Clinical, radiological, and pathological features of idiopathic and secondary interstitial pneumonia cases with pleuroparenchymal fibroelastosis undergoing lung transplantation

胸膜肺実質線維弾性症を伴う特発性間質性肺炎および二次性間質性肺炎の肺移植症例の臨床的、画像的、病理学的特徴

池上　直弥

Histopathology

Histopathology Accepted 06 November 2021
Published Online 08 November 2021

主論文

Title: Clinical, radiological, and pathological features of idiopathic and secondary interstitial pneumonia cases with pleuroparenchymal fibroelastosis undergoing lung transplantation

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Running title: Features of idiopathic and secondary PPFE (41 characters)

Word counts: 2,498/2,500 words (Abstract 250/250 words)

Abstract

Aims: Idiopathic pleuroparenchymal fibroelastosis (PPFE) is a rare type of idiopathic interstitial pneumonia, and pathological PPFE is also observed in secondary interstitial pneumonia. This study aimed to evaluate the pathological findings associated with radiological PPFE-like lesions and the clinical and morphological features of patients with pathological PPFE.

Methods and Results: We retrospectively reviewed the pathology of the explanted lungs from 59 lung transplant recipients with radiological PPFE-like lesions. Pathological PPFE lesions were identified in 14 patients with idiopathic cases and 12 patients with secondary cases. Pathological PPFE was associated with previous pneumothorax, a volume loss in the upper lobes and a flattened chest. Patients with idiopathic and secondary cases with pathological PPFE had similar clinical, radiological, and pathological findings, while fibroblastic foci were more common in patients with idiopathic cases, and patients with secondary cases more frequently showed alveolar septal thickening with elastosis or fibrosis. Post-transplantation survival did not differ between patients with idiopathic and secondary cases with pathological PPFE (log-rank; P=0.57) and was similar between patients with idiopathic cases with pathological PPFE and patients with idiopathic pulmonary fibrosis (IPF) (log-rank; P = 0.62).

Conclusions: Not all patients with interstitial pneumonia with radiological PPFE-like lesions have pathological PPFE. Characteristic clinical features can suggest the presence of pathological PPFE, and idiopathic and secondary cases with pathological PPFE are similar except for fibroblastic foci in idiopathic cases and alveolar septal thickening with elastosis or fibrosis in secondary cases. Patients with pathological PPFE have a similar prognosis to those with IPF after transplantation.

Keywords: pleuroparenchymal fibroelastosis, interstitial lung disease, haematopoietic stem cell transplantation, lung transplantation

Introduction

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) was first reported as idiopathic pulmonary upper lobe fibrosis in 1992 and has been increasingly recognized since the 2013 American Thoracic Society/European Respiratory Society statement of classification for idiopathic interstitial pneumonias (IIPs) categorized as IPPFE as a rare but separate IIP.[1, 2] IPPFE is characterized by bilateral subpleural airspace consolidations in the upper lobes (PPFE-like lesions) radiologically and pathological intra-alveolar fibrosis and elastosis (IAFE).[2, 3] These features are observed in not only IPPFE but also other IIPs (e.g., idiopathic pulmonary fibrosis [IPF] and unclassifiable cases),[4-7] fibrotic interstitial lung diseases (fibrotic ILDs) secondary to extrinsic causes (e.g., asbestosis,[8] aluminium,[9] hypersensitive pneumonitis [HP],[10] late-onset noninfectious pulmonary complications [LONIPC] after haemopoietic stem cell transplantation [HSCT],[11, 12] or chemotherapy,[13] chronic lung allograft dysfunction[14]), and connective tissue disease-associated ILD [CTD-ILD][15, 16]. Although radiological PPFE-like lesions are seen in more than 10% of fibrotic ILD patients,[17, 18] pathological confirmation is not feasible in most cases due to the high risks associated with surgical lung biopsy (SLB).[19]

No effective medical treatment is currently available for IPPFE and secondary lung diseases with PPFE; thus, lung transplantation (LT) is the therapeutic option for patients with advanced cases.[20-22] Lungs explanted during LT enable pathological evaluation of the entire lung, a procedure that is desirable for comprehensively investigating the frequency and distribution of pathological PPFE lesions and their associated pathological features.

The objective of this study was to evaluate the pathological findings associated

with radiological PPFE-like lesions and their clinical and morphological features according to the presence of extrinsic causes or underlying diseases. We reviewed the pathology of explanted lungs from consecutive LT recipients with radiological PPFE-like lesions and compared features between patients with idiopathic and secondary cases with confirmed pathological PPFE. Post-LT prognosis in these patients with pathological PPFE was also analysed.

Methods

Study patients

The cohort inclusion diagram is shown in Figure 1. Among all patients who underwent LT (cadaveric or living donor) at Kyoto University Hospital between July 1, 2009, and March 31, 2018, those with a pre-transplantation diagnosis of fibrotic ILD or LONIPCs after HSCT or chemotherapy were identified from the prospective registry database. The pre-transplantation diagnosis was determined based on the multidisciplinary diagnosis at the individual referring institutions. Of these LT recipients, only those with radiological PPFE-like lesions (described below) in the upper lobe before LT were included in the study cohort. Patients younger than 18-year-old or those who had undergone re-transplantation (a second LT) were excluded from analysis. This study was approved by Kyoto University Hospital's Institutional Review Board (R2401).

Radiological evaluation

The high-resolution computed tomography (HRCT) scans of all recipients with fibrotic ILDs and post-HSCT/chemotherapy LONIPCs obtained the day before LT were reviewed for this study by two observers (T.K. and N.I.) blinded to clinical information.

Interobserver disagreement was resolved by consensus.

First, study patients were screened by the presence of radiological PPFE-like lesions. We selected patients with bilateral subpleural airspace consolidations in the upper lobes without any identifiable aetiology, according to previous reports[19, 23]. The diagnosis of radiological PPFE-like lesions could be made with or without the following findings, but all patients underwent further radiological evaluation including these findings: presence of PPFE-like lesions in other lobes, coexistence of other ILD patterns in any of the lobes, or other findings characteristic of PPFE (subpleural consolidation or upper lobe volume loss[2]). Other coexisting ILD patterns were diagnosed according to the current guidelines of IPF.[24] The ratio of the anteroposterior diameter of the thoracic cage to the transverse diameter of the thoracic cage (APDT/TDT) was calculated at the level of the 6th thoracic vertebra, as described previously.[25]

Pathological evaluation

Two or more tissues were excised from each lobe of the explanted lungs of all patients with a radiological PPFE pattern, and slides of the sections were prepared. Each slide stained with haematoxylin and eosin and elastic van Gieson or elastica-Masson was digitalized. All digital slides were reviewed by three observers (A. Y., N. N., and N. I.). Interobserver disagreement was resolved by consensus.

