Clinical Impact of Emphysema Evaluated by High-Resolution Computed Tomography on Idiopathic Pulmonary Fibrosis Diagnosed by Surgical Lung Biopsy

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For editorial comment see p. 215

Key Words

Idiopathic pulmonary fibrosis · Emphysema · Prognosis · Combined pulmonary fibrosis and emphysema

Abstract

Background: The prognosis of combined cases of pulmonary fibrosis and emphysema is unresolved partially because radiological differentiation between usual interstitial pneumonia and nonspecific interstitial pneumonia is difficult in coexisting emphysema cases. **Objective:** The purpose of this study was to clarify the clinical impact of emphysema on the survival of patients with idiopathic pulmonary fibrosis (IPF). **Methods:** One hundred and seven patients with interstitial lung diseases were diagnosed by surgical lung biopsies between 2006 and 2012, and 47 patients were diagnosed with IPF through multidisciplinary discussion. Emphysema on high-resolution computed tomography scans was evaluated semiquantitatively by visual scoring. **Results:** Eight out of the 47 IPF patients showed a higher emphysema score (>3) and were diagnosed to have IPF-emphysema. The median survival time of patients with IPF-emphysema (1,734 days)

from the initial diagnosis was significantly shorter than that of patients with IPF alone (2,229 days) by Kaplan-Meier analysis ($p = 0.007$, log-rank test). Univariate Cox proportional hazard regression analyses revealed that a higher total emphysema score (>3.0) was a significantly poor prognostic factor in addition to Krebs von den Lungen-6, surfactant protein-D, arterial oxygen tension, percent forced vital capacity, and percent diffusing capacity of carbon monoxide (%DLCO). Multivariate Cox proportional hazard regression analyses with the stepwise method showed that higher total emphysema score (>3) and %DLCO were significantly poor prognostic factors. **Conclusions:** The prognosis of IPF-emphysema was significantly worse than that of IPF alone.

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Introduction

Idiopathic pulmonary fibrosis (IPF) has been reported to be one of the diseases associated with smoking [1–3]. The coexistence of pulmonary fibrosis and emphysema was first described by Wiggins et al. [4] in 1991. Cottin et

al. [5] individualized the syndrome of combined pulmonary fibrosis and emphysema (CPFE) based on high-resolution computed tomography (HRCT) of the chest in a homogeneous group of 61 patients in 2005. The radiological features of CPFE are emphysematous changes in the upper lobe predominance and fibrotic changes in the lower lobe predominance. The clinical features of CPFE included predominance in male smokers, severe dyspnea during exertion, preserved or slightly reduced lung volume in relation to the extent of fibrotic changes in the lungs with a disproportionate reduction in diffusing capacity of carbon monoxide (DLCO), and a high prevalence of pulmonary hypertension (PH) [5]. The prognosis of CPFE was poor, with a median survival of 6.1 years [5].

Although several reports have discussed the conditions under which pulmonary fibrosis and emphysema coexist [6–15], after Cottin et al. [5] reported the pathophysiology of CPFE, the clinical impact of emphysematous changes on pulmonary fibrosis has remained unresolved; Mejia et al. [7] and Sugino et al. [8] found worse survival in IPF with emphysema than in IPF alone, while Bodlet et al. [9], Kurashima et al. [10] and Todd et al. [11] reported opposite results. Ryerson et al. [12] and Jankowich and Rounds [13] showed that IPF with/without emphysema had similar mortality. These conflicting results were supposed to be caused by the mistaken inclusion of non-IPF cases along with cases of IPF with emphysema [6] in addition to the difference of the functional disturbance, the extent of fibrosis and emphysema, because the radiological diagnosis of IPF can sometimes be difficult in an emphysema-combined case, as we have previously reported [16]. Hence, it might be better for the impact of emphysema on IPF patient survival to be evaluated only in pathologically diagnosed IPF cases.

