Disease course and prognosis of pleuroparenchymal fibroelastosis compared with idiopathic pulmonary fibrosis

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Highlights

- The present study revealed clinically important characteristics of idiopathic pleuroparenchymal fibroelastosis (iPPFE) by comparison with those in idiopathic pulmonary fibrosis (IPF).
- Patients with iPPFE had similar frequencies of acute exacerbations and lower incidences of lung cancer than those with IPF.
- The most common cause of death in patients with iPPFE were chronic respiratory failure.
- Subsequently, patients with iPPFE exhibited significantly worse survivals than those with IPF.

Abbreviations:

iPPFE: idiopathic pleuroparenchymal fibroelastosis

c-iPPFE: clinically diagnosed idiopathic pleuroparenchymal fibroelastosis

pPPFE: pathologically diagnosed idiopathic pleuroparenchymal fibroelastosis

ILDs: interstitial lung diseases

SLB: surgical lung biopsy

IPF: idiopathic pulmonary fibrosis

AE: acute exacerbation

HRCT: high resolution computed-tomography

KL-6: Krebs von den Lungen-6

SP-D: surfacetant protein-D

FVC: forced vital capacity

$FEV_{1.0}$: forced expiratory volume in 1.0 second

DLCO: diffusing capacity of the lung for carbon monoxide

ABSTRACT

Background: Idiopathic pleuroparenchymal fibroelastosis (iPPFE) is a rare interstitial lung disease characterised by unique radiological and pathological findings. However, pathological evaluations are available only in a limited number of patients. Therefore, several clinical diagnostic criteria have been proposed. Nevertheless, the applicability of these criteria has not yet been validated. Moreover, the clinical course of iPPFE and its prognosis have not yet been completely elucidated.

Methods: The present study assessed previously proposed clinical diagnostic criteria by comparing the clinical features between pathologically diagnosed iPPFE (p-iPPFE) and clinically diagnosed iPPFE (c-iPPFE). Subsequently, the clinical features of iPPFE were characterized and compared with those of idiopathic pulmonary fibrosis (IPF, n=323).

Results: Clinical characteristics of c-iPPFE (n=27) and p-iPPFE (n=35) were similar. No significant difference was observed in terms of prognosis between c-iPPFE and p-iPPFE. The number of patients with iPPFE (both c-iPPFE and p-iPPFE) who developed lung cancer was significantly lower than that of patients with IPF. However, acute exacerbation (AE) showed similar incidence in patients with iPPFE and IPF. Survival of patients with iPPFE was significantly worse than that of patients with IPF (5-year survival rate: 38.5% vs. 63.5%, $p<0.0001$), and the most common cause of death was chronic respiratory failure (73.8%), followed by AE (14.3%). Male gender was the only poor prognostic factor of iPPFE.

Conclusion: The present study demonstrated efficiency of clinical diagnosis and also revealed clinically important characteristics of iPPFE that should be considered for management of iPPFE.

INTRODUCTION

Idiopathic pleuroparenchymal fibroelastosis (iPPFE), a rare interstitial lung disease (ILD), was recently considered as a type of idiopathic interstitial pneumonia in the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [1]. A definitive iPPFE diagnosis requires histologic confirmation following surgical lung biopsy (SLB). However, in clinical practice, SLB is not performed in substantial numbers of cases owing to the lack of curative treatment, presence of poor pulmonary function and risk of prolonged postoperative pneumothorax [2]. Therefore, clinical criteria that did not include SLB are required for iPPFE diagnosis. In relation to this context, several clinical diagnostic criteria for iPPFE have been proposed [3-5], but the applicability have not yet validated.

Although increasing evidences have recently emerged for iPPFE, each evidence is based on relatively small number of patients and large discrepancies noted among these studies. For example, prognoses of iPPFE reported widely vary, with 5-year survival rates and median survival durations ranging from 29% to 58% and 2.0 to 8.0 years, respectively [3, 6-12]. The prognostic factors for iPPFE have not been completely assessed. Further, it has become evident that patients with iPPFE develop acute exacerbation (AE), as observed in those with idiopathic pulmonary fibrosis (IPF) [7, 8, 11, 13]. Moreover, the actual incidence and risk factors of AE in individuals with iPPFE have not yet been completely elucidated. These results indicate that the clinical characteristics of iPPFE have not yet been completely assessed.

Therefore, the present study aimed to validate the applicability of clinical diagnostic criteria that were previously proposed. Moreover, clinical characteristics of iPPFE, such as AE incidence and prognosis, in the largest cohort of patients with iPPFE were assessed and compared with those of IPF.

METHODS

Subjects

This retrospective study was conducted on cohorts of 62 patients with iPPFE and 323 patients with IPF from Nationwide-cohort [6] and Hamamatsu-cohort [11]; 18 biopsy-proven iPPFE and 195 biopsy-proven IPF from Nationwide-cohort, and 44 iPPFE (n=9, biopsy-proven iPPFE; n=35, clinically diagnosed iPPFE) and 128 IPF (n=44, biopsy-proven IPF; n=84, clinically diagnosed IPF [cIPF]) from Hamamatsu-cohort. IPF and biopsy-proven iPPFE diagnosis was based on the ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) criteria, whereas clinical iPPFE diagnosis was based on the following previously proposed criteria [3]: 1) PPFE radiographic pattern on chest computed tomography (CT; defined as bilateral subpleural dense consolidation with or without pleural thickening in the upper lobes, less marked or absent involvement of lower lobes according to Reddy's radiological criteria [4]); 2) radiological confirmation of disease progression (defined as an increase in upper-lobe consolidation with or without pleural thickening and/or a decrease in upper-lobe volume on serial radiological assessments) and 3) exclusion of other lung diseases with identifiable etiologies (e.g., connective tissue disease-related ILDs, chronic hypersensitivity pneumonitis, pulmonary sarcoidosis, pneumoconiosis and active pulmonary infection).

