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Prognostic value of coexisting conditions and complications in pleuroparenchymal fibroelastosis: A single-center retrospective study

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Abstract. *Background:* Pleuroparenchymal fibroelastosis (PPFE) is a rare idiopathic interstitial lung disease (ILD) characterized by subpleural parenchymal fibrosis and elastosis mainly in the upper lobes. PPFE occurs in a secondary form that overlaps with underlying medical conditions or complications. This study evaluated the clinical impact of coexisting factors on the survival of patients with PPFE. *Methods:* Fifty-five PPFE patients were retrospectively evaluated. The patients' diagnoses were categorized as "idiopathic PPFE" with no known cause or "secondary PPFE" with underlying medical conditions or complications. The clinical characteristics and survival rates of these groups were compared. *Results:* Twenty-eight patients (50.9%) were diagnosed with idiopathic PPFE and 27 (49.1%) with secondary PPFE, including cases of occupational dust exposure, connective tissue disease (CTD), post-hematopoietic stem cell transplantation (HSCT), and a family history of ILD. The idiopathic and secondary PPFE groups had similar clinical features, laboratory tests, and pulmonary function profiles, including a low body mass index, normal Krebs von den Lungen-6, high surfactant protein-D, and high residual volume/total lung capacity. In the secondary PPFE group, post-HSCT was associated with a worse prognosis, and CTD was associated with better prognosis. A multivariate analysis demonstrated that post-HSCT and a reduced forced vital capacity were significantly associated with a worsened survival in patients with PPFE. *Conclusions:* The prognosis of PPFE is highly influenced by underlying medical conditions or complications. Patients with post-HSCT PPFE should be monitored particularly closely, as they are at higher risk of a poor prognosis than others.

Key words: pleuroparenchymal fibroelastosis, PPFE, interstitial pneumonia, pulmonary fibrosis, hematopoietic stem cell transplantation

Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare idiopathic interstitial pneumonia characterized by visceral pleural and subpleural parenchyma elastic fibrosis and atelectasis, mainly in the upper lobes. The concept was proposed by Frankel et al. in 2004 as an issue causing subpleural elastic fibrosis and atelectasis mainly in the upper lobes. Although the clinical entity had been acknowledged for at least 20 years, PPFE was formally recognized as a rare idiopathic interstitial pneumonia (IIP) in the revised international classification of IIPs published by the American Thoracic Society/European Respiratory Society in 2013 (1, 2).

The clinical and physiological features and longitudinal disease behavior of PPFE include a flat

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thorax, rapid decrease in forced vital capacity (FVC), high residual volume/total lung capacity (RV/TLC) ratio on pulmonary function tests, recurrent pneumothorax, pneumonia, and type 2 respiratory failure (3, 4). Although this is a clinicopathological entity, recent studies have proposed diagnostic criteria for PPFE in patients without a surgical lung biopsy (5).

The etiology of PPFE has yet to be clearly established; however, possible etiologies have been described for a large proportion of reported PPFE cases, including lung transplantation and hematopoietic stem cell transplantation (HSCT), connective tissue disease (CTD), chronic hypersensitivity pneumonitis, occupational exposure after the inhalation of dust (e.g. asbestos and aluminum), and a genetic predisposition (6-13). These cases are described as "secondary PPFE". However, the similarities and differences between idiopathic and secondary PPFE have not yet been sufficiently investigated. Furthermore, while numerous studies have explored the prognostic value of the annual decline in the pulmonary function, visual and computer-based computed tomography assessments, and distinct clinical phenotypes (14, 15), the impact of the etiology of PPFE on the survival has not been fully examined.

The present study compared the clinical features, disease course, and prognosis of PPFE patients with several underlying conditions.