We hypothesized that the prognosis of IPF patients with emphysema on HRCT scans is worse than that of IPF patients without emphysema. In order to clarify this hypothesis, we evaluated radiological findings and clinical characteristics of surgical lung biopsy (SLB)-proven IPF cases.

Material and Methods

Subjects

The Kinki-Chuo Chest Medical Center (KCCMC) SLB database was surveyed between January 2006 and December 2012, and 156 patients underwent SLB for diagnosis of diffuse parenchymal lung diseases. The selected subjects (fig. 1) were 47 patients with IPF. Chronic hypersensitivity pneumonia was diagnosed according to the criteria of Ohtani et al. [17]. Collagen vascular disease-

Fig. 1. Flowchart of subject selection. The KCCMC SLB database was surveyed between January 2006 and December 2012, and 156 patients underwent SLB for diagnosis of diffuse parenchymal lung diseases (DPLDs). Among these 156 patients, 48 were excluded due to diagnoses other than interstitial pneumonias (IPs). One patient was excluded due to pneumothorax, which prevented the evaluation of a CT score in the initial HRCT. Among the 107 patients, 12 patients were diagnosed with IIPs other than non-IPF (IIPs non-IPF), 22 patients with collagen vascular disease-associated interstitial pneumonias (CVD-IPs), and 26 patients with chronic hypersensitivity pneumonia (CHP). The remaining 47 patients with IPF were the subjects of this study. IIPs non-IPF include NSIP (n = 5), pleuroparenchymal fibroelastosis (n = 2), desquamative interstitial pneumonia (n = 1), respiratory bronchiolitis interstitial lung disease (n = 1), and unclassifiable interstitial pneumonia (n = 3). CVD-IPs (n = 22) include rheumatoid arthritis (n = 5), dermatomyositis (n = 1), Sjögren syndrome (n = 9), vasculitis (n = 3), and systemic sclerosis (n = 4).

associated interstitial pneumonias were diagnosed with each diagnostic criterion [18–20]. Patient demographics are described in table 1. The review board of KCCMC approved this retrospective study (IRB No. 353, approval date: May 24, 2012).

Measurements

Pulmonary function test was performed with CHESTAC-8800 (Chest M.I. Inc., Tokyo, Japan). Serum markers, including Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D, were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (ED046, Eizai Co. Ltd., Tokyo, Japan; SP-D ELISA, Yamasa Co., Tokyo, Japan, respectively). The cutoff levels of serum KL-6 and SP-D were 500 U/ml and 110 ng/ml, respectively [21]. Echocardiography evaluated systolic pulmonary artery pressure (SPAP) [22]. PH was defined by SPAP ≥ 45 –50 Torr, although the diagnosis of PH based on echocardiography underestimates its true prevalence. All these clinical findings were collected from medical records.

Table 1. Baseline patient characteristics (all IPF patients)

Parameters	n or median (IQR)
Patients	47
Gender, male/female	33/14
Smoking status, ES or CS/NS	35/12
Age, years	62 (56–67)
Observation period, days	1,582 (1,213–1,935)
Dead/alive	16/31
Acute exacerbation ^a , yes/no	11/36
Lung cancer, yes/no	0/47
Pulmonary hypertension by echocardiography ^a , yes/no	7/25
Pneumothorax or pneumomediastinum ^a , yes/no	10/27
Upper emphysema score	1.0 (0.0–1.5)
Total emphysema score	2.0 (0.0–3.0)

ES = Ex-smoker; CS = current smoker; NS = non-smoker.
^a Occurrence during the observation period.

Diagnosis of IPF

The final diagnosis was determined by a multidisciplinary discussion organized between chest radiologists, pulmonary pathologists, and pulmonologists. The diagnosis of IPF was based on ‘An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management’ [23]. We categorized IPF cases into definite IPF, probable IPF, and possible IPF.