The pathological PPFE pattern was diagnosed when conspicuous intra-alveolar fibrosis and elastic deposition on the alveolar wall (IAFE) was the predominant pathological feature in the upper lobes according to previous reports[3, 19, 26]. We evaluated intra-alveolar fibrosis (IAF) (prominent or not) and the deposition of elastic fibres (no, mild, moderate or severe elastosis) (Supplementary Figure 1)

semiquantitatively and defined IAFE as both prominent IAF and moderate or severe elastosis. In addition to the lobar pathological pattern, individual pathological features were evaluated for the presence and distribution of elastosis and collagenous fibrosis, fibrotic changes, cellular infiltrates, vascular changes, and other findings (e.g., organizing pneumonia, hyaline membranes, constrictive bronchiolitis obliterans [CBO], granuloma, emphysema). Elastosis was recorded in the presence or absence of collagenous fibrosis, while collagenous fibrosis was recorded only without coexisting elastosis.

Clinical variables

The clinical variables included in the analysis were demographics, body mass index (BMI) at the time of LT, smoking history, previous and therapeutic history before LT, and LT procedure type (bilateral vs. single, and cadaveric vs. living-donor related), as well as some parameters obtained at the time of evaluation for LT (serum Krebs von den Lungen-6 (KL-6), arterial blood gas analysis, 6-minute walk distance, pulmonary function tests).

The clinical diagnosis for all LT recipients was established based on clinical data, pre-transplantation HRCT scans and explanted lung specimens as a usual practice. For patients with pathological PPFE in the upper lobes, the final diagnosis was revisited for this study through multidisciplinary consensus.

Statistical analysis

Wilcoxon and Fisher's exact tests were used for group comparisons. The post-transplantation survival time was calculated from the date of LT until the patient's

death, with patients right-censored at the time of the last contact or second LT. Kaplan–Meier curves and the log-rank test were used to demonstrate and compare overall post-transplantation survival time. Statistical analyses were performed using R (version 3.44; The R Foundation for Statistical Computing, Vienna, Austria) and EZR (version 1.35; Saitama Medical Center, Jichi Medical University, Saitama, Japan). For all analyses, a *P* value < 0.05 was considered statistically significant.

Results

Patient characteristics

Among the 178 consecutive LT recipients, 79 (44.4%) had a pre-transplantation diagnosis of fibrotic ILD, and 28 (15.7%) had post-HSCT/chemotherapy LONIPCs. A radiological PPFE pattern was observed in 59 patients (55.1% of patients with fibrotic ILD or post-HSCT/chemotherapy LONIPC; 33.1% of all LT recipients) (Figure 1, Figure 2A, 2B). The clinical features of LT recipients with radiological PPFE-like lesions are shown in Table 1.

Features of patients with pathological PPFE

Among 59 patients with radiological PPFE-like lesions, 26 patients (14 [40%] of 35 IIP patients and 12 [50%] of 24 secondary lung disease patients) had a pathological PPFE pattern confirmed in the explanted upper lobes. Representative features of the pathological PPFE patterns are shown in Figure 2C, 2E, Supplementary Figure 1A and 1B. Patients without a pathological PPFE pattern did not have IAFE because they lacked significant alveolar septal elastosis or conspicuous intra-alveolar fibrosis. In addition, pleural fibrosis was more common in patients with pathological

PPFE, while honeycombing was more frequent in patients without PPFE (Supplementary Table 1). The pathological findings of patients without significant IAFE are shown in Figure 2D, 2F, Supplementary Figure 1C, 1D and 1E.

The clinical and radiological features of patients with or without pathological PPFE were compared. The pathological PPFE pattern was significantly associated with previous pneumothorax, a lower level of KL-6, and a higher level of $PaCO_2$ (Table 2) and was radiologically characterized by a volume loss in the upper lobes and lower APDT/TDT (Supplementary Table 2).

Clinical, radiological and pathological comparison of patients with idiopathic and secondary cases with pathological PPFE

Among 26 patients with pathological PPFE in the upper lobe, 14 (54%) had a multidisciplinary diagnosis of IIPs (idiopathic cases), and 12 (46%) had a diagnosis of secondary lung disease (secondary cases). Their diagnoses are listed in Table 2, and the clinical features of these patients with idiopathic and secondary cases with pathological PPFE are summarized in Table 3. LT recipients with secondary cases were younger and had a lower BMI and a higher percentage of the predicted ratio of the residual volume to total lung capacity (%RV/TLC).

The HRCT features of patients with idiopathic and secondary cases are shown in Supplementary Table 3. More than half of all patients also had PPFE-like lesions in the middle or lower lobes. Other coexisting ILD patterns were seen in approximately 60% of both groups. The median APDT/TDT was lower in patients with secondary cases.

The pathological features of the whole lungs and those of the upper and lower

lobes were compared between idiopathic and secondary cases (Table 4). Secondary cases had more frequent alveolar septal thickening with elastosis or fibrosis (Supplementary Figure 2), granulomas and CBO, while fibrotic changes associated with UIP (fibroblastic foci and honeycombing) were more common in idiopathic cases.

Post-transplantation survival

The five-year survival of patients with pathological PPFE was 68.6% (95% confidence interval [CI]: 46.8-82.9). Post-transplantation survival was similar between patients with idiopathic cases and those with secondary cases (log-rank; P=0.57) (Figure 3A).

The post-transplantation survival of patients with idiopathic cases was also compared to that of patients with IPF. Of 178 recipients undergoing LT in the same period as the study patients, 17 had a diagnosis of IPF, excluding one recipient with IPF with pathological PPFE. Two idiopathic cases with pathological PPFE coexisting with pathological UIP in lobes other than the upper lobes were diagnosed as unclassifiable IIPs through multidisciplinary discussion. The clinical features of patients with idiopathic cases with pathological PPFE and IPF patients are compared and shown in Supplementary Table 4.

The five-year survival rate of patients with IPF was 52.9% (95% CI: 27.6-73.0). Post-transplantation survival was similar between the two groups (log-rank; P = 0.62) (Figure 3B).

Discussion

We pathologically reviewed the whole explanted lungs from consecutive LT

recipients with radiological PPFE-like lesions and compared the characteristics of idiopathic and secondary cases with pathological PPFE. More than half of patients with radiological PPFE-like lesions showed no pathological PPFE pattern. Patients with idiopathic and secondary cases with pathological PPFE were similar in clinical, radiological, and pathological features. Post-LT survival was comparable in patients with idiopathic and secondary cases with pathological PPFE and IPF.

Our study suggests that radiological PPFE-like lesions cannot be an alternative to the pathological PPFE pattern in all patients because several patients with radiological PPFE-like lesions did not have a corresponding pathological PPFE pattern. Pleural fibrosis and subjacent IAFE have been used as pathological criteria for the diagnosis of PPFE.[3, 26, 27] Based on these preceding studies, we adopted IAFE as a key feature to diagnose the pathological PPFE pattern. Mimickers of IAFE included subpleural fibrosis/elastosis without intra-alveolar involvement and subpleural collagenous fibrosis alone without elastosis.