Methods

Patient selection and data collection

The study protocol was approved by the Ethics Review Committee of Kanazawa University Hospital (approval number: 3652), and the need for individual consent for this retrospective analysis was waived. We reviewed the medical record research database of the Department of Respiratory Medicine, Kanazawa University Hospital between January 2004 and December 2020. High-resolution computed tomography (HRCT) data were carefully reviewed by at least two interstitial lung disease specialists, and a diagnosis of PPFE was made based on the clinical diagnostic criteria for PPFE described by Enomoto et al. (5), with some modifications. In brief, a diagnosis of PPFE was made based on the following two criteria: (1) a pattern of PPFE (predominantly bilateral upper lobe with subpleural infiltration, banding shadows, and few or no lower lobe lesions) on chest CT and (2) worsening of the shadows on imaging. Since this study intended to compare these etiologies, we decided not to use the third criterion "cases with a known cause excluded."

Patients with known underlying conditions, such as CTD, occupational dust exposure, post-HSCT, and a family history of interstitial lung disease (ILD), were classified as having secondary PPFE. CTD was diagnosed by a rheumatologist or dermatologist using appropriate classification criteria (16-18). Occupational dust exposure and familial connection were determined based on medical records or a questionnaire with a detailed exposure history and family history (two or more primary biological family members diagnosed with ILD) distributed at the initial visit. Cases in which no possible causes were identified were classified as idiopathic PPFE. The patterns of ILD in the lower lobes were assessed according to official clinical practice guidelines (19), with categories including a "usual interstitial pneumonia (UIP) pattern," "probable UIP pattern," "indeterminate for UIP pattern," and "alternative diagnosis." Chest CT findings were evaluated by two observers (K.I. and S.W.), and CT reports were obtained from radiologists. Disagreements between observers were resolved by consensus. As an indicator of thoracic flattening, we assessed the "flat chest index" defined as the ratio of the anteroposterior diameter of the thoracic cage to the transverse diameter of the thoracic cage, measured at the height of the sixth thoracic vertebra (20, 21).

The following baseline data were collected from the medical records: age, sex, body mass index (BMI), smoking status, occupational exposure, previous illness, medications, clinical symptoms (dyspnea, cough, etc.), chest CT findings, and pulmonary function test results. We also collected the following follow-up data: the occurrence of pneumothorax, pneumonia, respiratory failure, acute exacerbation, and outcome. The diagnosis of "acute exacerbation" was based on the criteria reported by the International Working Group of Acute Exacerbation of IPF with minor modifications: (1) acute worsening or development of dyspnea of with less than a one-month duration, (2) chest CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background PPFE, and (3) deterioration fully explained by heart failure and fluid overload (22). Pneumonia was defined as clinically

significant respiratory deterioration characterized by evidence of a new widespread alveolar abnormality that required antibacterial treatment. We compared the clinical features at baseline and outcomes of the groups.

Statistical analyses

Continuous values are presented as medians and ranges. The Mann-Whitney U test was used to compare the two groups. Qualitative variables were compared using Fisher's exact test. Kaplan-Meier survival curves were generated, and the groups were compared using the log-rank test. Cox proportional hazards modeling was used for the univariate and multivariate analyses. All statistical analyses were performed using the software programs EZR on R Commander version 1.54 (23) and IBM SPSS Statistics version 20. P <0.05 was considered to indicate a significant difference.

Results

Of 4,441 patients with interstitial lung disease from the medical record research database between January 2004 and December 2020, 55 met the diagnostic criteria of PPFE. These 55 patients included 32 men (58.2%) and 23 women (41.8%), with a median age of 62 years old at the initial diagnosis. Most patients had a relatively low BMI (median, 17.8 kg/m^2). The Krebs von den Lungen-6 (KL-6) levels were almost within the normal limits (median, 512 U/mL; normal range, <500 U/mL), whereas the surfactant protein-D (SP-D) levels were high (median 189.4 ng/mL; normal range, <126 pg/mL). Pulmonary function tests showed a low FVC and high RV/TLC, consistent with previous studies (3, 10). The median follow-up period was 31 (16-92) months. During the follow-up period, pneumothorax, pneumonia, and acute exacerbations occurred in 28 (50.9%), 26 (47.3%), and 8 (14.5%) patients, respectively (Table 1).

