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# BMJ Open

## Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema

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6 1 **Prognosis of acute exacerbation in idiopathic pulmonary fibrosis**  
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8 2 **with pulmonary emphysema**  
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26 **Abstract**

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

29 **Design:** A multicenter retrospective cohort study

30 **Setting:** Two university hospitals in Japan

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

33 **Interventions:** None

34 **Primary and secondary outcome measures:** 90-day mortality rate

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

37 **Results:** Among 62 patients (median age, 75 years; 48 men) admitted for AE of IPF, 29  
38 patients (46%) presented with concomitant pulmonary emphysema. There was no significant  
39 difference in the arterial partial oxygen pressure/fraction of inhaled oxygen (P/F) ratio or other  
40 laboratory and radiographic data between patients with and without emphysema. The 90-day  
41 mortality rate was significantly lower in patients with emphysema than in those with IPF alone  
42 (23% vs. 52%,  $p = 0.03$ ). The median survival time was significantly longer in patients with  
43 emphysema than in those with IPF alone (405 vs. 242 days,  $p = 0.02$ ).

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

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## 46 **Strengths and limitations of this study**

- 47 ● We explored the prognosis of patients with combined pulmonary fibrosis and  
48 emphysema who developed acute exacerbations.
  - 49 ● The studied population was diagnosed based on a multidisciplinary discussion.
  - 50 ● We could not estimate the incidence of acute exacerbation among patients with  
51 idiopathic pulmonary fibrosis and emphysema because of the retrospective design of  
52 this study.
- For peer review only

## 53 **Background**

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

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

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

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## 79 **Methods**

## 80 *Patients*

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

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

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

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

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## 104 *Clinical and laboratory parameters*

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



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5 107 Super Spiro DISCOM-21FX III spirometer (CHEST Corp., Tokyo, Japan) by trained clinical  
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7 108 technicians. The predicted values of forced vital capacity (FVC) and forced expiratory volume  
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9 109 in 1 s (FEV<sub>1</sub>) were calculated using a previously reported equation.[10] In patients without  
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11 110 arterial blood gas data at the time of admission, the partial pressure of arterial oxygen (PaO<sub>2</sub>)  
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13 111 was calculated based on percutaneous arterial oxygen saturation (SpO<sub>2</sub>) using the Hill  
14  
15 112 formula.[11] The serum levels of Krebs von Lungen-6 (KL-6) were measured using an  
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17 113 electrochemi-luminescence immunoassay and Lumipulse G1200 Analyzer (Rebio, Fuji,  
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19 114 Japan). The surfactant protein D (SP-D) levels were measured using commercially available  
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21 115 enzyme-linked immunosorbent assay kits (RayBiotech, Norcross, GA, USA).  
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#### 25 117 *Radiographic evaluation of thoracic CT and diagnosis IPF*

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27 118 Thoracic CT with 1.5-mm-thick axial sections was obtained at 1-cm intervals throughout the  
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29 119 entire thorax in the inspiratory phase. Emphysema was defined as demarcated areas of  
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31 120 decreased attenuation compared to contiguous normal lung tissue and marginated by a very  
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33 121 thin or no wall, with upper-zone predominance. The existence of emphysema and diagnostic  
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35 122 categories of usual interstitial pneumonia (UIP) based on CT patterns [12,13] were diagnosed  
36  
37 123 based on a discussion between two pulmonologists and a radiologist.  
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#### 41 125 *Statistical analysis*

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43 126 The data are expressed as mean ± standard deviation or median and interquartile range for  
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45 127 continuous variables, and number and percentage for categorical data. Group comparisons  
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47 128 were made using the Mann–Whitney U test for continuous variables and Fisher’s exact test  
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49 129 for categorical variables. Kaplan–Meier survival curves and log-rank tests were used to  
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51 130 evaluate the survival. Cox proportional hazards regression analysis of mortality within 90  
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53 131 days was performed using age, sex, and other factors with  $p < 0.1$  in univariate analysis and  
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55 132 data available in > 90% of the cases. A statistical analysis was performed using IBM SPSS  
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5 133 Statistics software ver. 21 (IBM, Chicago, IL, USA). The level of statistical significance was  
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7 134 set at  $p < 0.05$ .

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11 136 *Patient and public involvement*

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13 137 This was a retrospective cohort study with no direct patient and public engagement.  
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18 139 **Results**

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20 140 *Clinical characteristics prior to AE*

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22 141 We identified 62 patients (median age, 75 years; 48 men and 14 women) admitted to  
23  
24 142 hospitals due to AE-IPF during the study period. Notably, 29 patients (46.7%) had  
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26 143 emphysema (IPF with emphysema group) and 33 patients had IPF without emphysema (IPF  
27  
28 144 alone group).

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30 145 The clinical characteristics at baseline (within 12 months before AE) are presented in Table  
31  
32 146 1. All the patients with emphysema were smokers, whereas 19 patients (58%) with IPF alone  
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34 147 were never smokers. The total exposure to cigarette smoke (pack-years) was greater in the  
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36 148 IPF with emphysema group than in the IPF alone group ( $p < 0.001$ ). Age, sex, and proportion  
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38 149 of patients with lung cancer, under long-term oxygen therapy, or on pharmacotherapy with  
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40 150 prednisolone or antifibrotic agents were not significantly different between the groups. The  
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42 151 data of pulmonary function tests within one year prior to AE were available in 20 cases in the  
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44 152 IPF with emphysema group and 17 cases in the IPF alone group. The FVC, %FVC of the  
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46 153 predicted value, and FEV<sub>1</sub> were significantly higher in the IPF with emphysema group ( $p =$   
47  
48 154 0.045, 0.002, and 0.001, respectively), whereas the FEV<sub>1</sub>/FVC was not significantly different  
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50 155 between the groups. The diagnostic categories of UIP based on CT patterns were not  
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52 156 significantly different between the groups. One case, which was categorized as an alternative  
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54 157 pattern, was diagnosed as IPF upon autopsy.  
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158 **Table 1. Baseline characteristics in patients with idiopathic pulmonary fibrosis with**  
 159 **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 <sub>1</sub> (L)	1.9±0.5	1.3±0.4	0.001
FEV <sub>1</sub> /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

160 IPF, interstitial pulmonary fibrosis; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in one  
 161 second; KL-6, Krebs von Lungen-6

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164 *Clinical characteristics upon admission due to AE*

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

171 **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 <sup>3</sup> /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 <sub>2</sub>	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

172 AE, acute exacerbation; IPF, interstitial pulmonary fibrosis; KL-6, Krebs von Lungen-6;  
 173 SP-D, surfactant protein D; P/F ratio, PaO<sub>2</sub>/FIO<sub>2</sub> ratio; SIRS, systemic inflammatory response syndrome;  
 174 NIPPV, non-invasive intermittent positive pressure ventilation; IPPV, intermittent positive pressure  
 175 ventilation.