Evaluation of HRCT Findings

A chest radiologist (M.A.) classified HRCT findings before SLB of each cases into a usual interstitial pneumonia (UIP) pattern or a non-UIP pattern, as previously reported [16, 24]; the combination of subpleural fibrotic changes, lower zone predominance, and minimal to no ground glass infiltration was classified as a UIP pattern. The emphysematous lesions (emphysema score) and fibrotic lesions (fibrosis score) were also evaluated without knowledge of clinical information. It is impossible to strictly distinguish emphysema, cysts, and emphysematous cysts radiologically. Therefore, emphysematous lesions were defined as well-demarcated areas of decreased attenuation compared to contiguous normal lung and marginated by a very thin (<1 mm) or absent wall, and/or multiple bullae (>1 cm in diameter) [5]. Fibrotic lesions were defined as lesions of reticular shadow and honeycombing.

The lungs were divided into six zones (upper, middle, and lower zones in both lungs), and each zone was evaluated separately. The upper zone was defined as the part of the lung above the level of the tracheal carina, the lower zone as the part of the lung below the level of the inferior pulmonary vein, and the middle zone as the portion of the lung between the upper and lower zones [25]. The extent to which emphysema and fibrosis [16] were present in each lung zone was semiquantitatively scored: score 0, none; score 0.5, <5%; score 1, 5–24%; score 2, 25–49%; score 3, 50–74%; score 4, >75% [25]. The scores of each zone or upper two zones were added to form the total emphysema score or upper emphysema score.

Definition of IPF with Emphysema

In this report, we defined IPF-emphysema as IPF cases with mean scores of all 6 zones of >0.50 and total emphysema scores of >3.0 and IPF alone as IPF with a total emphysema score of ≤3.0. The cutoff emphysema score was considered to be the minimum, visually quantifiable unit, although it is difficult to accurately quantify findings, such as traction bronchiectasis, expanded honeycomb lungs, and huge emphysematous cysts in a portion where emphysematous changes and fibrosis coexist [3].

Statistical Analyses

We used the χ^2 test, Fisher exact test, or Wilcoxon rank-sum test as appropriate to show the bivariate associations of emphysematous change in IPF. Survival was evaluated by Kaplan-Meier methods. The prognostic significance of each parameter was evaluated by univariate and multivariate Cox proportional hazard analysis. Correlation of clinical parameters was evaluated by Spearman’s rank correlation. Statistical analysis was performed using SPSS Statistics v. 21 (IBM, USA), and $p < 0.05$ was considered significant.

Results

Prognosis and the Definition of IPF with Emphysema

The median survival time for patients with IPF-emphysema (1,734 days) with a total emphysema score >3.0 from the initial HRCT diagnosis was significantly shorter than that of patients with IPF alone (2,229 days) by Kaplan-Meier analysis ($p = 0.007$, log-rank test) (fig. 2a). There was no significant difference in survival between IPF with emphysema ($n = 34$) with a total emphysema score >0 on initial HRCT, and IPF with no emphysema (total emphysema score = 0) ($n = 13$) ($p = 0.217$, log-rank test) (fig. 2b). In cases where the cutoff value of a total emphysema score was changed to 2.5 and 2.0, no significant difference in survival between IPF alone and IPF with emphysema was observed ($p = 0.345$ and $p = 0.459$, respectively).

Distribution of Emphysema in IPF-Emphysema on the Initial HRCT

We examined the distribution of emphysema in IPF-emphysema cases ($n = 8$). The initial upper emphysema score versus total emphysema score was 0.58 (range: 0.40–0.80). Thus, emphysema was distributed predominantly in upper lung fields.

Clinical Differences between IPF-Emphysema and IPF Alone

The characteristic differences between IPF-emphysema and IPF alone are described in table 2. IPF-emphyse-

Fig. 2. Kaplan-Meier plots of survival time of IPF patients in relation to emphysema. **a** The survival of IPF-emphysema patients with total emphysema score >3 [solid line, $n = 8$, median survival time (MST): 1,734 days] was significantly worse than that of patients with IPF alone with total emphysema score ≤ 3 (dotted line,