The study protocol was approved by the Ethical Committee of Hamamatsu University School of Medicine (E14-360), and was conducted in accordance with the approved guidelines. The need for patient approval and/or informed consent was waived owing to the retrospective study design.

Data collection

Clinical data of the Nationwide and Hamamatsu cohorts were collected from the cloud-based integrated database [6] and patient medical records, respectively. AE was diagnosed based on the ATS guidelines [14 15]

HRCT

Chest HRCT images obtained at the time of ILD diagnosis and/or within 3 months prior to SLB were analysed. The presence of lower-lobe ILD in patients with iPPFE was assessed on HRCT according to the ATS/ERS/JRS/ALAT guidelines [16].

Statistical analysis

Discrete variables were expressed as total number (percentages) and continuous variables as median (interquartile range). Continuous and categorical variables were compared using the Mann–Whitney and Fisher's exact tests, respectively, for independence. Overall survival duration and AE-free period were assessed from the date of iPPFE and IPF diagnosis. The Kaplan–Meier method was used to examine cumulative survival probabilities and AE incidences, and differences were evaluated using the log-rank and Gray's tests, respectively. Propensity score matching was performed using the following algorithm: 1:1 optional match with a ±0.05 calliper and no replacement. To predict mortality and AE incidence, univariate and multivariate analyses were performed using the Cox proportional hazards regression model and Fine-Gray proportional hazards model, respectively. All analyses were two-tailed, and P-values of <0.05 were considered significant.

RESULTS

Clinical characteristics of patients with pathologically and clinically diagnosed iPPFE

First, to validate the clinical diagnostic criteria for iPPFE, we compared the clinical characteristics between pathologically diagnosed iPPFE (p-iPPFE) and clinically diagnosed iPPFE (c-iPPFE) **(Table1)**. All cases of p-iPPFE met the diagnostic criteria for c-iPPFE. Patients of both iPPFE groups were aged approximately 70 years. Moreover, most patients were men, and approximately 60%–70% were never smokers. Most patients showed severe-to-moderate restrictive spirometric impairment and decreased lung diffusion capacity for carbon monoxide (DLCO). No significant differences were observed in terms of sex, smoking habits, pulmonary function test results and laboratory and bronchoalveolar lavage (BAL) findings. Lower-lobe ILD was observed in 88.9% and 82.9% of patients with p-iPPFE and c-iPPFE, respectively, with no significant difference in incidence. Moreover, the proportion of patients with p-iPPFE and c-iPPFE having HRCT pattern was similar (***TableS1***). These observations suggested that clinical characteristics are similar between patients with c-iPPFE and p-iPPFE.

Prognosis of patients with p-iPPFE and c-iPPFE

Among 62 patients, 20 patients with p-iPPFE and 22 with c-iPPFE died during the observation period. The most common cause of death was chronic respiratory failure, followed by AE, in both groups (**Table2**). The cause of deaths and prognosis were not significantly differed between both iPPFE groups (p=0.4439, **Figure1A)**; the median survival duration and 5-year survival rate were 34.6 months and 34.3% in patients with p-iPPFE and 47.8 months and 41.3% in those with c-iPPFE, respectively. Because male gender and lower percentage of forced vital capacity (%FVC) are associated with worse survival in patients with iPPFE [9, 11, 17], propensity score matching for sex and %FVC was performed. We

established 14 well-matched pairs between patients with p-iPPFE and c-iPPFE (***TableS2)***. Despite adjusting for sex and %FVC, the prognosis of patients with c-iPPFE did not significantly differ from that of patients with p-iPPFE; the median survival duration and 5-year survival rate were 30.5 months and 27.3% in patients with p-iPPFE and 37.1 months and 28.6% in those with c-iPPFE (**Figure1B**).

Characteristic differences between patients with iPPFE and those with IPF

On comparing patients with iPPFE (both p-iPPFE and c-iPPFE) and those with IPF, the former showed less male predominance and smoking habit than the latter (**Table1)**. During the observation period, lung cancer (LC) incidence was significantly higher in patients with IPF than that in those with iPPFE. The pulmonary function tests revealed that patients with iPPFE had significantly lower %FVC and forced expiratory volume in 1 s (FEV_1) than those with IPF. %DLCO was not significantly different. However, a tendency for greater impairment was noted in patients with IPF. Additionally, patients with iPPFE exhibited significantly higher $PaCO_2$ and lower KL-6 levels than those with IPF. SP-D level and BAL findings were similar between the iPPFE and IPF groups.

AE incidence in iPPFE and IPF groups

Among 62 patients with iPPFE and 323 with IPF, 16 (25.8%) and 94 (29.4%) had experienced AE, respectively. There were no AE associated with surgical lung biopsy. The median time of AE incidences and 2- and 5-year AE incidences in patients with iPPFE were 46.4 (18.0–78.5) months and 8.1% and 17.7%, respectively, whereas those in patients with IPF were 39.3 (19.5–59.2) months and 8.4% and 22.0%, respectively. The cumulative AE incidence in patients with iPPFE was slightly lower, although not significant, than that in patients with IPF (Fine-Gray test, p=0.3490, **Figure2**).

Further, we attempted to assess the predictive factors for AE in patients with iPPFE and IPF. The univariate analysis showed that lower %FVC, lower $\%FEV_1$ and higher KL-6 levels were associated with AE in patients with iPPFE (***Table3***).