176  
 177 All the patients, except for one patient who was not treated with prednisolone, were treated  
 178 with high-dose prednisolone and oxygen therapy. There was no difference in the proportion  
 179 of patients treated with methylprednisolone pulse therapy and/or immunosuppressive  
 180 therapy between the groups. Four patients with IPF and emphysema and 12 patients with  
 181 IPF alone required a high-flow nasal cannula or positive-pressure ventilation for the treatment  
 182 of respiratory failure.

#### 184 *Short-term prognosis within 90 days after admission*

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

188 ratio were lower ( $p = 0.02$  and  $0.06$ , respectively) in the deceased patients (Table 3). The  
 189 survival rate was significantly higher in patients with emphysema than in those without  
 190 emphysema ( $p = 0.03$ ), and the 90-days survival rate was higher in patients with emphysema  
 191 (76% and 50%, respectively; Figure 1). The age, sex, smoking history (pack-years), serum  
 192 KL-6 levels, comorbidity of lung cancer, long-term oxygen therapy, and the proportion of  
 193 patients using prednisolone and/or antifibrotic agents before AE were not significantly  
 194 different between patients who died and those who survived for the first 90 days (Table 3). A  
 195 Cox proportional hazards regression analysis revealed that the presence of emphysema  
 196 (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–  
 197 0.99],  $p = 0.01$ ) were predictors of mortality within 90 days after adjustment for age and sex  
 198 (Table 4).

200 **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
<b>Baseline clinical characteristics</b>			
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 <sub>1</sub> /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
<b>Clinical data on admission</b>			
Respiratory rate (/min)	26±5	23±6	0.18
Laboratory data			
Leukocytes (×10 <sup>3</sup> /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 <sub>2</sub>	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

201 FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; IPPV, intermittent positive  
 202 pressure ventilation; KL-6, Krebs von Lungen-6; NIPPV, non-invasive intermittent positive pressure  
 203 ventilation; P/F ratio, PaO<sub>2</sub>/FIO<sub>2</sub> ratio; SIRS, systemic inflammatory response syndrome; SP-D, surfactant  
 204 protein D.

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207 **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 <sub>2</sub> /FIO <sub>2</sub> ratio	0.99	0.98-0.99	0.01

208 Adjusted for age and sex

209

210

211 In the multivariate analysis, FVC was not included because of the high rate of missing values.

212 Therefore, we performed a sub-analysis by dividing the patients into four subgroups

213 according to the presence or absence of emphysema and baseline FVC (≥60% or <60% of

214 the predicted value). A Kaplan–Meier estimate according to this subgrouping revealed that

215 the presence of emphysema tended to have a good prognosis regardless of the %FVC

216 (Supplemental Figure 1). A Cox proportional hazards regression analysis including

217 the %FVC revealed that the presence of emphysema remained a predictor of mortality within  
218 90 days (hazard ratio, 0.30 [95%CI 0.09–0.98],  $p = 0.04$ ). (Supplemental Table 1)

219

### 220 *Long-term prognosis*

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

226

227 **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%)	-

228 IPF, idiopathic pulmonary fibrosis

229

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

237

238 **Discussion**

239 We retrospectively analyzed 62 consecutive patients admitted for AE-IPF in two hospitals.

240 Approximately half of the patients with AE-IPF exhibited pulmonary emphysema, who

241 showed higher exposure to cigarette smoking, better FVC before AE, and higher levels of

242 KL-6 and SP-D at AE. The patients with emphysema had better short-term survival than

243 those without emphysema, although the long-term survival of the survivors was equivalent.

244 Several possibilities may explain why the presence of emphysema was associated with

245 better short-term prognosis in patients with IPF. First, the higher baseline FVC observed in

246 the IPF with emphysema group may have contributed to a better survival rate. However,

247 several studies have demonstrated that higher FVC values were not associated with better

248 prognosis in patients with AE of chronic fibrosing interstitial pneumonia (CFIP).[14,15]

249 Furthermore, the co-presence of emphysema may have masked the decrease in FVC in the

250 IPF with emphysema group and greater FVC does not suggest a better capacity for alveolar

251 gas exchange, which is essential for favorable oxygenation. In fact, there was no difference

252 in the P/F ratio at exacerbation, an essential factor associated with the poor prognosis of AE-

253 IPF, between patients with and without emphysema. Ikuyama et al. also reported that

254 patients with CPFE had better baseline %FVC and better prognosis after exacerbation than

255 those with IPF alone;[16] however, there was no difference in the %DLCO or GAP score

256 between the groups. Therefore, the higher baseline FVC observed in the IPF with

257 emphysema group is unlikely to be the cause of the better short-term prognosis in these

258 patients. Although substantial FVC data were lacking in the present study, pulmonary

259 emphysema was an independent factor in determining the short-term prognosis even after

260 adjustment for FVC values.

261 Ikuyama et al. reported that patients with CPFE exhibited significantly lower serum KL-6

262 levels on admission and postulated that lung damage was less extensive in these patients.

263 [16] Another recent study also reported that higher serum KL-6 levels on admission were



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5 264 associated with a poorer prognosis in patients with AE-IPF.[17] However, in our study, the  
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7 265 serum KL-6 levels were higher in patients with IPF and emphysema. Therefore, patients with  
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9 266 IPF and emphysema had better short-term survival, regardless of their serum KL-6 levels on  
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11 267 admission.