$n = 39$, MST: 2,229 days) ($p = 0.007$, log-rank test). **b** The survival of IPF-emphysema patients with total emphysema score >0 (solid line, $n = 34$, MST: 1,994 days) was not significantly different from that of patients with IPF alone (total emphysema score = 0) (dotted line, $n = 13$, MST: 2,229 days) ($p = 0.216$, log-rank test).

ma cases were all males with a history of smoking and who had less arterial oxygen tension (PaO_2) at rest ($p = 0.02$). The age at the first visit tended to be younger in IPF-emphysema cases. There was no significant difference in other clinical parameters including frequency of autoantibodies (table 2). In the radiological evaluation, the frequency of the HRCT pattern (UIP/non-UIP) and fibrosis scores did not differ between IPF-emphysema and IPF alone.

Treatment and Outcome of IPF-Emphysema and IPF Alone

We observed no significant difference in treatment between the two groups (table 3). During the observation period, the occurrence of acute exacerbation did not differ between IPF-emphysema and IPF alone (table 2). The frequency of elevated serum brain natriuretic protein (BNP) and N-terminal prohormone of BNP, and the frequency of PH evaluated by cardiac ultrasonography increased during the observation period. However, there was no significant difference between IPF alone and IPF-emphysema. Four patients with IPF-emphysema and 12 with IPF alone died during the ob-

servation period (table 2). Lung cancer did not occur in either group.

Prognostic Significance of Emphysema in IPF Cases

Univariate Cox proportional hazard regression analyses revealed that serum KL-6, serum SP-D, PaO_2 , percent predicted value of forced vital capacity (%FVC), and percent predicted value of diffusing capacity of carbon monoxide (%DLCO) were significant prognostic factors (table 4). Total emphysema score (>3.0) was also a significant factor for poor outcomes. In multivariate Cox proportional hazard regression analyses with stepwise method using these factors, %DLCO and total emphysema score (>3.0) were significant factors in poor prognoses (table 4).

Correlation between Radiological Findings and Other Clinical Parameters

Correlations between clinical parameters were evaluated using Spearman's rank correlation (table 5). There was no correlation between fibrosis score and emphysema score. Emphysema and fibrosis scores correlated significantly with %DLCO.

Table 2. Baseline patient characteristics (IPF patients)

Parameters	IPF-emphysema	IPF alone	p value
Number of cases	8	39	
<i>At the diagnosis of IPF</i>			
Gender, male/female	8/0	25/14	0.084*
Age, years	56 (50–63)	63 (58–68)	0.077
Age, mean $\pm$ SE, years	56.8 $\pm$ 2.4	61.4 $\pm$ 1.3	0.862**
BMI	25.4 (23.5–29.1)	25.3 (21.2–26.8)	0.330
Smoking status, ES or CS/NS	8/0	27/12	0.093*
Pack-years	39 (32–62)	30 (0–48)	0.104
Pack-years, mean $\pm$ SE	46.6 $\pm$ 6.8	29.2 $\pm$ 4.7	0.136**
Elevation of BNP or NTproBNP ^c , yes/no	0/5	4/25	1.000*
Pulmonary hypertension by echocardiography, yes/no	1/4	6/21	1.000*
LDH, U/ml	220 (198–257)	224 (174–251)	0.943
KL-6, U/ml	1,135 (852–1,648)	876 (598–1,503)	0.369
SP-D, ng/ml	131 (101–309)	193 (123–331)	0.384
ANA $\geq$ 40	3/5	24/14	0.246
ANA $\geq$ 160	0/8	3/35	1.000*
RF >15 U/ml or RAPA $\geq$ 40, yes/no	2/5	9/29	1.000*
Other autoantibodies, yes/no	1 ^a /7	5 ^b /34	1.000*
PaO ₂ at rest, Torr	75.7 (67.8–82.5)	85.3 (76.4–91.9)	0.020
%FVC, %	89.7 (82.7–100.7)	80.0 (67.8–89.0)	0.088
%FVC (mean $\pm$ SE)	89.7 $\pm$ 4.1	82.2 $\pm$ 3.3	0.243**
%FEV ₁ , %	90.1 (81.0–96.5)	83.3 (71.9–89.4)	0.327
FEV ₁ /FVC, %	84.0 (79.8–87.2)	87.3 (83.9–90.3)	0.136
%DLCO	50.4 (40.7–78.0)	59.4 (45.2–71.3)	0.694
%DLCO, mean $\pm$ SE	56.5 $\pm$ 6.7	59.1 $\pm$ 3.0	0.806**
Observation period, days	1,424 (762–1,707)	1,588 (1,239–1,969)	0.865
<i>Occurrence during observation period</i>			
Dead/alive	4/4	12/27	0.416*
Acute exacerbation, yes/no	2/6	9/30	1.000*
Pulmonary hypertension by echocardiography, yes/no	1/3	7/14	1.000*
Elevation of BNP or NTproBNP ^c , yes/no	4/1	15/16	0.342*
Pneumothorax or pneumomediastinum, yes/no	3/5	7/32	0.218*
<i>HRCT findings at the diagnosis of IPF</i>			
HRCT pattern, UIP/non-UIP	5/3	17/22	0.446*
Total emphysema score	5.3 (5.0–9.0)	1.5 (0.0–2.5)	<0.001
Total fibrosis score	4.5 (4.0–7.0)	6.0 (4.5–7.5)	0.321