Differences in prognosis between iPPFE and IPF groups and their prognostic factors

During the observation period, 42 (67.4%) patients with iPPFE and 152 (47.1%) with IPF died. The most common cause of death in patients with iPPFE were chronic respiratory failure (73.8%), followed by AE (14.3%); none of the patients with iPPFE developed LC. Further, 69 (45.4%), 45 (29.6%) and 19 (12.5%) patients with IPF presented with chronic respiratory failure, fatal AE and LC, respectively. These results indicated that patients with iPPFE had a significantly higher frequency of chronic respiratory failure and lower fatal AE and LC incidence (**Table2**); these patients significantly worse survival than those with IPF ($p<0.0001$; median survival duration: 47.2 vs. 81.2 months; 5-year survival rate: 38.5% vs. 63.5%; **Figure3A**). In patients with iPPFE and those with IPF, significant differences were observed in terms of sex and %FVC, which are the prognostic factors of IPF; therefore, a propensity-matched analysis with these two variables was performed using 44 well-matched pairs between iPPFE and IPF (***TableS3)***. Despite adjusting for sex and %FVC, patients with iPPFE exhibited a worse prognosis than those with IPF ($p=0.0110$, **Figure3B**).

Next, we explored prognostic factors in patients with iPPFE and IPF using Cox-hazard regression analyses. Age, male gender, and SP-D levels were significant by univarate analyses. Multivariate analysis, including age, gender, and SP-D levels, revealed that male gender was an independent prognostic factor in patients with iPPFE (**Table4**). By contrast, age, AE incidence, lower %FVC and higher SP-D level were independently associated with poor prognosis in patients with IPF (***TableS4)***.

DISCUSSION

In the present study, we demonstrated clinical important characteristics of iPPFE by comparison with those in IPF using largest cohort. The patients with iPPFE exhibited similar frequencies of AE, lower incidences of LC and died of chronic respiratory failure. Subsequently, patients with iPPFE exhibited significantly worse survivals than those with IPF. Additionally, this study first validated the previously proposed clinical diagnostic criteria for iPPFE, and showed clinical and prognostic concordance between c-iPPFE and p-IPPFE. Collectively, these observations confirmed the efficiency of the clinical diagnostic criteria for iPPFE and revealed clinically important characteristics of iPPFE.

Currently, histologic confirmation is required to obtain a definite iPPFE diagnosis. However, several challenges, such as persistent post-operative pneumothorax and severe pulmonary function impairment, inhibit the performance of SLB in clinical practice. Therefore, several clinical diagnostic criteria excluding SLB for iPPFE have been proposed [3-5]. The present study demonstrated that patients with c-iPPFE and p-iPPFE shared similar clinical features in terms of gender predominance, smoking habits, lower-lobe ILD incidence, pulmonary function test results and laboratory and BAL findings. Moreover, the prognosis of patients with c-iPPFE did not differ from that of patients with p-iPPFE. These data collectively suggest that our clinical diagnostic criteria for iPPFE extract similar population to that of p-iPPFE and are highly feasible in clinical practice.

Further, the clinical characteristics, prognosis and prognostic factors of iPPFE were compared with those of IPF. To the best of our knowledge, this study included the largest number of patients with iPPFE. Beside the characteristic radiologic features, there were several differences between iPPFE and IPF. Remarkably, LC incidence was extremely lower in the iPPFE group than in the IPF group (overall incidence, $p<0.0001$). Indeed, none of the patients with iPPFE developed LC during a median observation period of 34.6 months.

Interestingly, spirometric impairment and increased $PaCO_2$ levels were observed in patients with iPPFE. Consistent with previous studies [3, 7, 9, 11, 18-20], the present study showed that serum KL-6 levels in these patients remained around the upper limit of the normal range, whereas the serum SP-D levels increased approximately twice than the upper limit.

Importantly, we observed that AE occurred in iPPFE, with similar incidence to that of IPF. Recently, patients with iPPFE developed AE in several case studies [7, 8, 11, 13]. However, its annual incidence and risk factors as well as its impact on the clinical course of iPPFE remain unknown. Considering this, the present study first showed that AE incidence between patients with iPPFE and those with IPF was similar. In addition, higher serum KL-6 levels and lower %FVC and $\%FEV_1$ were considered risk factors for AE in patients with iPPFE.

Notably, patients with iPPFE had significantly worse survival than those with IPF, and this prognostic difference remained significant despite adjusting for propensity score matching. To date, only few studies have compared the prognosis between patients with iPPFE and IPF. Our previous study, including only 18 patients with p-iPPFE, showed that these patients have poorer prognosis than those with IPF [6]; the present study confirmed this result in a larger cohort with iPPFE. Importantly, significant differences were observed in terms of the causes of death between patients with iPPFE and those with IPF. The proportion of patients with chronic respiratory failure was significantly higher in the iPPFE group than in the IPF group. Meanwhile, fatal AE development was higher in patients with IPF than in those with iPPFE, although AE incidence was similar. LC accounted for 12.5% of deaths in patients with IPF and in none of the patients with iPPFE. Collectively, our data indicate the typical features of iPPFE, with approximately 80% patients presenting with rapid disease progression, thereby making iPPFE the worst type of ILD.

Furthermore, we explored the prognostic factors of iPPFE and IPF. Interestingly, different factors were associated with mortality among patients with iPPFE and IPF. The

multivariate analysis revealed that only male gender was the independent prognostic factor in iPPFE and age and lower %FVC, besides SP-D levels and AE incidence, were independently correlated to poor prognosis in IPF. To date, several prognostic factors have reportedly been associated with iPPFE. Consistent with this study, Khiroya et al. have reported that only male sex was correlated to an increased mortality risk in 43 p-iPPFE cases [17]. Moreover, we have previously found that male gender and low elector spinae muscle attenuation , as determined via CT scan, were independent poor prognostic factors in patients with iPPFE [11].