However, except for LT patients, pathological confirmation of PPFE patterns is usually difficult, and SLB is unavailable in most patients because of low pulmonary function and a high risk for complications.[19] In contrast, a low BMI, high predicted %RV/TLC, and a flattened chest are useful for the diagnosis of PPFE, [28, 29] which is supported by the results of our study. Disease progression (an increase in upper lobe consolidation or a decrease in upper lobe volume) is also useful to distinguish IPPFE from other fibrotic interstitial lung diseases or apical caps.[28]

When comparing patients with idiopathic and secondary cases with pathological PPFE, those with secondary cases were younger and showed lower BMI and higher predicted %RV/TLC. Radiological and pathological features were similar,

although fibroblastic foci were more common in patients with idiopathic cases, while patients with secondary cases showed a higher frequency of alveolar septal thickening with elastosis, CBO, and granuloma. Oda et al. reported that the frequency and prognostic impact of radiological UIP patterns were different between IPPFE and secondary PPFE (mainly associated with HP or CTD).[30] Khiroya et al. reported that 35% of patients with PPFE showed granulomas.[31] In previous studies, PPFE and NSIP pattern fibrosis were frequently found in the pathology of lungs with post-HSCT/CT LONIPCs.[11, 12, 32] Tsubosaka et al. reported a case of chemotherapy-related PPFE with NSIP-like distribution of fibroelastosis along bronchovascular bundles and alveolar walls and hypothesized that elastic fibre-rich NSIP-like changes caused by chemotherapy lead to the development of PPFE.[32] Because we examined peripheral sections of the lungs, fibroelastosis along bronchovascular bundles was not evaluated pathologically; however, peribronchial fibrosis on HRCT and pathological findings of NSIP-like alveolar thickening with fibroelastosis were frequently seen, especially in secondary cases (Supplementary Table 3). Although Tsubosaka's hypothesis cannot be concluded from our data, post-HSCT/CT LONIPC is considered to be an important disease in elucidating the pathogenesis of PPFE. Among the excluded patients in this study, four patients with either non-fibrotic ILD or non-post-HSCT/CT LONIPCs (bronchiectasis, primary ciliary dyskinesia, and diffuse panbronchiolitis) showed radiologically PPFE-like subpleural consolidations, although none of them had a volume loss in the upper lobes, unlike patients with interstitial pneumonias with pathological PPFE.

The post-transplantation survival of patients with IIPs with pathological PPFE was comparable to that of IPF patients. LT provided similar outcomes in patients with

idiopathic and secondary cases with pathological PPFE. The prognosis of IPPFE varied from 2.8 to 8 years between reports.[6, 33] PPFE coexisting with UIP patterns was reported to have a worse prognosis than IPF.[4, 7] However, the survival of patients with radiological PPFE waiting for LT was reported to be non-inferior to that of patients with fibrotic ILDs without radiological PPFE[17] or those with other IIPs.[34] Recently, a few reports have shown the overall survival and physical outcome of patients with PPFE after LT.[35-37] Our study revealed acceptable post-transplantation survival in patients with advanced PPFE, suggesting the rationale of LT for them (both idiopathic and secondary).

This study has some limitations. Multidisciplinary diagnostic criteria for PPFE have not been standardized compared with those for IPF[24] and HP.[38] Other radiological and pathological features frequently coexist with the PPFE pattern, and discordant pathological patterns are also common, so the morphological and clinical spectrum of PPFE can be highly variable. Thus, we reviewed the cases of all patients with the pathological PPFE pattern in the explanted upper lobe, regardless of pathological diagnoses of other lobes and multidisciplinary diagnosis of the whole explanted lung. Notably, our "idiopathic" cases included not only IPPFE but also unclassifiable cases with discordant pathology. Although one of the largest LT recipient cohorts in Asia was used, the number of patients with pathological PPFE was insufficient to adjust for potential confounders. The single-institution study design may also have biased the post-transplantation outcomes.

Conclusions

In conclusion, we demonstrated that some LT recipients with advanced

interstitial pneumonias with radiological PPFE-like lesions showed no pathological PPFE. Patients with pathological PPFE showed some unique clinical features (previous pneumothorax, a volume loss in the upper lobes, and a flattened chest). Patients with idiopathic interstitial pneumonia with pathological PPFE had clinical, radiological, and pathological findings that were similar to those of patients with secondary interstitial pneumonia with PPFE, although we found some different clinical and pathological features between them. Patients with confirmed pathological PPFE are expected to have a favourable prognosis after LT.

Acknowledgements

This study was supported in part by grants from the Japan Society for the Promotion of Science (No. 20K08925) to T.H. and from the Japan Society for the Promotion of Science KAKENHI (No. 19K08648) to K.T. We thank Dr Naoki Yamada and Dr Ryobu Mori for editing a draft of this manuscript.

Conflicts of interest

The authors have no potential conflicts of interest with any companies or organizations whose products or services may be discussed in this paper.

List of online Supporting Information

Supplementary Table 1. Pathological features of patients with pathological PPFE pattern and without it in those with radiological PPFE-like lesion

Supplementary Table 2. High-resolution computed tomography features of idiopathic and secondary cases with a pathological PPFE pattern in the upper lobe

Supplementary Table 3. High-resolution computed tomography features of patients with pathological PPFE and without it in those with radiological PPFE-like lesions.

Supplementary Table 4. Characteristics of idiopathic cases with pathological PPFE in the upper lobes and cases with idiopathic pulmonary fibrosis

Supplementary Figure1. The evaluation of subpleural intra-alveolar fibrosis (IAF) and elastic deposition on the alveolar wall in the subpleural area.

Supplementary Figure 2. Histological images of alveolar septal thickening with elastosis or fibrosis.

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Table 1. Patient characteristics with radiological PPFE-like lesions (n = 59)

Age at LT, years	49	(29.5, 56.5)
Male	33	(56)
BMI, kg/m^2	17.8	(15.6, 20.0)
Ever-smoking	33	(56)
Diagnosis		
Idiopathic	35	(59)
IPF	13	(22)
IPPFE	5	(8)
Other IIPs	17	(29)
Secondary	24	(41)
Post-HSCT LONIPC	13	(22)
Post-CT LONIPC	3	(5)
CTD-ILD	4	(7)
HP	3	(5)
HTLV-1-associated pulmonary disease	1	(2)
Pre-LT complications		
Pulmonary hypertension	36	(61)
Pneumothorax	34	(58)
Pre-LT treatment		
Corticosteroid	36	(61)
Immunosuppressive agent	25	(42)
Antifibrotic agent	21	(36)
LT procedures		
Bilateral cadaveric	9	(15)
Single cadaveric	17	(29)
Living-related, bilateral	33	(56)
KL-6, U/mL	859	(520, 1490)
PaO_2, Torr	82.8	(68.7, 98.0)
$PaCO_2$, Torr	49.8	(41.9, 59.3)
6MWD, m	317.5	(203.5, 407.5)
%FVC, predicted	36.1	(27.3, 43.6)
%TLC, predicted	41.5	(34.1, 62.0)
%RV/TLC, predicted	160.1	(126.8, 181.4)
$\%DL_{CO}$, predicted	28.5	(20.2, 37.1)

The data are presented as numbers (percentages) or medians (interquartile ranges). Abbreviations: LT, lung transplantation; BMI, body mass index; IPF, idiopathic pulmonary fibrosis; IPPFE, idiopathic pleuroparenchymal fibroelastosis; HSCT, hemopoietic stem cell transplantation; LONIPC, late-onset non-infectious pulmonary complication CT, chemotherapy; CTD-ILD, connective tissue disease-associated interstitial lung disease; HP, hypersensitivity pneumonia; HTLV-1, human T-cell leukaemia virus type 1; KL-6, Krebs von den Lungen-6; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; 6MWD, six-minute walk distance; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DL_{CO}, diffusion capacity for carbon monoxide.