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13 268 The heterogeneity of prognosis in patients with AE-IPF may be due to different pathological  
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15 269 changes in the lungs during AE. Diffuse alveolar damage is the major pathological finding in  
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17 270 the lungs with AE-IPF in autopsy cases, accounting for approximately 80% of cases, followed  
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19 271 by alveolar hemorrhage.[18] In contrast, lung specimens obtained by surgical biopsy often  
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21 272 show organizing pneumonia. Churg et al.[19] reported that 6 of 12 patients with AE-CFIP  
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23 273 presented with organizing pneumonia and survived the acute phase, whereas half of the  
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25 274 patients presenting with diffuse alveolar damage died. Currently, there is no histopathological  
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27 275 information explaining the different prognoses of AE-IPF due to emphysema, and further  
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29 276 studies are required.

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31 277 The Kaplan–Meier estimate revealed significantly better short-term survival in the IPF with  
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33 278 emphysema group than in the IPF alone group. However, in the survivors of acute phase,  
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35 279 long-term prognosis was not significantly different between patients with and without  
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37 280 emphysema. The major cause of death was AE-IPF, observed in 33 cases, comprising 11  
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39 281 patients (52%) with emphysema and 22 patients (81%) without emphysema. This  
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41 282 observation may be consistent with a previous report which stated that patients with IPF who  
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43 283 never smoked and developed AE had poorer prognoses than those with IPF who  
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45 284 smoked.[17]

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47 285 This study has several limitations. First, this was a retrospective study of cases in two clinical  
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49 286 centers; therefore, the number of patients studied was limited. In addition, we could not  
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51 287 estimate the incidence of AEs in patients with IPF and pulmonary emphysema because of  
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53 288 the retrospective design of this study. Prospective multicenter studies, such as the Japan  
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55 289 Idiopathic Interstitial Pneumonias Registry are currently ongoing in Japan and are warranted.  
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57 290 Second, due to the real-world nature of the study, some clinical data, especially data on the  
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5 291 diffusion capacity and/or the six-minute walk test, which are used to calculate GAP scores to  
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7 292 evaluate the IPF severity,[20,21] were missing in most cases. However, we propose that the  
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9 293 presence or absence of emphysema on thoracic CT may be associated with the prognosis  
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11 294 of AE, which is a leading cause of death in patients with IPF.  
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15 296 **Conclusion**

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17 297 Patients with AE-IPF and concomitant pulmonary emphysema had better short-term  
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19 298 prognoses than those without emphysema. Further studies are required to identify the  
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21 299 histopathological characteristics of AE-IPF lungs with emphysema associated with better  
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23 300 prognosis.  
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5 302 **Abbreviations**  
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7 303 AE, acute exacerbation; CFIP, chronic fibrosing interstitial pneumonia; CPFPE, combined  
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9 304 pulmonary fibrosis and emphysema; CT, computed tomography; FEV<sub>1</sub>, forced expiratory  
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11 305 volume in one second; FIO<sub>2</sub>, fraction of inhaled oxygen; FVC, forced vital capacity; IPF,  
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13 306 idiopathic pulmonary fibrosis; KL-6, Krebs von Lungen-6; PaO<sub>2</sub>, arterial partial oxygen  
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15 307 pressure; P/F ratio, PaO<sub>2</sub>/FIO<sub>2</sub> ratio; SpO<sub>2</sub>, oxygen saturation measured by pulse oximetry;  
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17 308 SP-D, surfactant protein D  
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15 314 or not-for-profit sectors.  
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19 316 **Availability of data and material**  
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21 317 The dataset used in this study is available from the corresponding author upon request.  
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23 318  
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25 319 **Authors' contributions**  
26

27 320 YH, TT, and KA participated in the conception and design of the study, analyzed and  
28  
29 321 interpreted the data, and wrote the manuscript. YH, TT, and KN evaluated radiological  
30  
31 322 images. FT, KE, JT, KT, KN, ST, NH, YI, and TO collected and analyzed the clinical data. All  
32  
33 323 authors read and approved the final draft.  
34

35 324  
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37 325 **Competing interests**  
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39 326 The authors declare no competing interests regarding of this study.  
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43 328 **Consent for publication**  
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45 329 Informed consent was obtained from the Tokai University Hospital website as an opt-out.  
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47 330 Patients who were rejected were excluded.  
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51 332 **Ethics approval**  
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53 333 This study was approved by the Institutional Review Board of Tokai University Hospital (17R-  
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55 334 198) and Tokai University Oiso Hospital (18R-241).  
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5 **399 Figure legends**

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8 400 Figure1.

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10 401 Kaplan–Meier survival curves for patients admitted to the hospital with AE-IPF with

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12 402 pulmonary emphysema (solid line, n = 29) and without emphysema (dashed line, n = 33).  
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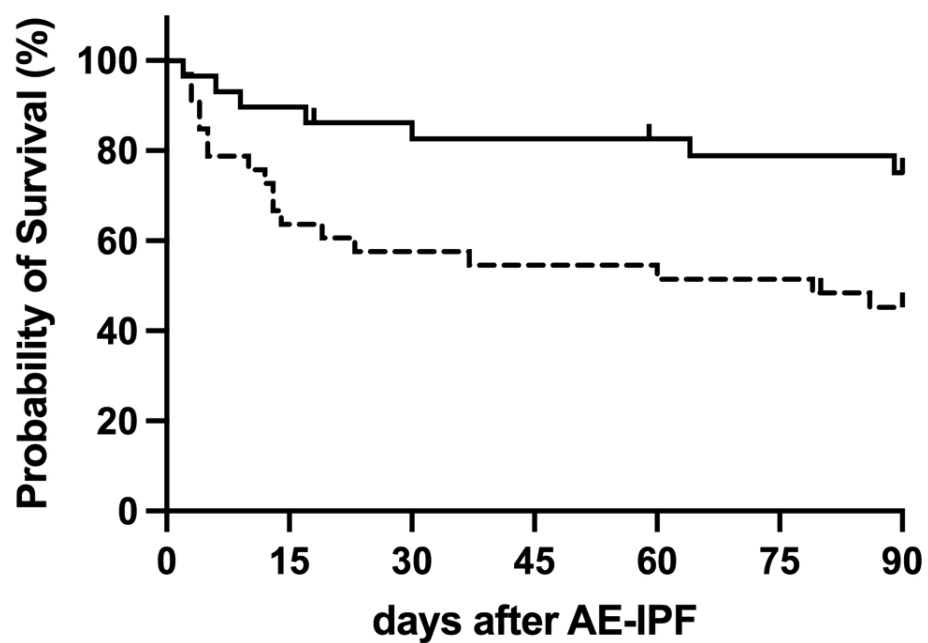