Lower %FVC [9], presence of lower-lobe ILD/lower-lobe UIP pattern [8, 9] and higher KL-6 levels [7] were reported as significant prognostic determinants of iPPFE. However, these factors were not significant in our cases. The causes of these discrepancies are not fully elucidated, and the differences in the cohort characteristics might cause such discrepancies. Regarding the presence of lower-lobe ILD, Kono et al. recently revealed that patients with iPPFE having lower-lobe ILD, particularly lower-lobe UIP pattern, exhibited significantly worse survival than those without lower-lobe ILD [9]. By contrast, Enomoto et al. showed no significant difference in prognosis between patients with iPPFE who presented with lower-lobe UIP/possible UIP pattern and those without [3]. In the present study, because most patients with iPPFE (88.7%) had lower-lobe ILD, conducting a statistical analysis between patients with and without lower-lobe ILD was challenging.

The present study had several limitations. Although a relatively large number of patients with iPPFE and IPF were enrolled, the number of patients is small, and a retrospective analysis was performed. Addiionally, this study only used one series of criteria among several proposed clinical diagnostic criterias [3-5]. Third, composition of the subjects was unbalanced; approximately 70 % of patients with IPF were pathologically confirmed IPF/UIP, the frequencies were relatively higher than those in clinical setting. Fourth, the present study evaluated AE incidence and prognosis in patients with iPPFE, but detailed clinical course of

iPPFE, such as lower-lobe ILD development and insidious spirometric decline before iPPFE diagnosis, were not assessed. Therefore, further population-based studies must be conducted to examine these issues.

In conclusion, the present study first validated efficiency of the clinical diagnostic criteria for iPPFE, and showed clinical and prognostic similarities between c-iPPFE and p-iPPFE. Moreover, we found crucial features of iPPFE in practice. The occurrence of LC was lower in patients with iPPFE than in those with IPF, although AE incidence was similar. Over 70% of patients with iPPFE died from chronic respiratory failure, and AE only accounted for 10% of the deaths. Importantly, the prognosis of iPPFE was significantly worse than that of IPF. Collectively, the present study provided novel knowledge for iPPFE in the context of diagnosis and disease courses. These clinically important characteristics of iPPFE should be considered for its diagnosis and management.

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Author contributions

YS: Conception, Methodology, Data Curation, Investigation, Formal analysis, Manuscript writing, and Final approve of manuscript, TF,HS, TT, CS: Conception and Data Curation, YH, MK, HH, MK, KF, NE, YN, NI,: Data Curation and Supervision, TS: Conception and Methodology, Manuscript writing, Final approve of manuscript and Project Administration.

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FIGURE LEGENDS

Figure 1. Survivals of patients with p-iPPFE and c-iPPFE.

Kaplan-Meier curves of patients with p-iPPFE and c-iPPFE (A). Gender and %FVC matched p-iPPFE and c-iPPFE (B).

Figure 2. Cumulative incidences of AE in patients with iPPFE and IPF.

Cumulative incidences of AE in patients with iPPFE and IPF.

Figure 3. Survivals of patients with iPPFE and IPF.

Kaplan-Meier curves of patients with iPPFE and IPF (A). Gender and %FVC matched iPPFE and IPF (B).

432 ***Table 1. Clinical characteristics of 62 iPPFE patients and 323 IPF patients***

	p-iPPFE (n=27)	c-iPPFE (n=35)	p-iPPFE vs c-iPPFE *p*-values	iPPFE (n=62)	IPF (239 IPF/UIP, 84 cIPF) (n=323)	iPPFE vs IPF *p*-values
Age, yr	68.0 [63.0-72.0]	70.0 [65.0-77.0]	0.0443	69.0 [63.0-74.0]	67.0 [62.0-72.0]	0.0562
Sex, male/female	19 (70.4%) / 8 (29.6%)	19 (54.3%) / 16 (45.7%)	0.2931	38 (61.3%) / 24 (38.7%)	253 (78.3%) / 70 (21.7%)	0.0060
Observation period, mo	32.0 [14.2-56.6]	40.3 [21.0-70.0]	0.2774	34.6 [18.4-63.3]	53.3 [30.0-79.5]	0.0059
Smoking; never / former	17 (63.0%), 10 (37.0%)	24 (68.6%), 11 (31.4%)	0.7876	41 (66.1%), 21 (33.9%)	74 (22.9%), 249 (77.1%)	<0.0001
Smoking pack-year	0 [0-22.5]	0 [0-10.0]	0.6433	0 [0-12.5]	30.0 [1.4-52.5]	<0.0001
Acute exacerbation, yes	11 (40.7%)	5 (14.3%)	0.0386	16 (25.8%)	94 (29.4%)	0.6471
Lung cancer development	0 (0%)	0 (0%)	1.000	0 (0%)	50 (15.5%)	<0.0001
CTD development	0 (0%)	0 (0%)	1.000	0 (0%)	8 (2.5%)	0.3644
Family history, yes	2 (7.4%)	5 (14.3%)	0.4550	7 (11.3%)	16 (5.0%)	0.0738
Pulmonary Function Test						
FVC, %-pred	65.7 [45.4-79.8] (n=26)	53.0 [45.3-67.8] (n=32)	0.2110	57.5 [46.4-72.0] (n=58)	82.0 [68.5-93.8] (n=308)	<0.0001
FVC, L	1.86 [1.48-2.42] (n=26)	1.54 [1.05-2.12] (n=32)	0.0632	1.68 [1.24-2.29] (n=57)	2.63 [2.07-3.16] (n=308)	<0.0001
FEV_1, %-pred	79.0 [55.7-94.5] (n=26)	66.6 [54.3-84.4] (n=32)	0.2841	73.1 [54.6-88.6] (n=58)	84.5 [72.4-93.5] (n=290)	0.0005
FEV_1, L	1.81 [1.32-2.11] (n=26)	1.44 [1.01-1.91] (n=32)	0.1326	1.63 [1.16-2.08] (n=58)	2.16 [1.72-2.57] (n=308)	<0.0001
FEV_1/FVC, %	93.5 [88.0-96.7] (n=26)	98.3 [92.0-100] (n=32)	0.0145	95.8 [90.1-100] (n=58)	83.1 [79.0-87.9] (n=309)	<0.0001
DLCO, %	75.1 [68.5-90.0] (n=16)	66.0 [42.7-111.6] (n=18)	0.3979	69.7 [53.3-93.4] (n=34)	67.8 [54.9-86.2] (n=214)	0.5942
CT images						
Presence of lower lobe	24 (88.9%)	29 (82.9%)	0.7192	53 (85.5%)	-	-