Table 2. Clinical features of patients with pathological PPFE and without it in those with radiological PPFE-like lesions

	With pathological PPFE		Without pathological PPFE		*P*-value
Number	26		33		
Age, years	49	(33, 56)	46	(28, 56)	0.367
Male	16	(62)	17	(52)	0.598
BMI, kg/m^2	17.0	(15.3, 18.5)	19.0	(16.2, 21.6)	0.058
Ever-smoking	12	(46)	14	(42)	0.798
Idiopathic	14	(54)	21	(64)	
IPF	1	(4)	10	(30)	
IPPFE	5	(19)	0	(0)	
Other IIPs	8	(31)	11	(33)	
Secondary	12	(46)	12	(36)	
Post-HSCT LONIPC	8	(31)	5	(15)	
Post-CT LONIPC	3	(12)	0	(0)	
CTD-ILD	0	(0)	4	(12)	
HP	1	(4)	2	(6)	
HTLV-1-associated pulmonary disease	0	(0)	1	(3)	
Pre-LT complications					
Pulmonary hypertension	13	(50)	10	(30)	0.179

Pneumothorax	20	(77)	14	(42)	0.009
Pre-LT treatment					
Corticosteroid	18	(69)	18	(55)	0.292
Immunosuppressive agent	10	(39)	15	(46)	0.608
Antifibrotic agent	6	(23)	15	(46)	0.102
LT procedures					
Bilateral cadaveric	4	(15)	5	(15)	
Single cadaveric	9	(35)	8	(24)	0.674
Living-related, bilateral	13	(50)	20	(61)	
KL-6, U/mL	557	(457, 1070)	1150	(710, 1920)	0.026
PaO_2, Torr	87.2	(74.7, 94.3)	80.9	(63.5, 99.9)	0.216
$PaCO_2$, Torr	55.0	(44.2, 67.5)	49.4	(41.4, 54.2)	0.046
6MWD, m	355	(299, 516)	300	(185, 380)	0.130
%FVC predicted, %	32.3	(21.4, 42.9)	36.8	(30.4, 43.3)	0.281
%TLC predicted, %	41.1	(34.4, 62.0)	42.6	(33.8, 57.7)	0.824
%RV/TLC predicted, %	167.8	(149.0, 189.5)	141.8	(119.8, 177.4)	0.182
%DL_{CO} predicted, %	32.2	(23.9, 36.8)	21.4	(19.5, 38.2)	0.236
Ratio of anteroposterior diameter to transverse diameter of the thorax, %	47.6	(43.4, 53.0)	53.8	(48.9, 58.3)	0.007

The data are presented as numbers (percentage) or medians (interquartile range).

Table 3. Clinical features of idiopathic and secondary cases with the pathological PPFE pattern in the upper lobe

	Idiopathic		Secondary		*P*-value
Number	14		12		
Age, years	52	(49, 58)	28	(25, 40.)	<0.001
Male	9	(64)	7	(58)	1.000
BMI, kg/m^2	17.9	(17.0, 19.4)	15.5	(14.6, 16.6)	0.005
Ever-smoking	9	(64)	3	(25)	0.062
Pre-LT complications					
Pulmonary hypertension	8	(57)	5	(42)	0.695
History of pneumothorax	9	(64)	11	(92)	0.170
Pre-LT treatment					
Corticosteroid	8	(57)	10	(83)	0.216
Immunosuppressive agent	4	(29)	6	(50)	0.422
Antifibrotic agent	5	(36)	1	(8)	0.170
LT procedures					
Bilateral cadaveric	1	(7)	3	(25)	
Single cadaveric	7	(50)	2	(17)	0.176
Living-related, bilateral	6	(43)	7	(58)	
KL-6, U/mL	859	(514, 1670)	520	(381, 885)	0.246
PaO_2, Torr	87.8	(70.5, 93.3)	86.9	(81.8, 96.3)	0.742
$PaCO_2$, Torr	49.5	(44.5, 62.2)	65.9	(43.5, 80.4)	0.150

6MWD, m	410	(315, 530)	300	(142, 390)	0.076
%FVC predicted, %	35.4	(30.6, 45.8)	26.3	(18.3, 40.3)	0.169
FVC/FEV_1, %	93.2	(85.9, 98.7)	94.3	(78.9, 96.1)	0.511
%TLC predicted, %	44.1	(37.1, 62.0)	36.7	(32.3, 49.9)	0.541
%RV/TLC predicted, %	149.0	(125.8, 169.5)	186.7	(167.4, 202.9)	0.011
%DLCO predicted, %	27.5	(23.6, 35.3)	34.9	(28.0, 36.7)	0.589

The data are presented as numbers (percentage) or medians (interquartile range).

Table 4. Pathological features of idiopathic and secondary cases with the pathological PPFE pattern

		Whole lungs				Upper lobes				Lower lobes			
		Idiopathic		Secondary		Idiopathic		Secondary		Idiopathic		Secondary	
Number		14		12		14		12		14		12	
Fibrosis/elastosis													
Subpleural-paraseptal	Elastosis*	14	(100)	12	(100)	14	(100)	12	(100)	13	(93)	12	(100)
	Collagenous**	0	(0)	0	(0)	0	(0)	0	(0)	2	(14)	0	(0)
Centrilobular	Elastosis	13	(93)	9	(75)	11	(79)	9	(75)	11	(79)	6	(50)
	Collagenous	0	(0)	1	(8)	0	(0)	0	(0)	1	(7)	2	(17)
Panacinar	Elastosis	11	(79)	11	(92)	10	(71)	7	(58)	9	(64)	7	(58)
	Collagenous	1	(7)	0	(0)	0	(0)	0	(0)	1	(7)	0	(0)
Alveolar septal thickening with fibrosis	Elastosis	5	(36) †	11	(92) †	3	(21)	5	(42)	4	(29) †	10	(83) †
	Collagenous	1	(7)	1	(8)	1	(7)	1	(8)	1	(7)	1	(8)
Bridging fibrosis		8	(57)	5	(42)	4	(29)	3	(25)	8	(57)	2	(17)
Pleural fibrosis		11	(79)	12	(100)	11	(79)	11	(92)	8	(57)	10	(83)
Fibroblastic foci		9	(64) †	1	(8) †	6	(43)	1	(8.3)	7	(50) †	1	(8) †
Honeycomb		5	(36)	3	(25)	2	(14)	1	(8)	2	(14)	1	(8)
Traction bronchiectasis		14	(100)	11	(92)	12	(86)	9	(75)	12	(6)	9	(75)
Cellular infiltrates													
Subpleural-paraseptal		13	(93)	12	(100)	11	(79)	12	(100)	13	(93)	10	(83)