Figure 1

90x62mm (300 x 300 DPI)



## Supplemental material

### **Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema**

Yukihiro Horio<sup>1</sup>, Takahisa Takihara<sup>1</sup>, Fuminari Takahashi<sup>3</sup>, Keito Enokida<sup>1</sup>, Noriko  
Nakamura<sup>2</sup>, Jun Tanaka<sup>1</sup>, Katsuyoshi Tomomatsu<sup>1</sup>, Kyoko Niimi<sup>1</sup>, Sakurako Tajiri<sup>3</sup>, Naoki  
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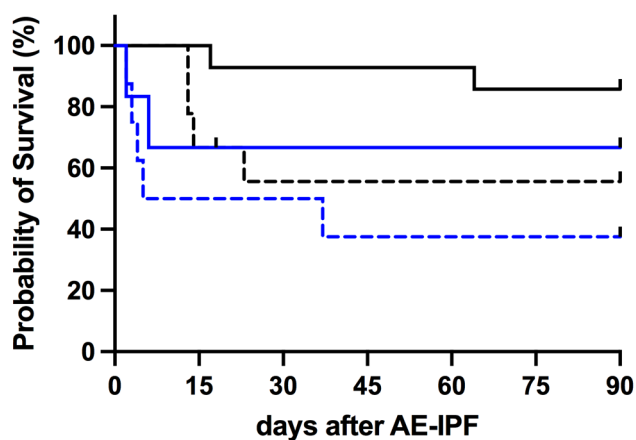
**Supplemental Table 1. Cox proportional hazards regression analysis of mortality within 90 days including data of forced vital capacity (FVC)**

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

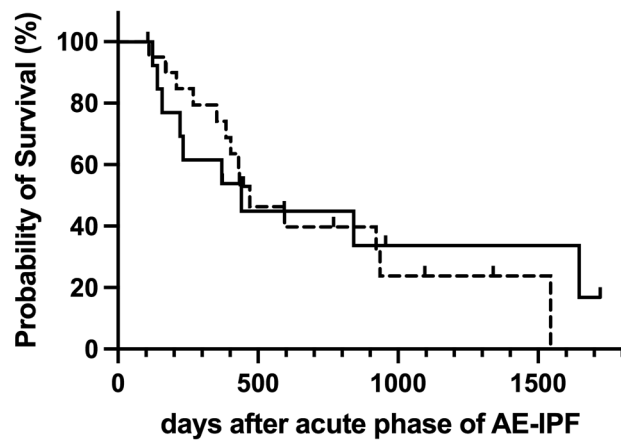
adjusted for age, sex, and %FVC>60%

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  $\geq 60\%$  or  $< 60\%$  of the predicted value): group 1 (black solid line,  $n = 14$ , with emphysema and baseline FVC  $\geq 60\%$ ), group 2 (black dashed line,  $n = 9$ , without emphysema and baseline FVC  $\geq 60\%$ ), 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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062236.R1
Article Type:	Original research
Date Submitted by the Author:	08-Jun-2022
Complete List of Authors:	<p>Horio, Yukihiro; Tokai University School of Medicine Graduate School of Medicine  Takahara, Takahisa; Tokai University School of Medicine Graduate School of Medicine  Takahashi, Fuminari; Tokai University Oiso Hospital, Department of Medicine  Enokida, Keito; Tokai University School of Medicine Graduate School of Medicine  Nakamura, Noriko; Tokai University School of Medicine, Department of Radiology  Tanaka, Jun; Tokai University School of Medicine Graduate School of Medicine  Tomomatsu, Katsuyoshi; Tokai University School of Medicine Graduate School of Medicine  Niimi, Kyoko; Tokai University School of Medicine Graduate School of Medicine  Tajiri, Sakurako; Tokai University Oiso Hospital, Department of Medicine  Hayama, Naoki; Tokai University School of Medicine Graduate School of Medicine  Ito, Yoko; Tokai University School of Medicine Graduate School of Medicine  Oguma, Tsuyoshi; Tokai University School of Medicine Graduate School of Medicine  Asano, Koichiro; Tokai University School of Medicine Graduate School of Medicine, Division of Pulmonary Medicine</p>
<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Intensive care, Medical management
Keywords:	Interstitial lung disease < THORACIC MEDICINE, Emphysema < THORACIC MEDICINE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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6 1 **Prognosis of acute exacerbation in idiopathic pulmonary fibrosis**  
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8 2 **with pulmonary emphysema: a retrospective cohort study in Japan**  
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26 **Abstract**

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

29 **Design:** A multicenter retrospective cohort study

30 **Setting:** Two university hospitals in Japan

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

33 **Interventions:** None

34 **Primary and secondary outcome measures:** 90-day mortality rate

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

37 **Results:** Among 62 patients (median age, 75 years; 48 men) admitted for AE of IPF, 29  
38 patients (46%) presented with concomitant pulmonary emphysema. There was no significant  
39 difference in the arterial partial oxygen pressure/fraction of inhaled oxygen (P/F) ratio or other  
40 laboratory and radiographic data between patients with and without emphysema. The 90-day  
41 mortality rate was significantly lower in patients with emphysema than in those with IPF alone  
42 (23% vs. 52%,  $p = 0.03$ ). The median survival time was significantly longer in patients with  
43 emphysema than in those with IPF alone (405 vs. 242 days,  $p = 0.02$ ).

