intellectual content. Noriko Nakamura analyzed the data (radiological images) and revised the manuscript critically for important intellectual content. Jun Tanaka contributed to the acquisition of data and revised the manuscript critically for important intellectual content. Katsuyoshi Tomomatsu contributed to the acquisition of data and revised the manuscript critically for important intellectual content. Kyoko Niimi contributed to the acquisition of data and revised the manuscript critically for important intellectual content. Sakurako Tajiri contributed to the acquisition of data and revised the manuscript critically for important intellectual content. Naoki Hayama contributed to the acquisition of data and revised the manuscript critically for important intellectual content. Yoko Ito contributed to the acquisition of data and revised the manuscript critically for important intellectual content.

Tsuyoshi Oguma contributed to the acquisition of data and revised the manuscript critically for important intellectual content. Koichiro Asano contributed to the conception and design of the study, analyzed and interpreted the data, and wrote the final version of the draft. All authors read and approved the final version of the draft, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The authors declare no competing interests regarding of this study.

Consent for publication

Informed consent was obtained from the Tokai University Hospital website as an opt-out. Patients who were rejected were excluded.

Ethics approval

This study was approved by the Institutional Review Board of Tokai University Hospital (17R-198) and Tokai University Oiso Hospital (18R-241).

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Figure legends

Figure1.

Kaplan–Meier survival curves for patients admitted to the hospital with AE-IPF with pulmonary emphysema (solid line, n = 29) and without emphysema (dashed line, n = 33).

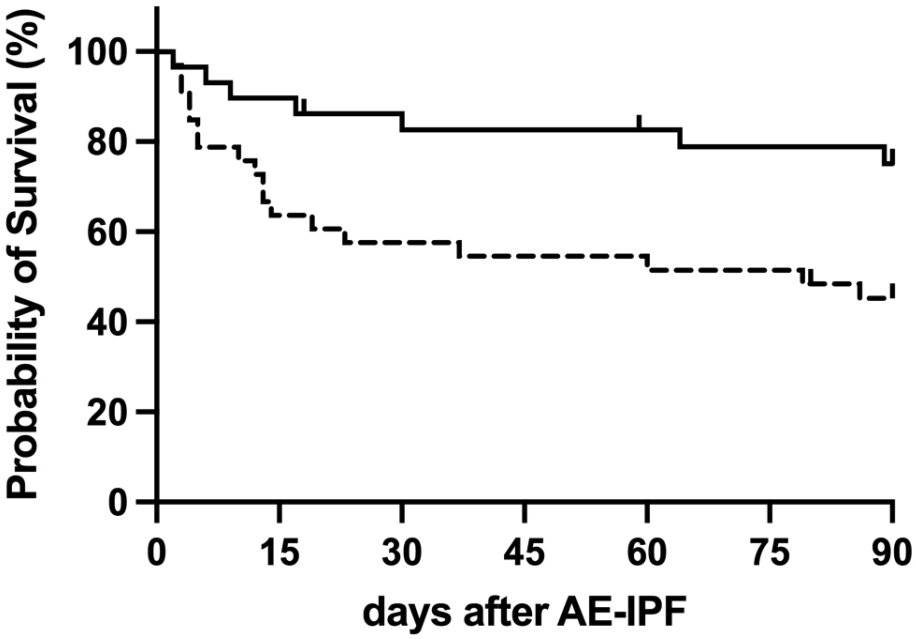

Figure 1

90x62mm (300 x 300 DPI)

Supplemental material

Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema: a retrospective cohort study in Japan

Yukihiro Horio[1], Takahisa Takihara[1], Fuminari Takahashi[3], Keito Enokida[1], Noriko Nakamura[2], Jun Tanaka[1], Katsuyoshi Tomomatsu[1], Kyoko Niimi[1], Sakurako Tajiri[3], Naoki Hayama[1], Yoko Ito[1] Tsuyoshi Oguma[1], and Koichiro Asano[1]

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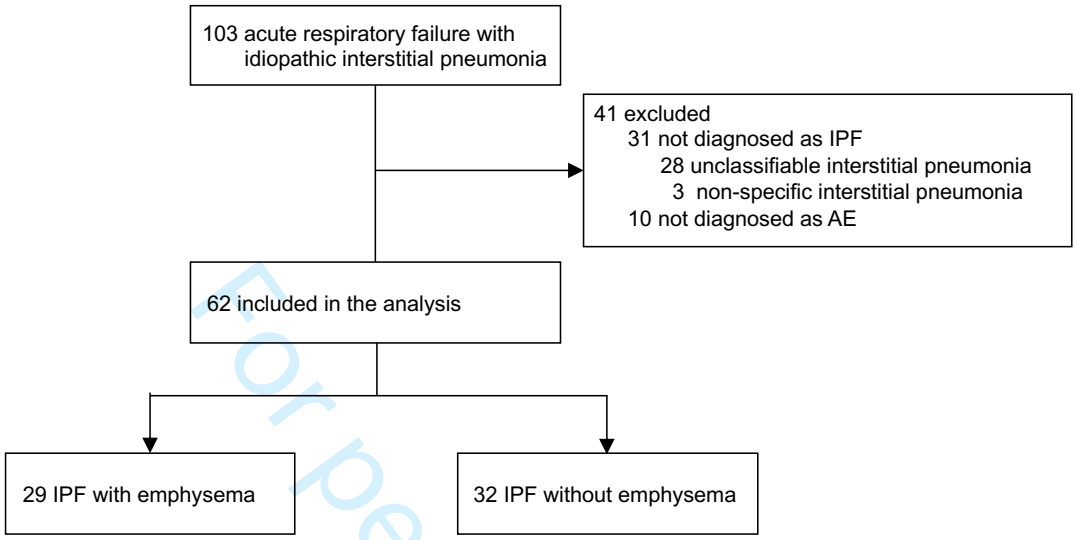
Supplemental Table 1. Cox proportional hazards regression analysis of mortality within 90 days including data of forced vital capacity (FVC)