ILD, yes						
Laboratory						
PaO_2, Torr	82.0 [72.1-92.8] (n=26)	80.2 [72.2-87.0] (n=30)	0.5057	80.6 [72.4-89.8] (n=56)	83.8 [75.7-90.7] (n=290)	0.1529
$PaCO_2$, Torr	46.3 [39.0-49.8] (n=26)	46.8 [41.8-49.1] (n=30)	0.5820	46.6 [40.0-49.2] (n=56)	41.3 [39.0-43.9] (n=290)	<0.0001
KL-6, U/ml	485 [425.-770] (n=27)	499 [333-636] (n=34)	0.2635	487 [368.-644] (n=61)	969 [610-1470] (n=299)	<0.0001
SP-D ng/ml	204 [98-343] (n=25)	167 [130-243] (n=33)	0.6264	168 [111-288] (n=58)	200 [130-318] (n=271)	0.2054
LDH, IU/l	200 [168-233] (n=27)	199 [182-234] (n=34)	0.6578	200 [178-233] (n=61)	225 [199-254] (n=314)	<0.0001
BAL						
MAC, (%)	90.0 [80.8-95.9] (n=21)	86.2 [74.7-92.0] (n=16)	0.2439	88.0 [76.7-92.9] (n=37)	88.2 [75.0-95.0] (n=237)	0.6141
Ly, (%)	8.0 [2.4-13.8] (n=21)	8.7 [5.1-19.3] (n=16)	0.3416	8.3 [4.4-14.9] (n=37)	6.3 [2.4-14.0] (n=236)	0.3305
Neut, (%)	0.9 [0.5-2.2] (n=21)	1.9 [1.0-5.1] (n=16)	0.0626	1.0 [0.6-3.8] (n=37)	1.0 [0.2-2.5] (n=233)	0.4089
Eos, (%)	1.0 [0-3.9] (n=21)	1.0 [0.1-1.6] (n=16)	0.7200	1.0 [0-2.0] (n=37)	1.0 [0.2-2.3] (n=230)	0.4610
CD4 / CD8	2.1 [1.3-3.4] (n=20)	1.9 [1.0-3.0] (n=13)	0.2171	1.9 [1.3-3.2] (n=33)	1.8 [0.9-3.5] (n=219)	0.5514
Treatment						
Anti-fibrotic agents	10 (37.0%)	5 (14.3%)	0.0706	15 (24.2%)	127 (39.3%)	0.0305

433

434 FVC; forced vital capacity, $FEV_{1.0}$; forced expiratory volume in 1.0 second, DLCO; diffuse capacity of the lung for carbon monoxide, KL-6;

435 Krebs von den Lunge-6, SP-D; surfactant protein-D, LDH; lactate dehydrogenase, BAL; broncho alveolar lavage, MAC; macrophage, Ly;

436 lymphocyte, Neyt; neutrophil, Eos; eosinophil

Table 2. Cause of Death in patients with 62 PPFE patients and 323 IPF patients

	p-iPPFE (n=27)	c-iPPFE (n=35)	p-iPPFE vs c-iPPFE *p*-values	iPPFE (n=62)	IPF (239 IPF/UIP, 84 cIPF) (n=323)	iPPFE vs IPF *p*-values
Chronic respiratory failure	15 (75.0%)	16 (72.7%)	1.0000	31 (73.8%)	69 (45.4%)	0.0015
Acute exacerbation	4 (20.0%)	2 (9.1%)	0.4004	6 (14.3%)	45 (29.6%)	0.0493
Lung cancer	0 (0%)	0 (0%)	1.0000	0 (0%)	19 (12.5%)	0.0153
Infection	0 (0%)	2 (9.1%)	0.4890	2 (4.8%)	6 (3.9%)	0.6842
Others	1 (5.0%)	2 (9.1%)	1.0000	3 (7.1%)	13 (8.6%)	1.0000

Table 3. Prediction of Acute Exacerbation in Patients with PPFE and IPF by Univariate Grey's Tests

	iPPFE			IPF		
Univariate analysis	HR	95% CI	p-value	HR	95% CI	p-value
Age, yr	0.9892	0.9512 – 1.0290	0.590	0.996	0.9745 – 1.018	0.71
Gender, male	1.411	0.2567 – 1.9560	0.510	1.072	0.6409 – 1.792	0.79
FVC, %-pred	1.018	0.9988 – 1.0370	0.067	0.9844	0.9749 – 0.994	0.0016
FEV, %-pred	1.018	1.003 – 1.033	0.022	0.9895	0.9797 – 0.9995	0.039
DLCO, %	1.012	0.9948 – 1.0300	0.170	0.9876	0.9777 – 0.9976	0.016
KL-6, U/ml	1.001	1.0000 – 1.0020	0.0032	0.9985	0.9959 – 1.001	0.25
SP-D, ng/ml	1.001	0.9985 – 1.0030	0.530	1.000	0.9967 – 1.004	0.91
LDH, IU/l	1.007	0.9921 – 1.0220	0.370	1.006	1.002 – 1.010	0.0013
Anti-fibrotic agents, yes	0.6229	0.1799 – 2.1560	0.450	1.182	0.7877 – 1.773	0.42
Presence of lower lobe ILD	1.7980	0.2310 – 14.0	0.580	-	-	-

BMI; body mass index, ESM_{CSA}; cross-sectional area of elector spine muscles, ESM_{MA}; muscle attenuation of elector spine muscles, FVC; forced vital capacity, $FEV_{1.0}$; forced expiratory volume in 1.0 second, DLCO; diffuse capacity of the lung for carbon monoxide,