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

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## 46 **Strengths and limitations of this study**

- 47 ● The studied population was patients with idiopathic pulmonary fibrosis (IPF) who  
48 developed acute exacerbations.
  - 49 ● The diagnosis of IPF, emphysema, and acute exacerbation was based on a  
50 multidisciplinary discussion by pulmonary physicians and a radiologist.
  - 51 ● The number of patients studied was limited as a retrospective study in two clinical  
52 centers.
  - 53 ● The incidence of acute exacerbation among patients with IPF with or without  
54 emphysema could not be analyzed because of the retrospective design of this study.
  - 55 ● Some data such as pulmonary function tests prior to acute exacerbation were not  
56 available.
- For peer review only

## 57 **Background**

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

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

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

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## 83 **Methods**

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5 84 *Patients*  
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7 85 Consecutive patients admitted to two university hospitals for AE-IPF between January 2007  
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9 86 and August 2018 were retrospectively analyzed. IPF was diagnosed based on a  
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11 87 multidisciplinary discussion (MDD) by two pulmonologists and a radiologist using the  
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13 88 patients' clinical history, physical examination, laboratory test results, and radiographic data  
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15 89 from high-resolution computed tomography (HRCT).  
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17 90 AE-IPF was diagnosed based on the following criteria:[2] 1) previous or concurrent diagnosis  
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19 91 of IPF; (2) acute worsening or development of dyspnea typically of duration <1 month; 3)  
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21 92 computed tomography with new bilateral ground-glass opacity and/or consolidation  
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23 93 superimposed on a background pattern consistent with the usual interstitial pneumonia  
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25 94 pattern; and 4) deterioration not fully explained by cardiac failure or fluid overload. The  
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27 95 patients with neoplasms undergoing active treatment, including radiation therapy,  
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29 96 chemotherapy with cytotoxic or molecular-targeted drugs, or immunotherapy with immune  
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31 97 checkpoint inhibitors, at the onset of AE were excluded.  
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33 98 AE-IPF was treated with an appropriate administration of oxygen and pharmacotherapy using  
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35 99 prednisone (0.5–1 mg/kg per day) with or without preceding methylprednisolone pulse  
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37 100 therapy (1 g/day for 3 days). The prednisone dose was tapered based on the response to  
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39 101 therapy. In refractory cases, immunosuppressive therapy with intravenous  
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41 102 cyclophosphamide (500 mg every 2–4 weeks) may have been added.  
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43 103 This study was approved by the Institutional Review Board of Tokai University Hospital (17R-  
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45 104 198) and Tokai University Oiso Hospital (18R-241), and was conducted in compliance with  
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47 105 the principles of the Declaration of Helsinki. Informed consent was obtained from the Tokai  
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49 106 University Hospital website as an opt-out. Patients who rejected were excluded.  
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53 108 *Clinical and laboratory parameters*  
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55 109 The clinical and laboratory data within 12 months prior to and at the onset of AE were  
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57 110 collected from medical charts. Spirometry was performed during stable disease using a  
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5 111 Super Spiro DISCOM-21FX III spirometer (CHEST Corp., Tokyo, Japan) by trained clinical  
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7 112 technicians. The predicted values of forced vital capacity (FVC) and forced expiratory volume  
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9 113 in 1 s (FEV<sub>1</sub>) were calculated using a previously reported equation.[10] In patients without  
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11 114 arterial blood gas data at the time of admission, the partial pressure of arterial oxygen (PaO<sub>2</sub>)  
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13 115 was calculated based on percutaneous arterial oxygen saturation (SpO<sub>2</sub>) using the Hill  
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15 116 formula.[11] The serum levels of Krebs von Lungen-6 (KL-6) were measured using an  
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17 117 electrochemi-luminescence immunoassay and Lumipulse G1200 Analyzer (Rebio, Fuji,  
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19 118 Japan). The surfactant protein D (SP-D) levels were measured using commercially available  
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21 119 enzyme-linked immunosorbent assay kits (RayBiotech, Norcross, GA, USA).  
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#### 25 121 *Radiographic evaluation of thoracic CT and diagnosis IPF*

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27 122 Thoracic CT with 1.5-mm-thick axial sections was obtained at 1-cm intervals throughout the  
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29 123 entire thorax in the inspiratory phase. Emphysema was defined as demarcated areas of  
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31 124 decreased attenuation compared to contiguous normal lung tissue and marginated by a very  
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33 125 thin or no wall, with upper-zone predominance. The extent of emphysema was evaluated by  
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35 126 low attenuation area (LAA) score in chest CT according to the method proposed by Goddard  
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37 127 et al. [12] The cases with LAA score > 0 was classified in the emphysema group. The  
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39 128 existence of emphysema and diagnostic categories of usual interstitial pneumonia (UIP)  
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41 129 based on CT patterns [12,13] were diagnosed based on a discussion between two  
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43 130 pulmonologists and a radiologist.  
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#### 47 132 *Statistical analysis*

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49 133 The data are expressed as mean ± standard deviation or median and interquartile range for  
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51 134 continuous variables, and number and percentage for categorical data. Group comparisons  
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53 135 were made using the Mann–Whitney U test for continuous variables and Fisher's exact test  
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55 136 for categorical variables. Kaplan–Meier survival curves and log-rank tests were used to  
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57 137 evaluate the survival. Cox proportional hazards regression analysis of mortality within 90  
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5 138 days was performed using age, sex, and other factors with  $p < 0.1$  in univariate analysis and  
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7 139 data available in  $> 90\%$  of the cases. A statistical analysis was performed using IBM SPSS  
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9 140 Statistics software ver. 21 (IBM, Chicago, IL, USA). The level of statistical significance was  
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11 141 set at  $p < 0.05$ .

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#### 14 143 *Patient and public involvement*

15 144 This was a retrospective cohort study with no direct patient and public engagement.

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### 17 146 **Results**

#### 18 147 *Clinical characteristics prior to AE*

19 148 Among 103 patients admitted to hospitals due to acute respiratory failure of idiopathic  
20 149 interstitial pneumonia during the study period, we identified 62 patients with AE-IPF (median  
21 150 age, 75 years; 48 men and 14 women, Supplemental Figure 1). Notably, 29 patients (46.7%)  
22 151 had emphysema (IPF with emphysema group) and 33 patients had IPF without emphysema  
23 152 (IPF alone group).