Among the 55 patients, 28 (50.9%) were diagnosed with idiopathic PPFE, and 27 (49.1%) were diagnosed with secondary PPFE. Secondary PPFE included occupational dust exposure (n=9), CTD (n=7), post-HSCT (n=6), a family history of interstitial lung disease (n=3), a family history of occupational dust exposure (n=1), and a family history of CTD (n=1). Occupational dust exposure included exposure to aluminum (n=2), iron (n=2), paint chemicals (n=2), asbestos (n=1), and unknown metals (n=2). CTD included systemic sclerosis (n=5), antineutrophil cytoplasmic antibody-related vasculitis (n=2), and Sjögren's syndrome (n=1). The underlying diseases of post-HSCT recipients included malignant lymphoma (n=2), acute myeloid leukemia (n=2), chronic myeloid leukemia (n=1), and myelodysplastic syndrome (n=1). All patients received chemotherapy, and two patients received total body irradiation.

Table 1. The comparison between idiopathic and secondary PPFE

Characteristics	Total cases (n=55)	Idiopathic PPFE (n=28)	Secondary PPFE (n=27)	P value
Age, years, median [IQR]	62 [54, 71]	62 [54, 70]	63 [54, 73]	0.794
Female, n (%)	23 (41.8)	8 (28.6)	15 (55.6)	0.058
Smoker, n (%)	25 (45.5)	15 (53.6)	10 (37.0)	0.282
BMI, kg/m^2, median [IQR]	17.8 [16.8, 19.9]	17.8 [16.4, 19.8]	17.8 [16.8, 19.9]	0.986
HRCT				
Flat chest index, median [IQR]	0.52 [0.48, 0.59]	0.52 [0.48, 0.58]	0.56 [0.48, 0.59]	0.853
Lung involvement in lower lobes	38 (69.1)	18 (64.3)	20 (74.1)	0.562
UIP pattern	3 (5.5)	2 (7.1)	1 (3.7)	0.673
Probable UIP pattern	3 (5.5)	1 (3.6)	2 (7.4)	-
Indeterminate for UIP pattern	8 (14.5)	5 (17.9)	3 (11.1)	-
Alternative diagnosis	24 (43.6)	10 (35.7)	14 (51.9)	-
Arterial blood gas analysis				
PaO_2, Torr, median [IQR]	87.2 [75.8, 98.2]	89.4 [76.9, 98.9]	86.2 [74.7, 98.6]	0.473

Table 1 continues

Table 1. The comparison between idiopathic and secondary PPFE *(continued)*

Characteristics	Total cases (n=55)	Idiopathic PPFE (n=28)	Secondary PPFE (n=27)	P value
$PaCO_2$, Torr, median [IQR]	44.8 [41.3, 47.4]	42.7 [39.0, 45.4]	46.3 [44.1, 49.1]	0.011
Biomarker				
KL-6, U/mL, median [IQR]	512 [341, 684]	512 [289, 670]	524 [359, 719]	0.482
SP-D, ng/mL, median [IQR]	189.4 [79.3, 335.0]	177 [76, 425]	200 [85, 331]	0.806
Pulmonary function tests				
FVC %pred, median [IQR]	72.0 [54.3, 93.8]	70.4 [59.0, 90.8]	77.6 [50.1, 94.7]	0.897
RV %pred, median [IQR]	90.9 [73.1, 106.8]	94.5 [68.5, 116.0]	87.9 [73.3, 101.7]	0.350
TLC %pred, median [IQR]	74.4 [61.8, 89.9]	72.0 [61.4, 101.3]	77.8 [61.1, 88.0]	0.776
RV/TLC, %, median [IQR]	40.7 [33.6, 49.0]	38.2 [33.6, 49.0]	42.5 [32.4, 48.4]	0.630
RV/TLC %pred, median [IQR]	122.4 [98.9, 141.6]	125.0 [100.9, 146.1]	122.2 [97.1, 141.0]	0.657
DLco %pred, median [IQR]	57.6 [42.4, 71.9]	56.2 [40.5, 72.5]	59.5 [44.8, 71.1]	0.582
Clinical course				
Pneumothorax, n (%)	28 (50.9)	15 (53.6)	13 (48.1)	0.790
Pneumonia, n (%)	26 (47.3)	12 (42.9)	14 (51.9)	0.593
Acute exacerbation, n (%)	8 (14.5)	4 (14.3)	4 (14.8)	1.000
Follow-up time, months, median [IQR]	31 [16, 92]	24 [16, 94]	38 [16, 90]	0.368
Death, n (%)	27 (49.1)	11 (39.3)	16 (59.3)	0.181

Abbreviations: PPFE, pleuroparenchymal fibroelastosis; IQR, interquartile range; BMI, body mass index; CT, computed tomography; UIP, usual interstitial pneumonia; KL-6, Krebs von den Lungen-6; SP-D, Surfactant protein D; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of the lung for carbon monoxide.