445 ***Table 4. Prediction of Mortality in Patients with 62 iPPFE by Univariate and Multivariate Cox-proportion Analyses***

Predictor	HR	95% CI	p-value	Predictor	HR	95% CI	p-value
Univariate analysis				**Multivariate analysis**			
Age, yr	1.0263	0.9930 – 1.0656	0.1509		1.0290	0.9911 – 1.0773	0.1795
Gender, male	2.2926	1.1828 – 4.7254	0.0178		2.3340	1.0982 – 5.3134	0.0332
AE, yes	1.0495	0.5521 – 2.1025	0.8864				
FVC, %-pred	0.9925	0.9769 – 1.0071	0.3335				
FEV, %-pred	0.9925	0.9793 – 1.0049	0.2497				
DLCO, %	0.9896	0.9772 – 1.0016	0.0972				
KL-6, U/ml	1.0001	0.9998 – 1.0016	0.1005				
SP-D, ng/ml	1.0013	1.0002 – 1.0021	0.0088		1.0009	0.9996 – 1.0018	0.1135
LDH, IU/l	1.0076	0.9994 – 1.0148	0.0497				
Anti-fibrotic agents, yes	1.4938	0.7268 – 2.8941	0.2502				
Presence of lower lobe ILD	1.0065	0.3998 – 3.380	0.9903				
Lower lobe ILD: UIP pattern	1.5623	0.5861-3.500	0.3189				

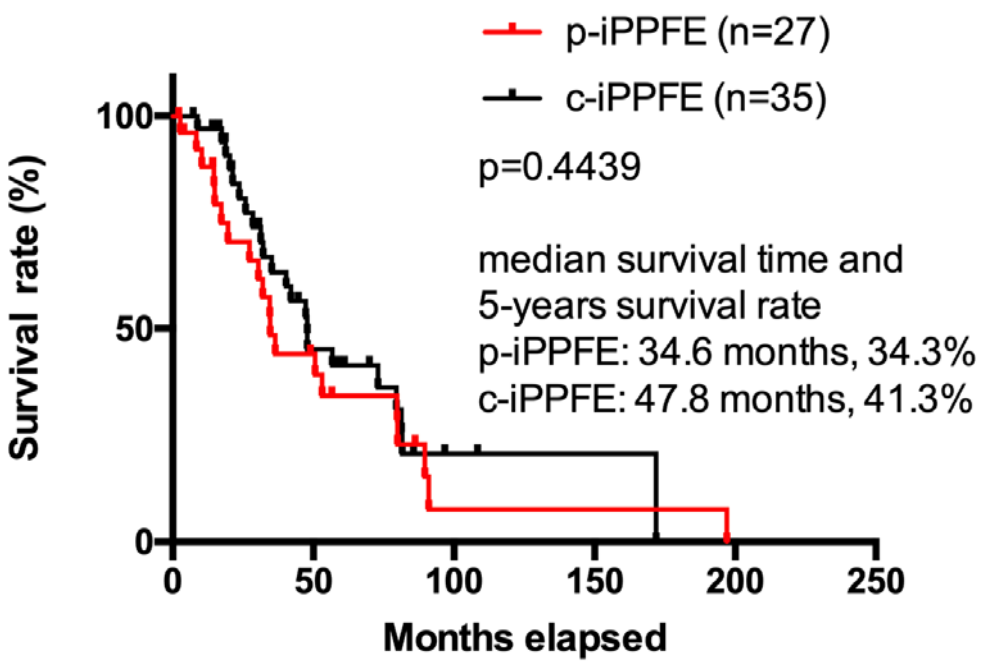
446

447 BMI; body mass index, ESM_{CSA}; cross-sectional area of elector spine muscles, ESM_{MA}; muscle attenuation of elector spine muscles, FVC;

448 forced vital capacity, $FEV_{1.0}$; forced expiratory volume in 1.0 second, DLCO; diffuse capacity of the lung for carbon monoxide,

Figure1

A)


Survival of patients with p-iPPFE and c-iPPFE
p-iPPFE (n=27)
c-iPPFE (n=35)
p=0.4439
median survival time and
5-years survival rate
p-iPPFE: 34.6 months, 34.3%
c-iPPFE: 47.8 months, 41.3%
Survival rate (%)
100
50
0
0
50
100
150
200
250
Months elapsed

B)