Distribution of each parameter was expressed by the number or median (IQR). SE = Standard estimate; ES = ex-smoker; CS = current smoker; NS = non-smoker; BMI = body mass index; NTproBNP = N-terminal pro-hormone BNP; LDH = lactate dehydrogenase; ANA = antinuclear antibody; RF = rheumatoid factor; RAPA = rheumatoid arthritis particle agglutination; %FEV₁ = percent predicted value of forced expiratory volume in 1 s. The frequency of each parameter was compared with the χ^2 test or Fisher's exact test (*). Medians were compared with the Mann-Whitney U test. Age, pack-years, %FVC and %DLCO were also expressed as mean $\pm$ SD and analyzed by Student's t test (**). IPF-emphysema patients had total emphysema score >3.0 and IPF alone patients had total emphysema score $\leq$ 3.0. ^a ds DNA antibody in 1 case. ^b ds DNA antibody in 3 cases, SSA antibody in 1 case and RNP antibody and SSA antibody in 1 case. ^c Frequency of BNP >18.4 pg/ml or NTproBNP >125 pg/ml is shown.

Table 3. Management of IPF-emphysema and IPF alone

Treatment	IPF-emphysema	IPF alone	p value
Total number of cases	8	39	
Pirfenidone	2 (25.0%)	9 (23.1%)	1.000
Corticosteroids	1 (12.5%)	15 (38.5%)	0.234
Immunosuppressants	1 (12.5%)	13 (33.3%)	0.405
Inhalation of N-acetyl cysteine	0	2 (5.1%)	1.000
Inhalation of bronchodilator	0	2 (5.1%)	1.000
Long-term oxygen therapy	2 (25%)	13 (33%)	1.000
No therapy	3 (37.5%)	14 (35.9%)	1.000

The frequency of each parameter was compared between IPF-emphysema and IPF alone with Fisher's exact test. IPF-emphysema patients had emphysema score >3.0, whereas IPF alone patients had emphysema score ≤3.0.

Table 4. Poor prognostic factors of IPF (Cox proportional hazard regression analysis)

Parameter	Hazard ratio	95% CI	p value
<i>Univariate analysis</i>			
Gender, male	1.724	0.552–5.376	0.329
Age at diagnosis	0.983	0.917–1.053	0.625
Smoking status, CS or ES	1.389	0.474–4.065	0.549
BMI	1.071	0.897–1.277	0.449
LDH (U/ml)	1.002	0.992–1.013	0.655
KL-6 (×100 U/ml)	1.080	1.006–1.159	0.034
SP-D (×10 ng/ml)	1.021	1.003–1.040	0.024
PaO ₂	0.950	0.907–0.995	0.031
%FVC	0.963	0.963–0.998	0.039
%FEV ₁	0.961	0.922–1.002	0.060
%DLCO	0.961	0.933–0.990	0.009
HRCT pattern, UIP	1.190	0.421–3.365	0.743
Total fibrosis score	1.049	0.864–1.275	0.629
Total emphysema score, >3.0	5.076	1.353–18.868	0.016
<i>Multivariate analysis with stepwise method^a</i>			
%DLCO	0.958	0.928–0.989	0.009
Total emphysema score, >3.0	5.436	1.418–20.833	0.014