24 153 The clinical characteristics at baseline (within 12 months before AE) are presented in Table  
25 154 1. All the patients with emphysema were smokers, whereas 19 patients (58%) with IPF alone  
26 155 were never smokers. The total exposure to cigarette smoke (pack-years) was greater in the  
27 156 IPF with emphysema group than in the IPF alone group ( $p < 0.001$ ). Age, sex, body mass  
28 157 index, proportion of patients with co-morbidities, under long-term oxygen therapy, or on  
29 158 pharmacotherapy with prednisolone or antifibrotic agents were not significantly different  
30 159 between the groups. The data of pulmonary function tests within one year prior to AE were  
31 160 available in 20 cases in the IPF with emphysema group and 17 cases in the IPF alone group.  
32 161 The FVC, %FVC of the predicted value, and FEV<sub>1</sub> were significantly higher in the IPF with  
33 162 emphysema group ( $p = 0.045$ ,  $0.002$ , and  $0.001$ , respectively), whereas the FEV<sub>1</sub>/FVC was  
34 163 not significantly different between the groups. The diagnostic categories of UIP based on CT



164 patterns were not significantly different between the groups. One case, which was  
 165 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 <sub>1</sub> (L)	1.9±0.5	1.3±0.4	0.001
FEV <sub>1</sub> /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<sub>1</sub>, forced expiratory volume in one second; KL-6, Krebs von Lungen-6

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167 *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<sub>2</sub>)  
 171 and the PaO<sub>2</sub>/FIO<sub>2</sub> (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 <sup>3</sup> /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 <sub>2</sub>	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<sub>2</sub>/FIO<sub>2</sub> 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

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

180

### 181 *Short-term prognosis within 90 days after admission*

182 Nine (15%), 15 (24%), and 23 (38%) patients died within 7, 30, and 90 days of admission  
 183 due to AE-IPF, respectively. The survivors were more likely to have emphysema (56%) than  
 184 the deceased (30%), with an odds ratio of 0.27 (95% CI, 0.07–0.88;  $p = 0.02$ ). FVC and P/F  
 185 ratio were lower ( $p = 0.02$  and 0.06, respectively) in the deceased patients (Table 3). The  
 186 survival rate was significantly higher in patients with emphysema than in those without  
 187 emphysema ( $p = 0.03$ ), and the 90-days survival rate was higher in patients with emphysema  
 188 (76% and 50%, respectively; Figure 1). The age, sex, smoking history (pack-years), serum  
 189 KL-6 levels, comorbidity of lung cancer, long-term oxygen therapy, and the proportion of  
 190 patients using prednisolone and/or antifibrotic agents before AE were not significantly  
 191 different between patients who died and those who survived for the first 90 days (Table 3). A  
 192 Cox proportional hazards regression analysis revealed that the presence of emphysema  
 193 (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–  
 194 0.99],  $p = 0.01$ ) were predictors of mortality within 90 days after adjustment for age and sex  
 195 (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
<b>Baseline clinical characteristics</b>			
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 <sub>1</sub> /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
<b>Clinical data on admission</b>			
Respiratory rate (/min)	26±5	23±6	0.18
Laboratory data			
Leukocytes (×10 <sup>3</sup> /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 <sub>2</sub>	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<sub>1</sub>, 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<sub>2</sub>/FIO<sub>2</sub> 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 <sub>2</sub> /FIO <sub>2</sub> ratio	0.99	0.98-0.99	0.01

Adjusted for age and sex

196 In the multivariate analysis, FVC was not included because of the high rate of missing values.  
 197 Therefore, we performed a sub-analysis by dividing the patients into four subgroups  
 198 according to the presence or absence of emphysema and baseline FVC ( $\geq 60\%$  or  $< 60\%$  of  
 199 the predicted value). A Kaplan–Meier estimate according to this subgrouping revealed that  
 200 the presence of emphysema tended to have a good prognosis regardless of the %FVC  
 201 (Supplemental Figure 2). A Cox proportional hazards regression analysis including  
 202 the %FVC revealed that the presence of emphysema remained a predictor of mortality within  
 203 90 days (hazard ratio, 0.30 [95%CI 0.09–0.98],  $p = 0.04$ ). (Supplemental Table 1)

204

### 205 *Long-term prognosis*

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

211

**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

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

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

219

## 220 Discussion

221 We retrospectively analyzed 62 consecutive patients admitted for AE-IPF in two hospitals.  
222 Approximately half of the patients with AE-IPF exhibited pulmonary emphysema, who  
223 showed higher exposure to cigarette smoking, better FVC before AE, and higher levels of  
224 KL-6 and SP-D at AE. The patients with emphysema had better short-term survival than  
225 those without emphysema, although the long-term survival of the survivors was equivalent.  
226 Several possibilities may explain why the presence of emphysema was associated with  
227 better short-term prognosis in patients with IPF. First, the higher baseline FVC observed in  
228 the IPF with emphysema group may have contributed to a better survival rate. However,  
229 several studies have demonstrated that higher FVC values were not associated with better  
230 prognosis in patients with AE of chronic fibrosing interstitial pneumonia (CFIP).[14,15]  
231 Furthermore, the co-presence of emphysema may have masked the decrease in FVC in the  
232 IPF with emphysema group and greater FVC does not suggest a better capacity for alveolar  
233 gas exchange, which is essential for favorable oxygenation. In fact, there was no difference  
234 in the P/F ratio at exacerbation, an essential factor associated with the poor prognosis of AE-  
235 IPF, between patients with and without emphysema. Ikuyama et al. also reported that  
236 patients with CPFE had better baseline %FVC and better prognosis after exacerbation than  
237 those with IPF alone;[16] however, there was no difference in the %DLCO or GAP score  
238 between the groups. Therefore, the higher baseline FVC observed in the IPF with  
239 emphysema group is unlikely to be the cause of the better short-term prognosis in these  
240 patients. Although substantial FVC data were lacking in the present study, pulmonary

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

243 Ikuyama et al. reported that patients with CPFE exhibited significantly lower serum KL-6  
244 levels on admission and postulated that lung damage was less extensive in these patients.

245 [16] Another recent study also reported that higher serum KL-6 levels on admission were  
246 associated with a poorer prognosis in patients with AE-IPF.[17] However, in our study, the  
247 serum KL-6 levels were higher in patients with IPF and emphysema. Therefore, patients with  
248 IPF and emphysema had better short-term survival, regardless of their serum KL-6 levels on  
249 admission.