Centrilobular	12	(86)	7	(58)	8	(57)	4	(33)	12	(86)	6	(50)
Parenchyma	9	(64)	10	(83)	6	(43)	5	(42)	8	(57)	9	(75)
Peribronchiolar	9	(64)	10	(83)	5	(36)	5	(42)	7	(50)	8	(67)
Arterial intimal thickening	12	(86)	11	(92)	12	(86)	10	(83)	11	(79)	7	(58)
Venous occlusion	1	(7)	0	(0)	1	(7)	0	(0)	0	(0)	0	(0)
Organizing pneumonia	3	(21)	4	(33)	1	(7)	1	(8)	3	(21)	2	(17)
Hyaline membranes	0	(0)	2	(17)	0	(0)	0	(0)	0	(0)	2	(17)
CBO	2	(14)	5	(42)	0	(0)	3	(25)	2	(14)	5	(42)
Granuloma	4	(29)	7	(58)	1	(7)	5	(42)	4	(29)	7	(58)
Emphysema	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)

The data are presented as numbers (percentage).

*With and without collagenous fibrosis. **Without elastosis. †$P < 0.05$.

Abbreviation: CBO, constrictive bronchiolitis obliterans.

Figure 1. Flow chart of cohort selection

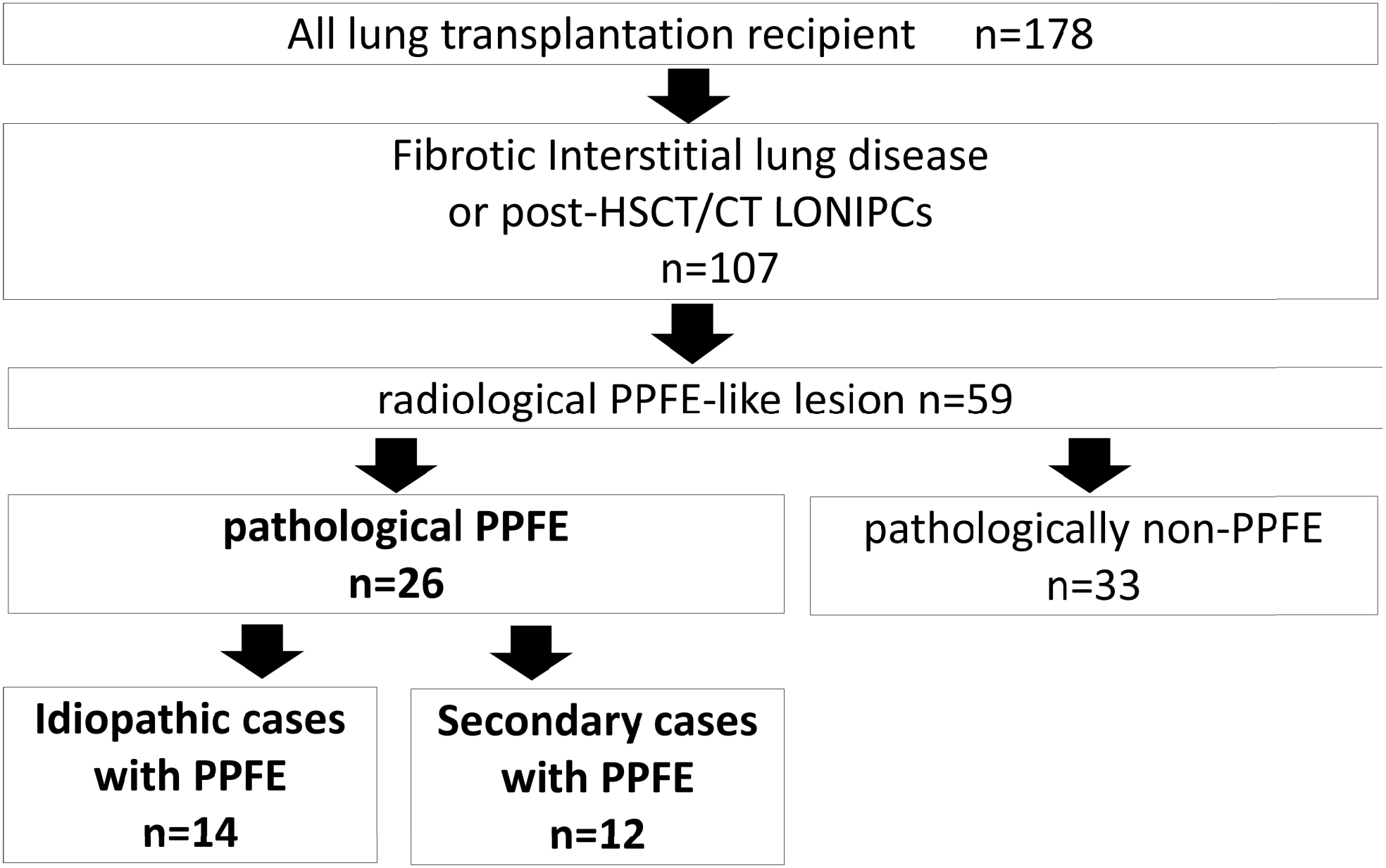


Figure 2. Radiological pleuroparenchymal fibroelastosis (PPFE)-like lesions and corresponding pathological lesions of cases with and without pathological PPFE.