Next, we compared the patients with idiopathic and secondary PPFE. Except for the greater number of female patients and higher partial pressure of carbon dioxide ($PaCO_2$) in the secondary PPFE group than in the idiopathic PPFE group, the characteristics of the patients in the two groups were similar. The survival curves did not differ markedly (log-rank p=0.540) (Figure 1).

Kaplan-Meier survival curves according to etiology are shown in Fig. 2. The median survival was 24 months for post-HSCT, not available for CTD, 45 months for dust exposure, and 52 months for a family history of ILD. Patients with post-HSCT PPFE showed a significantly worse survival than those without post-HSCT PPFE (log-rank test, P =0.002) (Figure 2A). All patients with post-HSCT PPFE died during the follow-up period. Causes of death in these patients included respiratory failure (n=4) and pneumonia (n=2). In contrast, patients with CTD showed a significantly better

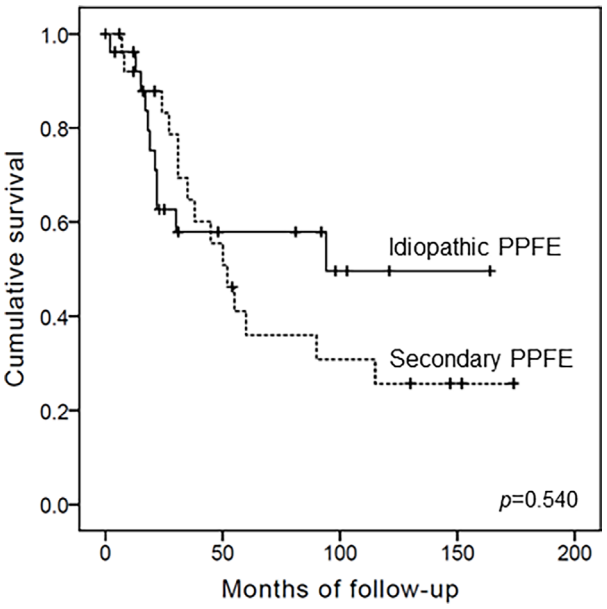

Figure 1. Kaplan-Meier survival curves. A comparison of idiopathic and secondary PPFE.