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

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

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5 267 This study has several limitations. First, this was a retrospective study of cases in two clinical  
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7 268 centers; therefore, the number of patients studied was limited. In addition, we could not  
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9 269 estimate the incidence of AEs in patients with IPF and pulmonary emphysema because of  
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11 270 the retrospective design of this study. Prospective multicenter studies, such as the Japan  
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13 271 Idiopathic Interstitial Pneumonias Registry are currently ongoing in Japan and are warranted.  
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15 272 Second, due to the real-world nature of the study, some clinical data, especially data on the  
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17 273 diffusion capacity and/or the six-minute walk test, which are used to calculate GAP scores to  
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19 274 evaluate the IPF severity,[20,21] were missing in most cases. However, we propose that the  
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21 275 presence or absence of emphysema on thoracic CT may be associated with the prognosis  
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23 276 of AE, which is a leading cause of death in patients with IPF.  
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## 27 278 **Conclusion**

29 279 Patients with AE-IPF and concomitant pulmonary emphysema had better short-term  
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31 280 prognoses than those without emphysema. Further studies are required to identify the  
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33 281 histopathological characteristics of AE-IPF lungs with emphysema associated with better  
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35 282 prognosis.  
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5 284 **Abbreviations**  
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7 285 AE, acute exacerbation; CFIP, chronic fibrosing interstitial pneumonia; CPFPE, combined  
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9 286 pulmonary fibrosis and emphysema; CT, computed tomography; FEV<sub>1</sub>, forced expiratory  
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11 287 volume in one second; FIO<sub>2</sub>, fraction of inhaled oxygen; FVC, forced vital capacity; IPF,  
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13 288 idiopathic pulmonary fibrosis; KL-6, Krebs von Lungen-6; PaO<sub>2</sub>, arterial partial oxygen  
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15 289 pressure; P/F ratio, PaO<sub>2</sub>/FIO<sub>2</sub> ratio; SpO<sub>2</sub>, oxygen saturation measured by pulse oximetry;  
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17 290 SP-D, surfactant protein D  
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5 291 **Acknowledgements**

6  
7 292 None.

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11 294 **Funding**

12  
13 295 This research received no specific grants from any funding agency in the public, commercial,  
14  
15 296 or not-for-profit sectors.

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19 298 **Availability of data and material**

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21 299 The dataset used in this study is available from the corresponding author upon request.

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25 301 **Authors' contributions**

26  
27 302 Yukihiro Horio contributed to the conception and design of the study, analyzed and  
28  
29 303 interpreted the data, and wrote the first version of the draft. Takahisa Takihara contributed to  
30  
31 304 the conception and design of the study, analyzed the data (radiological images), and wrote  
32  
33 305 the first version of the draft. Fuminari Takahashi contributed to the acquisition of data and  
34  
35 306 revised the manuscript critically for important intellectual content. Keito Enokida contributed  
36  
37 307 to the acquisition of data, analyzed the data (radiological images), and revised the manuscript  
38  
39 308 critically for important intellectual content. Noriko Nakamura analyzed the data (radiological  
40  
41 309 images) and revised the manuscript critically for important intellectual content. Jun Tanaka  
42  
43 310 contributed to the acquisition of data and revised the manuscript critically for important  
44  
45 311 intellectual content. Katsuyoshi Tomomatsu contributed to the acquisition of data and revised  
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47 312 the manuscript critically for important intellectual content. Kyoko Niimi contributed to the  
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49 313 acquisition of data and revised the manuscript critically for important intellectual content.  
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51 314 Sakurako Tajiri contributed to the acquisition of data and revised the manuscript critically for  
52  
53 315 important intellectual content. Naoki Hayama contributed to the acquisition of data and  
54  
55 316 revised the manuscript critically for important intellectual content. Yoko Ito contributed to the  
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57 317 acquisition of data and revised the manuscript critically for important intellectual content.  
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318 Tsuyoshi Oguma contributed to the acquisition of data and revised the manuscript critically  
319 for important intellectual content. Koichiro Asano contributed to the conception and design of  
320 the study, analyzed and interpreted the data, and wrote the final version of the draft. All  
321 authors read and approved the final version of the draft, and agreed to be accountable for all  
322 aspects of the work in ensuring that questions related to the accuracy or integrity of any part  
323 of the work are appropriately investigated and resolved.

324

### 325 **Competing interests**

326 The authors declare no competing interests regarding of this study.

327

### 328 **Consent for publication**

329 Informed consent was obtained from the Tokai University Hospital website as an opt-out.

330 Patients who were rejected were excluded.

331

### 332 **Ethics approval**

333 This study was approved by the Institutional Review Board of Tokai University Hospital (17R-

334 198) and Tokai University Oiso Hospital (18R-241).

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5 **399 Figure legends**

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8 400 Figure1.

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10 401 Kaplan–Meier survival curves for patients admitted to the hospital with AE-IPF with

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12 402 pulmonary emphysema (solid line, n = 29) and without emphysema (dashed line, n = 33).  
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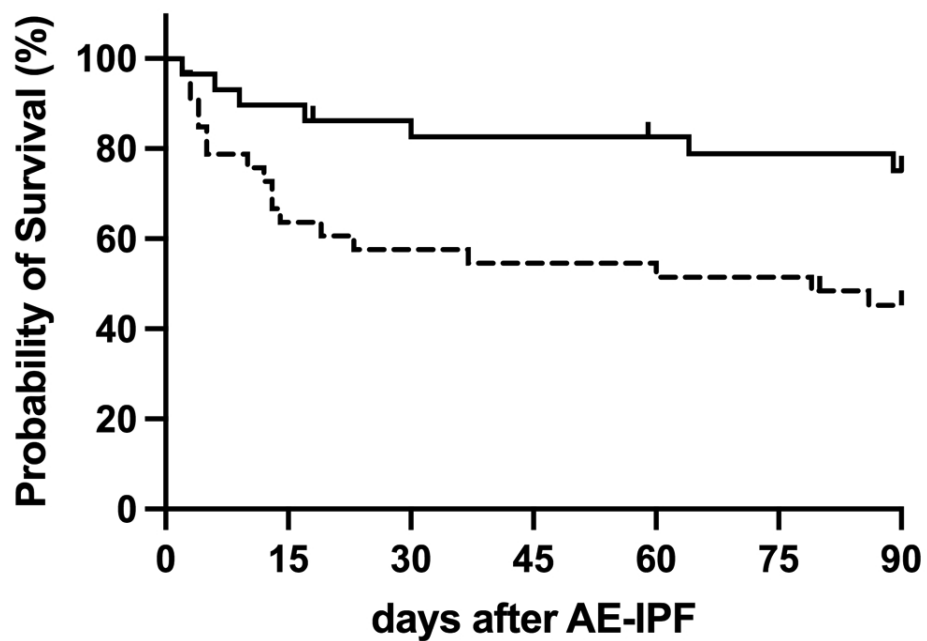