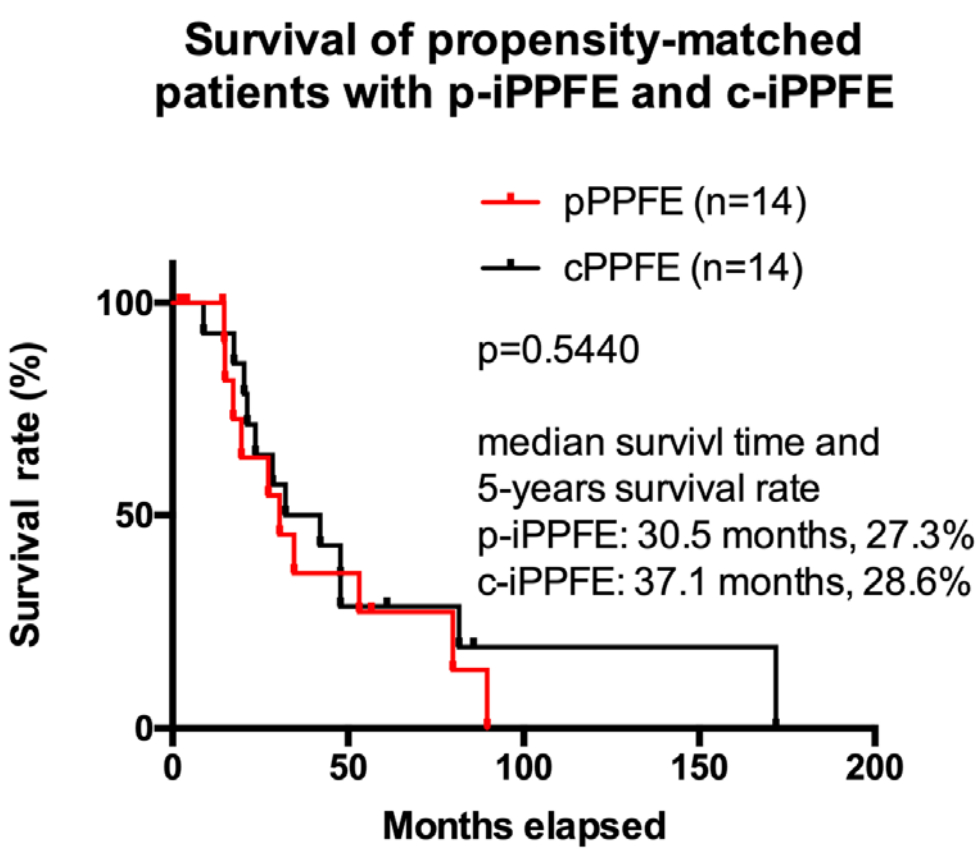

Survival of propensity-matched
patients with p-iPPFE and c-iPPFE
pPPFE (n=14)
cPPFE (n=14)
p=0.5440
median survivl time and
5-years survival rate
p-iPPFE: 30.5 months, 27.3%
c-iPPFE: 37.1 months, 28.6%
Survival rate (%)
100
50
0
0
50
100
150
200
Months elapsed