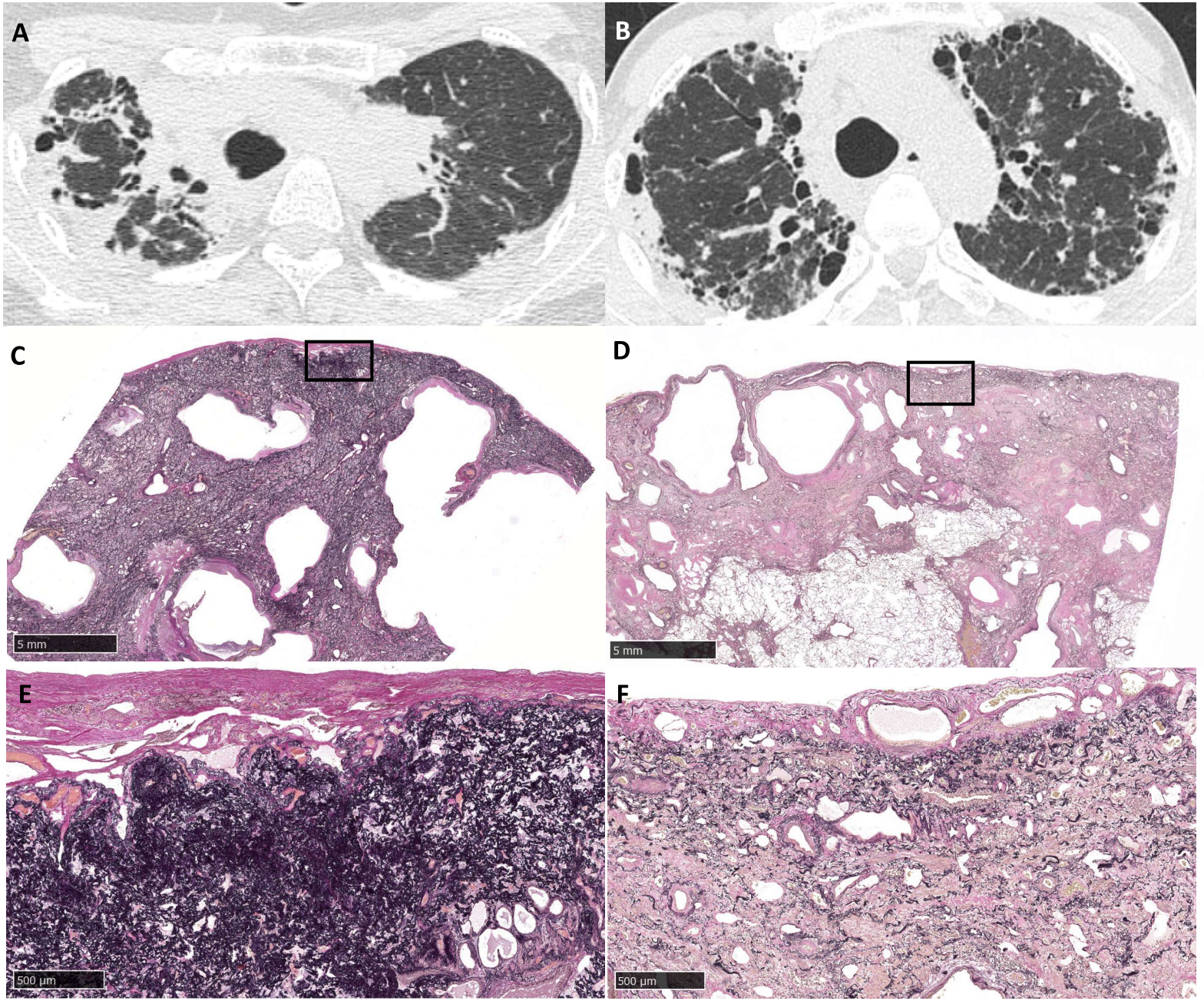


Figure 2. Radiological pleuroparenchymal fibroelastosis (PPFE)-like lesions and corresponding pathological lesions of cases with and without pathological PPFE.

A) Chest computed tomography (CT) image of a case with pathological PPFE (idiopathic PPFE) shows bilateral subpleural airspace consolidations in the upper lobes.

B) CT image of the PPFE-like lesion from a case without pathological PPFE also shows bilateral subpleural airspace consolidations in the upper lobes. This case is diagnosed as an unclassifiable IIP by multidisciplinary discussion.

C, E) Histopathology of a right upper lobe specimen from the corresponding case of Panel A shows subpleural fibrosis and intra-alveolar fibrosis and elastosis (IAFE) (Elastic van Gieson staining). Panel 2E is the high-power field of the box in Panel 2C.

D, F) Histopathology of a left upper lobe specimen from the corresponding case of Figure 2B lacks conspicuous elastic deposition on the alveolar wall (Elastic van Gieson staining), while subpleural collagenous fibrosis is present. Panel 2F is the high-power field of the box in Panel 2D.

Figure 3. Kaplan-Meier plots illustrating post-transplant survival in idiopathic cases with pathological PPFE (n=14) and secondary cases with pathological PPFE (n=12)

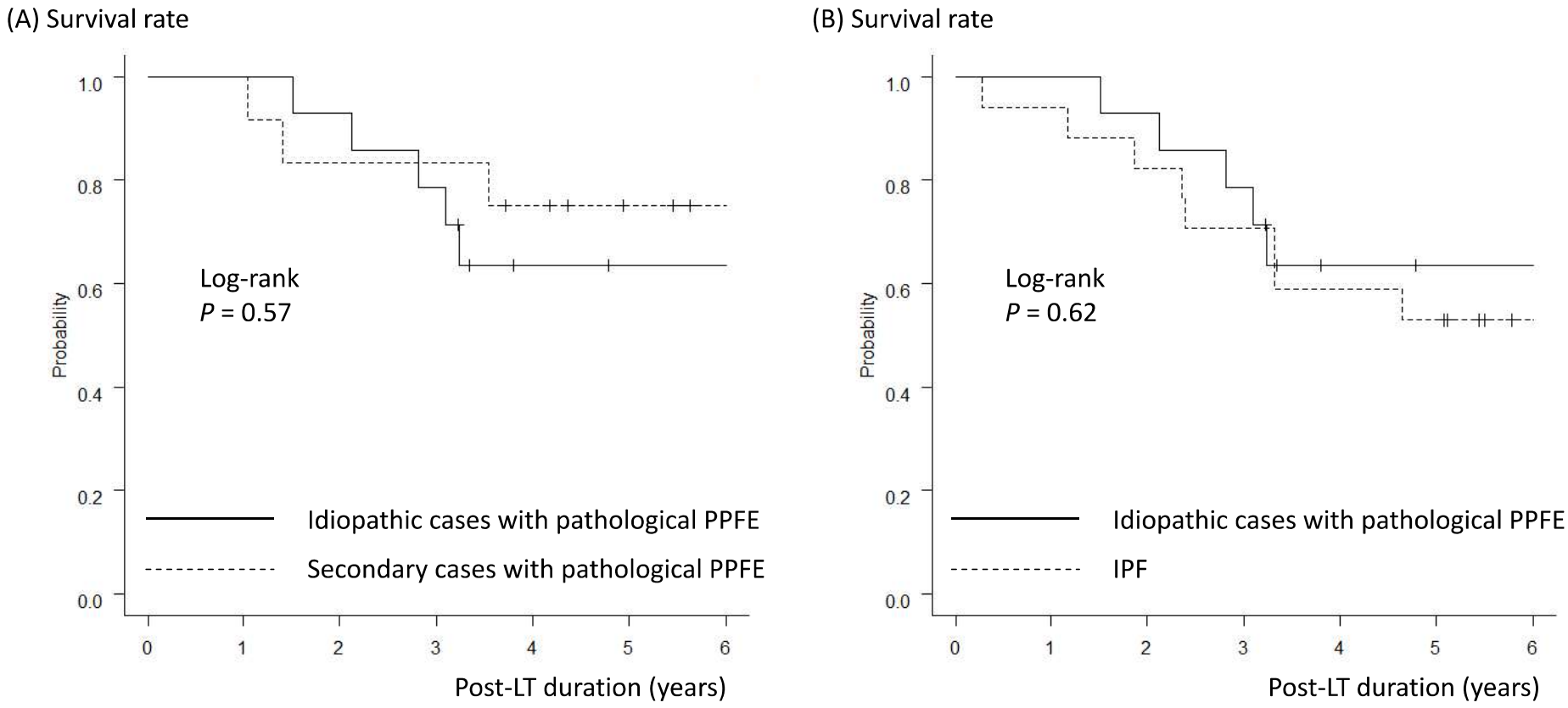


Figure 3. Kaplan-Meier plots illustrating post-transplant survival in idiopathic cases with pathological PPFE (n=14) and secondary cases with pathological PPFE (n=12) (A) and in idiopathic cases with pathological PPFE (n=14) and idiopathic pulmonary fibrosis (n=17) (B).