CS = Current smoker; ES = ex-smoker; BMI = body mass index; LDH = lactate dehydrogenase; %FEV₁ = percent predicted value of forced expiratory volume in 1 s. ^a All parameters analyzed by univariate analysis were used for multivariate analysis.

Discussion

In this study, we have shown the poor prognostic significance of emphysema evaluated by HRCT scans for IPF that was diagnosed by SLB and multidisciplinary dis-

cussion. Accurate diagnosis of IPF, establishing an appropriate definition of IPF with emphysema, and adjusting background characteristics, including extent of fibrosis and physiological parameters, are important characteristics when evaluating the prognosis of IPF with emphysema.

Akira et al. [16] have reported that the sensitivity, specificity, and accuracy of the diagnosis of UIP and nonspecific interstitial pneumonia (NSIP) were lower in patients with concurrent emphysema than in patients without concurrent emphysema. The extent of ground glass opacity and traction bronchiectasis between IPF/UIP with emphysema and NSIP with emphysema showed statistically significant differences [16]. Emphysematous spaces or cysts may be mistaken as honeycomb cysts. Thus, there is a possibility that the prognosis of clinically diagnosed IPF with emphysema may be better than pathologically diagnosed IPF with emphysema, as pathologically diagnosed cases of NSIP with emphysema can be mistakenly taken for IPF with emphysema [6]. Hence, the impact of emphysema on the survival of IPF patients should be investigated in SLB-proven IPF cases.

Cottin et al. [5] did not include the extent of emphysema in the definition of CPFE, and the percentage of emphysema on HRCT scans to diagnose CPFE has not always been previously defined [10, 13]. Mejía et al. [7] and Ryerson et al. [12] defined the emphysematous change of CPFE as >10% of the whole lung. This was because the population (emphysematous change >10%) was expected to have symptomatic and physiological consequences. Sugino et al. [8] diagnosed CPFE when chest CT scans showed emphysema occupying >25% of both upper lobes and a UIP pattern of fibrosis in the lower lobes.

Table 5. Correlation between radiological scores and other clinical parameters: Rho (p value)

	Emphysema score	Fibrosis score	%DLCO	%FVC	Serum KL-6	Serum SP-D
Emphysema score	1.000	0.194 (0.191)	−0.289 (0.049)	0.143 (0.337)	0.073 (0.627)	−1.06 (0.477)
Fibrosis score			−0.408 (0.004)	−0.169 (0.257)	0.339 (0.020)	0.400 (0.005)
%DLCO				0.410 (0.004)	−0.515 (<0.001)	−0.525 (<0.001)
%FVC					−0.370 (0.010)	−0.334 (0.022)
Serum KL-6						0.320 (0.029)
Serum SP-D						1.000

Spearman rank correlation was performed and evaluated by Rho.

Although Mejía et al. [7] and Ryerson et al. [12] adopted the same diagnostic criteria of CPFE, the survival impact of CPFE in both reports was not similar. Mejía's group reported an increased survival time after the diagnosis of non-CPFE IPF when compared to CPFE; however, Ryerson's group reported that the survival times of non-CPFE IPF and CPFE patients were identical [12]. This difference may be explained by the extent of fibrosis. The fibrosis in IPF alone was significantly milder in the cases of Mejía et al. [7] and worse in the cases of Ryerson et al. [12]. Hence, an adjustment for fibrosis is needed to evaluate survival differences between IPF alone and IPF with emphysema. Clinically diagnosed IPF cases supposedly have early to end-stage fibrosis. However, for SLB-diagnosed cases, IPF cases with severe fibrosis are generally excluded in order to safely perform SLB. As a result, the extent of fibrosis in IPF with emphysema and in IPF alone is anticipated to be similar in SLB-diagnosed cases. In our cohort of SLB-diagnosed cases, the extent of fibrosis in IPF alone did not significantly differ compared to IPF-emphysema (table 2), and the prognosis of IPF-emphysema was significantly worse than that of IPF alone by log-rank test.