Figure2

Culumative incidences of AE in patients with iPPFE and IPF

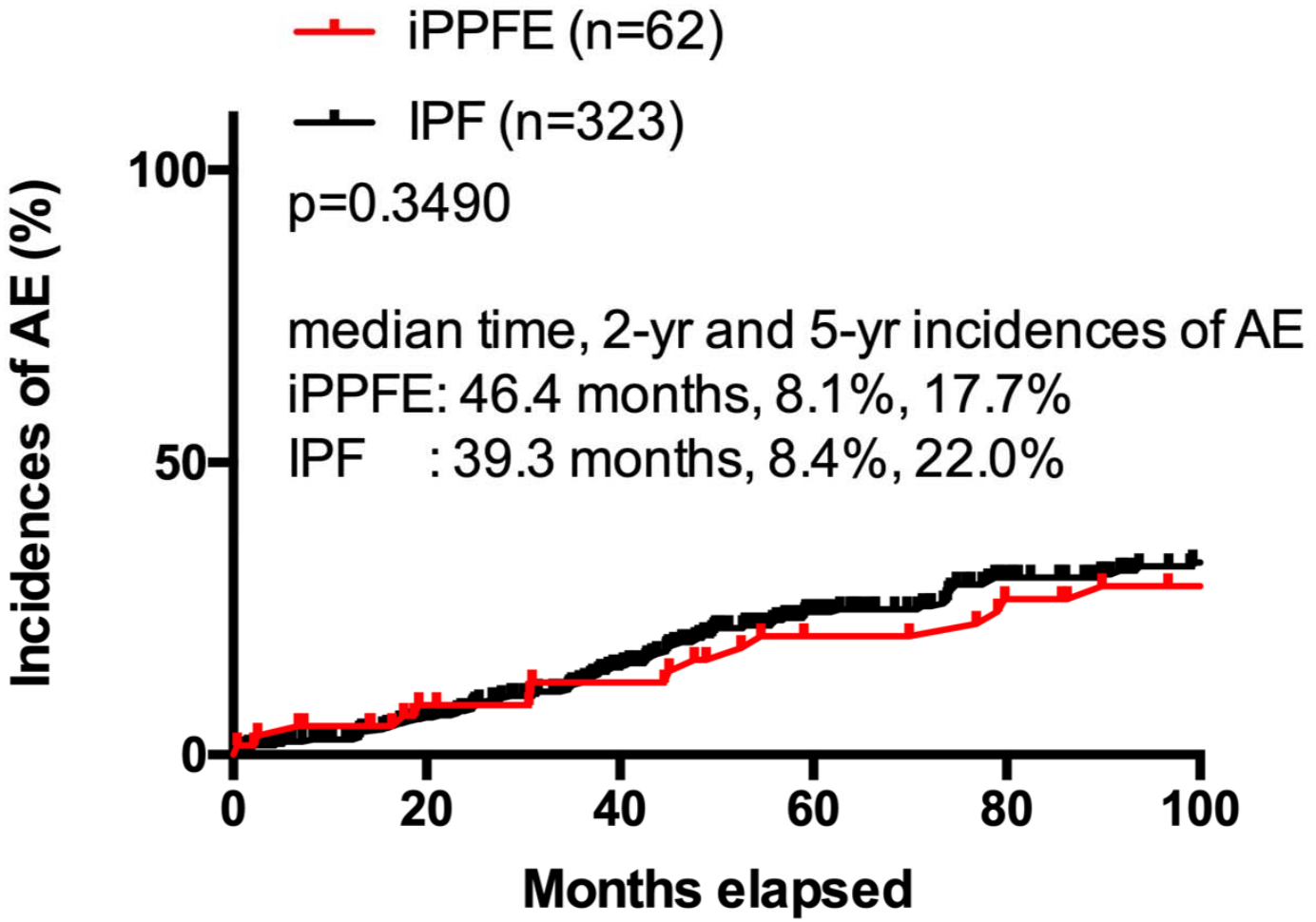
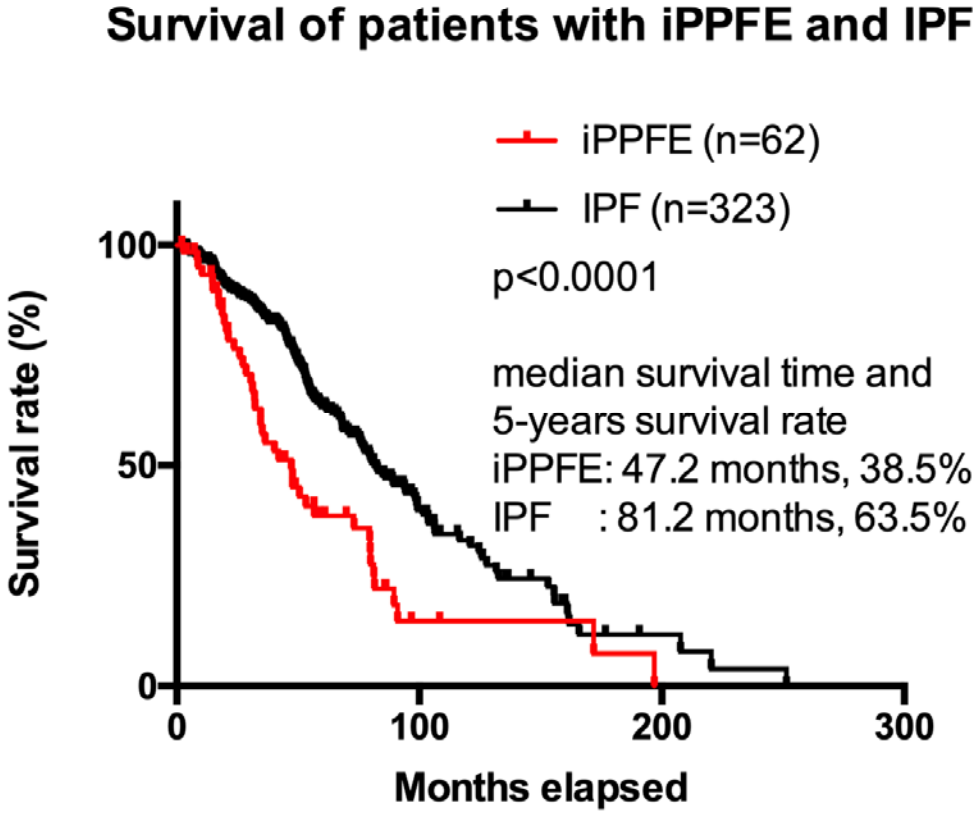
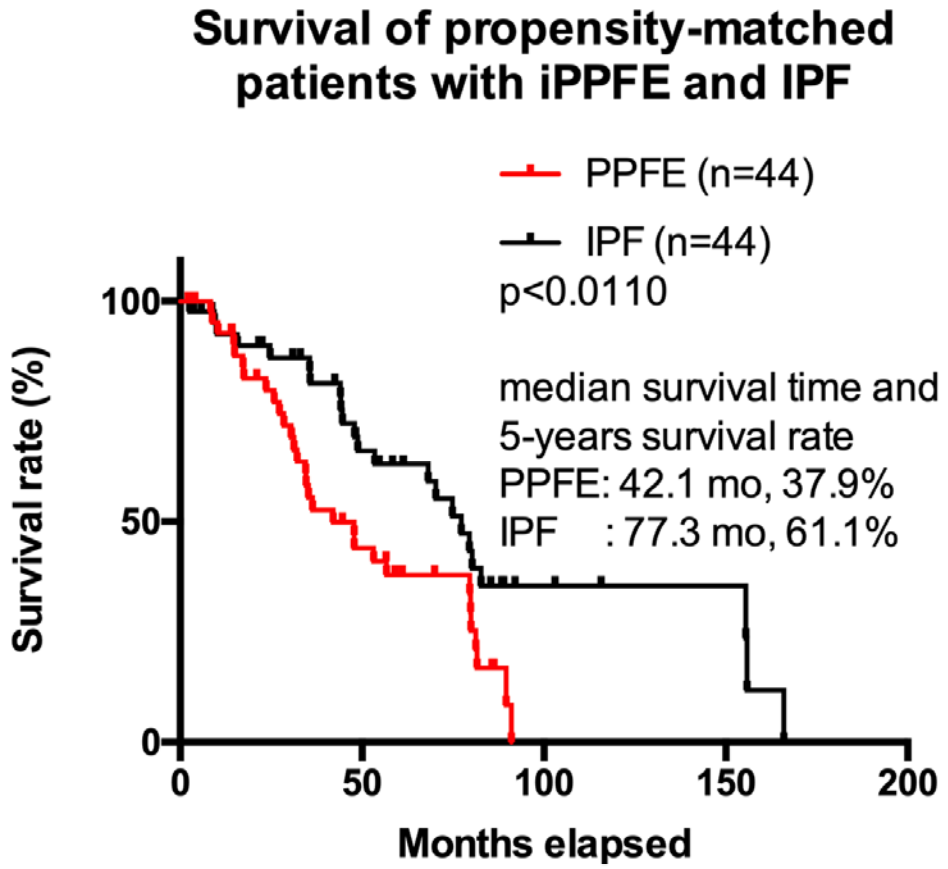


Figure3

A)


Survival of patients with iPPFE and IPF
iPPFE (n=62)
IPF (n=323)
p<0.0001
median survival time and
5-years survival rate
iPPFE: 47.2 months, 38.5%
IPF : 81.2 months, 63.5%
Survival rate (%)
100
50
0
0
100
200
300
Months elapsed

B)


Survival of propensity-matched
patients with iPPFE and IPF
PPFE (n=44)
IPF (n=44)
p<0.0110
median survival time and
5-years survival rate
PPFE: 42.1 mo, 37.9%
IPF : 77.3 mo, 61.1%
Survival rate (%)
100
50
0
0
50
100
150
200
Months elapsed