Supplementary Table 1. Pathological features of patients with pathological PPFE pattern and without it in those with radiological PPFE-like lesion

		Whole lungs				Upper lobes				Lower lobes			
		With pathological PPFE		Without pathological PPFE		With pathological PPFE		Without pathological PPFE		With pathological PPFE		Without pathological PPFE	
Number		26		33		26		33		26		33	
Fibrosis/elastosis													
Subpleural-paraseptal	Elastosis*	26	(100) †	24	(73) †	26	(100) †	24	(73) †	24	(92) †	19	(58) †
	Collagenous**	0	(0) †	7	(21) †	0	(0) †	6	(18) †	2	(8) †	10	(30) †
Centrilobular	Elastosis	22	(85)	23	(70)	20	(77)	19	(58)	17	(65)	15	(46)
	Collagenous	1	(4)	5	(15)	0	(0) †	6	(18) †	3	(12)	7	(21)
Panacinar	Elastosis	22	(85)	21	(64)	17	(65)	15	(46)	16	(62)	15	(46)
	Collagenous	1	(4)	4	(12)	0	(0)	4	(12)	1	(4)	5	(15)
Alveolar septal thickening with fibrosis	Elastosis	16	(62)	19	(58)	8	(31)	17	(52)	14	(54)	11	(33)
	Collagenous	2	(8)	2	(6)	2	(8)	1	(3)	2	(8)	2	(6)
Bridging fibrosis		13	(50)	14	(42)	7	(27)	7	(21)	10	(39)	11	(33)
Pleural fibrosis		23	(89) †	17	(52) †	22	(85) †	13	(39) †	18	(69) †	13	(39) †
Fibroblastic foci		10	(39)	20	(61)	7	(27)	15	(46)	8	(31)	15	(46)
Honeycomb		8	(31)	18	(55)	3	(12) †	12	(36) †	3	(12)	10	(30)

Traction bronchiectasis	25	(96)	29	(88)	21	(81)	25	(76)	21	(81)	26	(79)
Cellular infiltrates												
Subpleural-paraseptal	25	(96)	31	(94)	23	(89)	27	(82)	23	(89)	27	(82)
Centrilobular	19	(73)	24	(73)	12	(46)	21	(64)	18	(69)	20	(61)
Parenchyma	19	(73)	28	(85)	11	(42)	22	(67)	17	(65)	14	(61)
Peribronchiolar	19	(73)	24	(73)	10	(39)	19	(58)	15	(58)	17	(52)
Arterial intimal thickening	23	(89)	29	(88)	22	(85)	28	(85)	18	(69)	25	(76)
Venous occlusion	1	(4)	4	(12)	1	(4)	3	(9)	0	(0)	1	(3)
Organizing pneumonia	7	(27)	11	(33)	2	(8)	5	(15)	5	(19)	8	(24)
Hyaline membranes	2	(8)	4	(12)	0	(0)	3	(9)	2	(8)	2	(6)
CBO	7	(27)	13	(39)	3	(12)	9	(27)	7	(27)	8	(24)
Granuloma	11	(42)	22	(67)	6	(23)	14	(42)	11	(42)	15	(46)
Emphysema	0	(0)	2	(6)	0	(0)	1	(3)	0	(0)	1	(3)

The data are presented as numbers (percentage).

*With and without collagenous fibrosis. **Without elastosis. †$P < 0.05$.

Abbreviation: CBO, constrictive bronchiolitis obliterans.

Supplementary Table 2. High-resolution computed tomography features of patients with pathological PPFE and without it in those with radiological PPFE-like lesions.

	With pathological PPFE		Without pathological PPFE		*P*-value
Number	26		33		
Distribution of PPFE lesions*					
Limited in upper lobes	10	(38)	21	(64)	
Upper and other lobes	16	(62)	12	(36)	0.070
Traction bronchiectasis within PPFE lesions*	23	(89)	28	(85)	1.000
Volume loss of upper lobes	25	(96)	14	(42)	<0.001
Coexisting other ILD pattern					
None	10	(39)	4	(12)	0.030
UIP	2	(8)	4	(12)	
Probable UIP	1	(4)	0	(0)	
NSIP	0	(0)	3	(9)	0.513
OP	0	(0)	1	(3)	
Unclassifiable	13	(50)	21	(64)	
Other findings					
Mosaic attenuation	6	(23)	7	(21)	1.000
Peribronchial fibrosis	13	(50)	10	(30)	0.179

Significant nodules	2	(8)	14	(42)	0.003
Perilobular fibrosis	2	(8)	0	(0)	0.190
Pneumothorax/pneumomediastinum	16	(62)	10	(30)	0.020
Pleural effusion	10	(39)	2	(6)	0.003
Bulla	4	(15)	13	(39)	0.081
Ratio of the anteroposterior diameter to the transverse diameter of the thorax, %	47.6	(43.4, 53.0)	53.8	(48.9, 58.3)	0.007

The data are presented as numbers (percentage) or medians (interquartile range). *PPFE lesions represent subpleural airspace consolidations.

Supplementary Table 3. High-resolution computed tomography features of idiopathic and secondary cases with a pathological PPFE pattern in the upper lobe.

	Idiopathic		Secondary		*P*-value
Number	14		12		
Distribution of PPFE lesions*					
Limited in upper lobes	6	(43)	4	(33)	
Upper and other lobes	8	(57)	8	(67)	0.702
Traction bronchiectasis within PPFE lesions*	14	(100)	9	(75)	0.085
Volume loss of upper lobes	13	(93)	12	(100)	1.000
Coexisting other ILD pattern					
None	5	(36)	5	(42)	1.000
UIP	2	(14)	0	(0)	
Probable UIP	1	(7)	0	(0)	0.475
Unclassifiable	6	(43)	7	(58)	
Other findings					
Mosaic attenuation	3	(21)	3	(25)	1.000
Peribronchial fibrosis	6	(43)	7	(58)	0.695
Significant nodules	1	(7)	1	(8)	1.000
Perilobular fibrosis	0	(0)	2	(17)	0.200
Pneumothorax/pneumomediastinum	7	(50)	9	(75)	0.248

Pleural effusion	2	(14)	8	(67)	0.014
Bulla	2	(14)	2	(17)	1.000
Ratio of the anteroposterior diameter to the transverse diameter of the thorax, %	50.7	(46.8, 53.9)	43.3	(41.2, 49.4)	0.030