	Hazard ratio	95% confidence interval	P value
Emphysema	0.30	0.09-0.98	0.04

adjusting by age, sex, and %FVC>60%

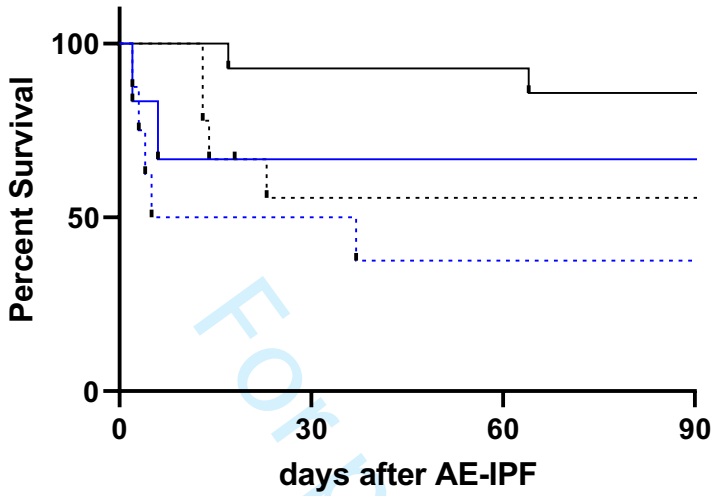
FVC, forced vital capacity

Supplemental Figure 1.



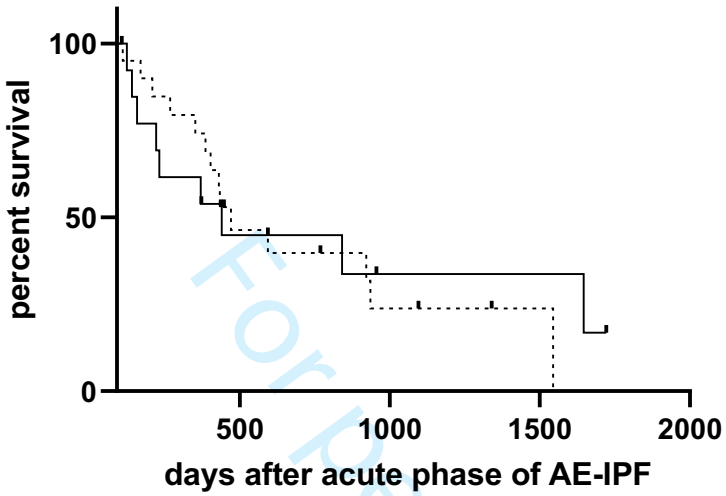
Flow diagram of patient selection. During the study period, 103 patients with idiopathic interstitial pneumonia admitted to hospitals due to acute respiratory failure. Thirty-one cases were not diagnosed as idiopathic pulmonary fibrosis (IPF) based on multidisciplinary discussion [unclassifiable interstitial lung disease (n = 28) and non-specific interstitial pneumonia (n = 3)] and excluded from the analysis. Another ten cases were excluded because the major cause of respiratory failure at admission was considered as infection or heart failure, but not an acute exacerbation (AE) of IPF, based on the clinical course after treatments. Patients with AE-IPF (n = 62) were divided into two groups according to the presence of concomitant pulmonary emphysema.

Supplemental Figure 2



Kaplan-Meier survival curves for the patients admitted to the hospitals due to acute exacerbation of idiopathic pulmonary fibrosis. The patients were divided into four subgroups according to the presence or absence of pulmonary emphysema and baseline forced vital capacity (FVC; ≥60% or <60% of the predicted value); Group 1 (black solid line, n = 14, with emphysema and baseline FVC ≥ 60%), group 2 (black dotted line, n = 9, without emphysema and baseline FVC ≥ 60%), group 3 (blue solid line, n = 6, with emphysema and baseline FVC < 60%), and group 4 (blue dotted line, n = 8, without emphysema and baseline FVC < 60%).

Supplemental Figure 3



Kaplan-Meier survival curves for the survivor of acute phase (90 days) after acute exacerbation of idiopathic pulmonary fibrosis with pulmonary emphysema (solid line, n = 22) and without emphysema (dotted line, n = 16).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1.2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10

		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.