Figure 1

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<sup>1</sup>, Takahisa Takihara<sup>1</sup>, Fuminari Takahashi<sup>3</sup>, Keito Enokida<sup>1</sup>, Noriko  
Nakamura<sup>2</sup>, Jun Tanaka<sup>1</sup>, Katsuyoshi Tomomatsu<sup>1</sup>, Kyoko Niimi<sup>1</sup>, Sakurako Tajiri<sup>3</sup>, Naoki  
Hayama<sup>1</sup>, Yoko Ito<sup>1</sup> Tsuyoshi Oguma<sup>1</sup>, and Koichiro Asano<sup>1</sup>

<sup>1</sup>Division of Pulmonary Medicine, Department of Medicine, <sup>2</sup>Department of Radiology, Tokai  
University School of Medicine, Kanagawa, Japan, <sup>3</sup>Department of Medicine, Tokai  
University Oiso Hospital, Kanagawa, Japan



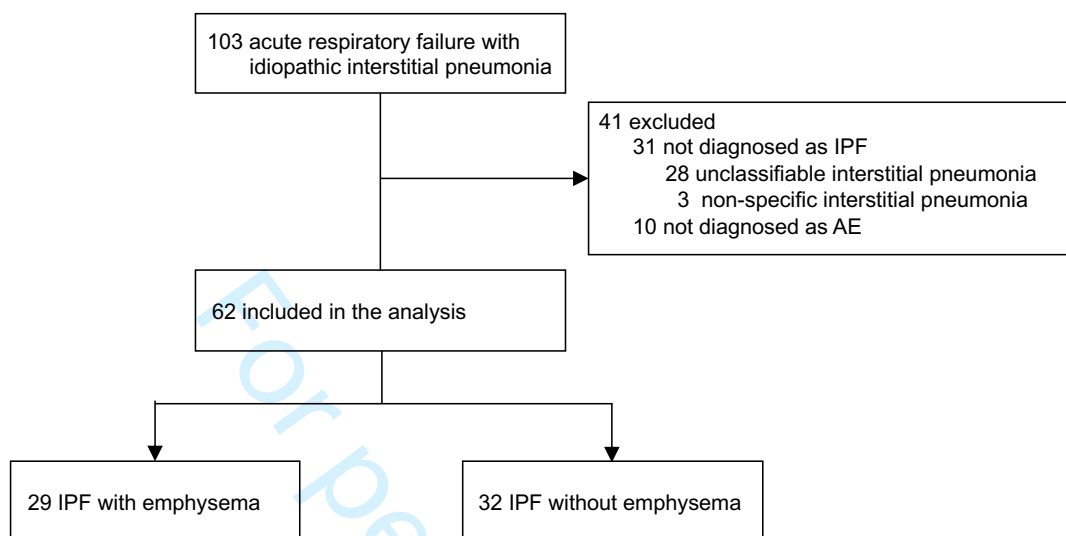
**Supplemental Table 1. Cox proportional hazards regression analysis of mortality within 90 days including data of forced vital capacity (FVC)**

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

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

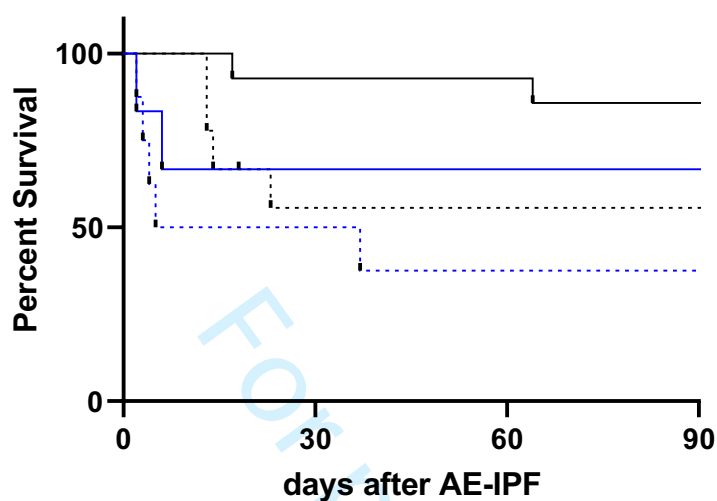
FVC, forced vital capacity

## Supplemental Figure 1.



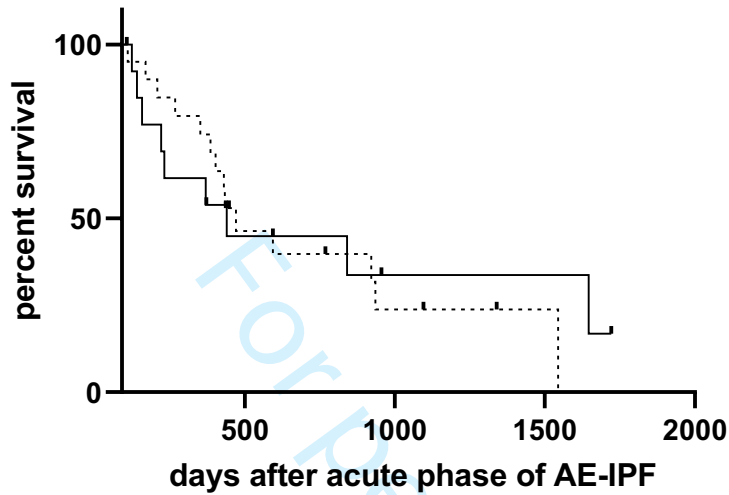
Flow diagram of patient selection. During the study period, 103 patients with idiopathic interstitial pneumonia admitted to hospitals due to acute respiratory failure. Thirty-one cases were not diagnosed as idiopathic pulmonary fibrosis (IPF) based on multidisciplinary discussion [unclassifiable interstitial 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;  $\geq 60\%$  or  $< 60\%$  of the predicted value); Group 1 (black solid line,  $n = 14$ , with emphysema and baseline FVC  $\geq 60\%$ ), group 2 (black dotted line,  $n = 9$ , without emphysema and baseline FVC  $\geq 60\%$ ), 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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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	
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).