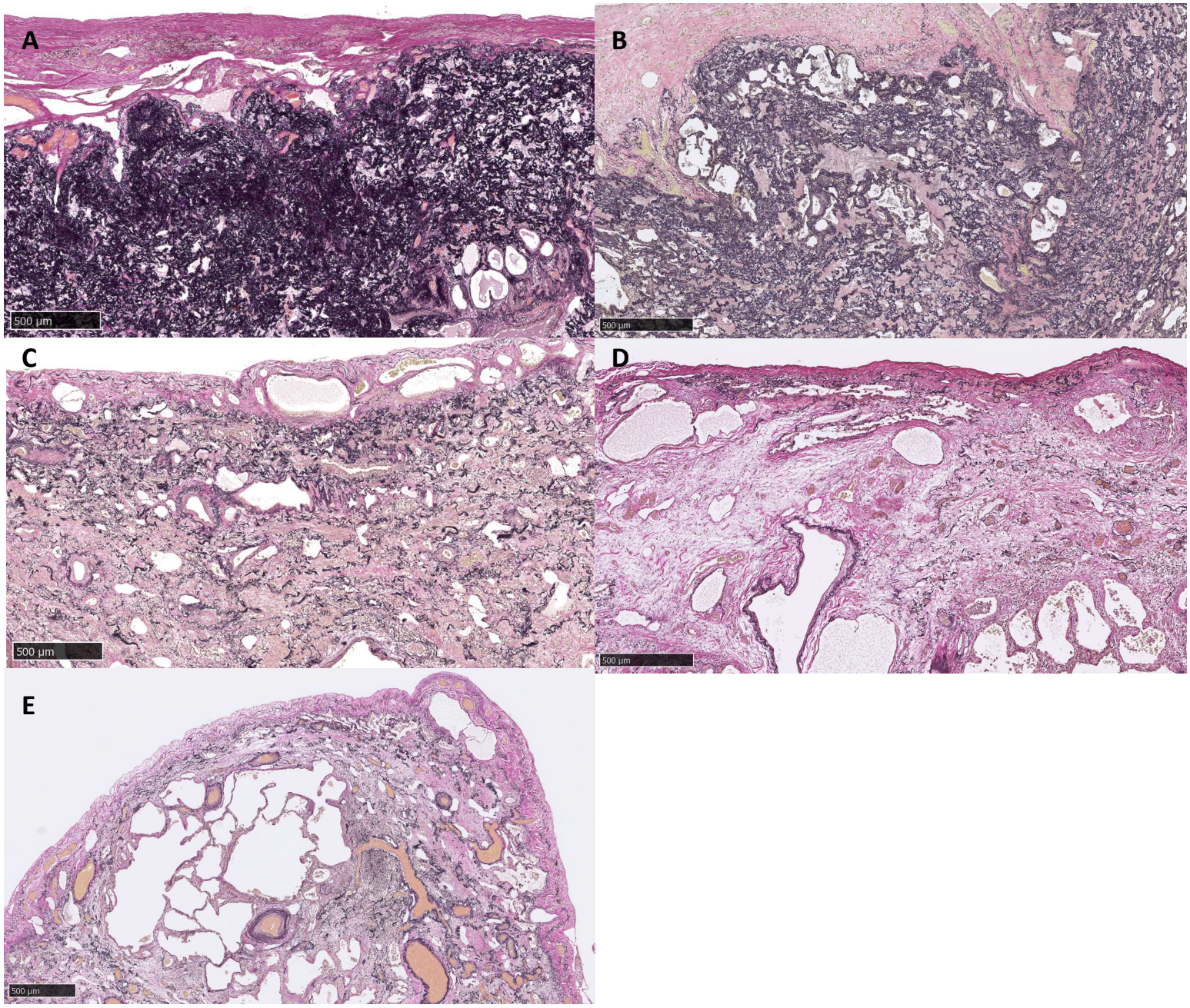
Supplementary Table 4. Characteristics of idiopathic cases with pathological PPFE in the upper lobes and cases with idiopathic pulmonary fibrosis

	Idiopathic cases with PPFE		IPF		*P*-value
Number	14		17		
Age, years	52	(49, 58)	56	(52, 61)	0.292
Male	9	(64)	13	(77)	0.693
BMI, kg/m^2	17.9	(17.0, 19.4)	20.4	(19.0, 23.4)	0.009
Ever-smoking	9	(64)	14	(82)	0.412
Pre-LT complications					
Pulmonary hypertension	8	(57)	3	(18)	0.031
History of pneumothorax	9	(64)	4	(24)	0.033
Pre-LT treatment					
Corticosteroid	8	(57)	8	(47)	0.722
Immunosuppressive agent	4	(29)	7	(41)	0.707
Antifibrotic agent	5	(36)	14	(82)	0.012
LT procedures					
Bilateral cadaveric	1	(7)	0	(0)	0.844
Single cadaveric	7	(50)	8	(47)	
Living-related, bilateral	6	(43)	9	(53)	
KL-6, U/mL	859	(514, 1670)	1980	(1200, 2200)	0.017
PaO_2, Torr	87.8	(70.5, 93.3)	76.7	(67.6, 95.7)	0.518

$PaCO_2$, Torr	49.5	(44.5, 62.2)	42.7	(39.7, 53.1)	0.039
6MWD, m	410	(315, 530	303	(194, 487)	0.181
%FVC predicted, %	35.4	(30.6, 45.8)	42.7	(36.2, 62.0)	0.146
%TLC predicted, %	44.1	(37.1, 62.0)	41.7	(39.3, 50.7)	0.841
%RV/TLC predicted, %	149.0	(125.8, 169.5)	109.2	(81.5, 143.7)	0.043
%DL_{CO} predicted, %	27.5	(23.6, 35.3)	28.1	(17.0, 36.9)	0.615
Ratio of the anteroposterior diameter to the transverse diameter of the thorax, %	50.7	(47.0, 54.8)	58.2	(55.3, 62.5)	0.017

The data are presented as numbers (percentage) or medians (interquartile range).

Supplementary Figure 1. The evaluation of subpleural intra-alveolar fibrosis (IAF) and elastic deposition on the alveolar wall in the subpleural area of the upper lobes.



Supplementary Figure 1. The evaluation of subpleural intra-alveolar fibrosis (IAF) and elastic deposition on the alveolar wall in the subpleural area of the upper lobes. The ratio of elastic deposition to whole subpleural fibrosis was categorized into four groups: no, mild, moderate and severe elastosis. We defined IAFE as the presence of IAF and moderate or severe elastic deposition.

(A) Severe elastosis (the same figure with Figure 2E). (B) Moderate elastosis. (C) Mild elastosis (the same figure with Figure 2F). (D) No elastosis (E) Absence of IAF or preserved alveolar structure within fibrosis.

Supplementary Figure 2. Histological images of alveolar septal thickening with elastosis or fibrosis.
(A) (C) (E) Hematoxylin & eosin staining shows diffuse alveolar septal thickening with fibrosis. Panel 2C and 2E is the high-power field of Panel 2A. (B) (D) (F) Elastica van Gieson staining shows deposition of elastic fibers. Panel 2D and 2F is the high-power field of the box in Panel 2B.