In the present study, %DLCO correlated significantly with fibrosis score and was a significantly poor prognostic factor in addition to higher total emphysema score by multivariate analysis. Thus, we suggest that the prognosis of IPF in our study was determined by the extent of emphysema and fibrosis. Choi et al. [14] also reported that survival with fibrotic idiopathic interstitial pneumonias (IIPs) and emphysema is worse than that of fibrotic IIPs without emphysema in SLB-diagnosed cases; however, there was no survival difference between the two groups in cases with severe fibrosis. In their cohort, emphysema scores and fibrosis scores were not significant prognostic factors; however, the combined score of fibrosis and em-

physema was a significant factor by Cox proportional hazard regression analysis [14]. Thus, in addition to Choi's group, we have also confirmed that both pulmonary fibrosis and emphysema affect the prognosis of fibrotic IIPs.

The high prevalence of PH and lung cancer is supposed to be a clinical feature of IPF with emphysema [5, 6]. However, our IPF-emphysema cases lacked these clinical features. Although a high frequency of PH in IPF with emphysema was reported by Cottin et al. [26] and Mejía et al. [7], only 25% of IPF-emphysema cases in our cohort were complicated by PH. This is because the mean %DLCO of IPF with emphysema in the report of Cottin's group (24%) and the mean %FVC in the report of Mejía's group (62%) were apparently worse than in our IPF-emphysema cases.

No lung cancer occurred in our IPF-emphysema during the observation period, although Sugino et al. [8] and Kwak et al. [27] reported that the occurrence of lung cancer after the diagnosis IPF with emphysema was 8.7 and 25%, respectively. The mean %FVC in these reports was similar to that of our cases. However, the older mean age of patients with IPF with emphysema in the reports by Sugino et al. [8] (71 years) and Kwak et al. [27] (66 years) possibly led to the higher incidence of lung cancer than in our IPF-emphysema cases.

The median survival of IPF-emphysema patients (1,734 days) in this study is much longer than that of patients with IPF with emphysema reported by Mejía et al. [7] (540 days). We suppose that this discrepancy is due to the older age and more severe functional disturbance of the population included in the report of Mejía et al. [7] compared with our cases.

The first limitation of this study was the small number of patients. Second, some atypical IPF/UIP patients were included in the study because SLB was not performed in

typical IPF cases. Not all IIPs with emphysema can be diagnosed by SLB in real life practice, and the clinical features might be different between SLB cases and clinically diagnosed cases. Third, we did not study the pathological features of IPF with emphysema as recently reported by Inomata et al. [28]. Fourth, we did not differentiate between centrilobular and paraseptal emphysema. Okinouchi et al. [29] reported that emphysema type was associated with the type and extent of fibrosis.

We conclude that there was a poor prognosis for patients with IPF-emphysema compared with those with IPF alone. Further studies are needed to reach definite conclusions.

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Acknowledgements

We would like to thank Akiko Matsumuro, Masaki Hirose, Chizuru Hirakawa, and Yoko Imai for data management, as well as Tomomi Homma and Sayaka Tanaka for secretarial work. This study was partially supported by a grant from the National Hospital Organization, Japan [H26-NHO (Kokyu)-01; Y.I., T.A., M.A., M.K.], and a grant from the Diffuse Lung Diseases Research Group from the Ministry of Health, Labour and Welfare [H26-Itaku (Nan)-Ippan-077; Y.I., T.A., Diffuse Lung Disease; Y.I.].

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