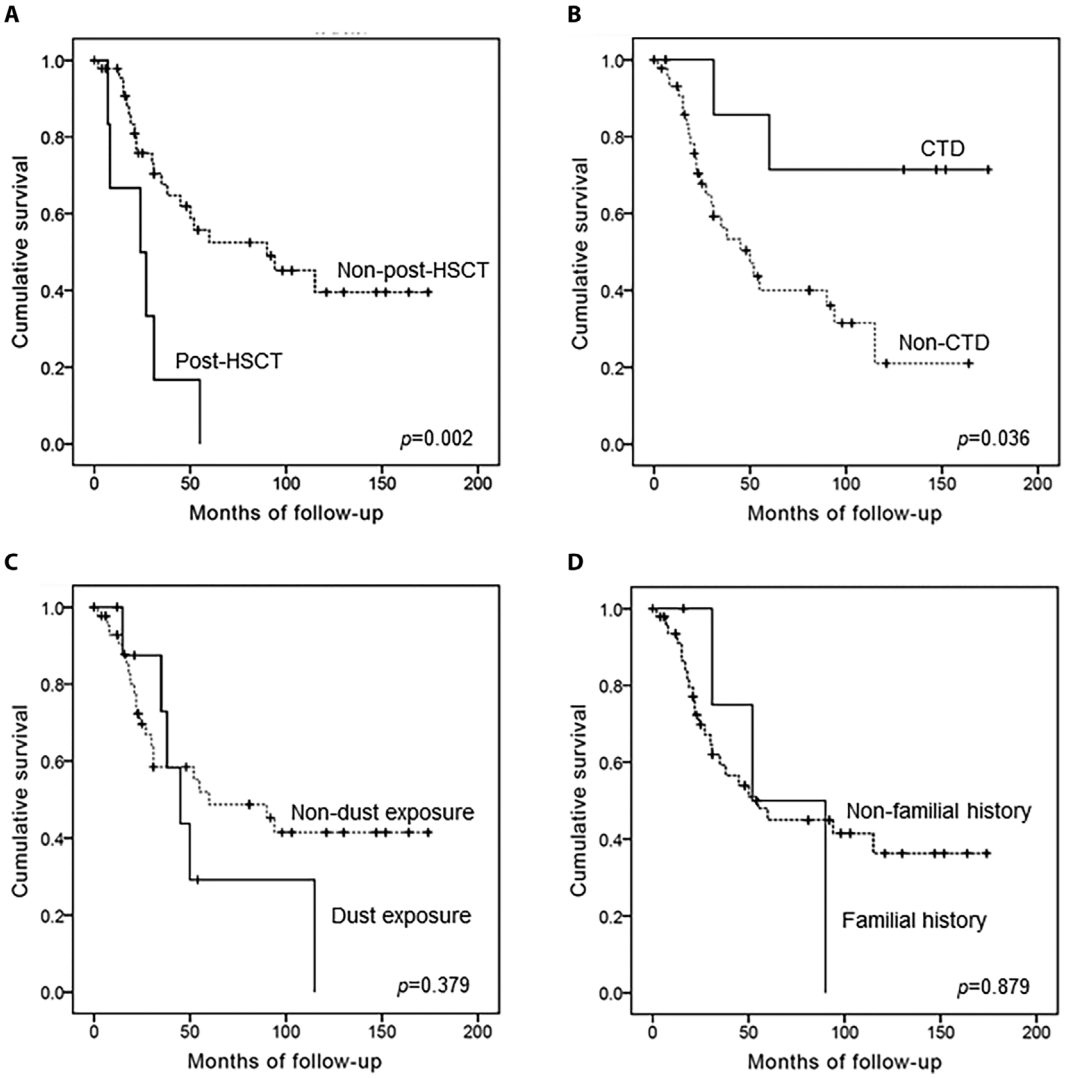

Figure 2. Kaplan-Meier survival curves. A comparison of PPFE patients with and without (A) post-HSCT, (B) CTD, (C) dust exposure, and (D) a family history of interstitial lung disease. HSCT, hematopoietic stem cell transplantation; CTD, connective tissue disease.

survival than those without CTD (log-rank test, p=0.036) (Figure 2B). Dust exposure and a family history of ILD did not affect the survival of patients with PPFE (Figure 2C and 2D).

The continuous variables were binarized as follows: age (< 65 vs. ≥ 65 years old), BMI (< 18 vs. ≥ 18 kg/m^2), flat chest index (< 0.57 vs. ≥ 0.57), KL-6 (< 500 vs. ≥ 500 U/ml), SP-D (< 110 vs. ≥ 110 ng/ml), FVC %pred (< 70 vs. ≥ 70%), and DLco %pred (< 80% vs. ≥ 80%). These cutoff values were determined according to previous studies (24). A univariate analysis showed that post-HSCT and FVC %pred <70% were associated with a worsened survival (Table 2). Although not statistically significant, CTD tended to be a favorable prognostic factor in patients with PPFE. The multivariate analysis used to predict a worsened survival was adjusted for the following factors: age, gender, post-HSCT, and FVC %pred <70%. The variables capable of the independent prediction of worsened survival were post-HSCT and FVC %pred <70% (Table 2).

Discussion

Our study demonstrated that the prognosis of PPFE is strongly influenced by underlying diseases and conditions. Although the clinical features of

Table 2. Univariate and multivariate analyses of factors associated with the survival in PPFE patients

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age (>65 years)	1.350	0.625-2.917	0.444	1.605	0.718-3.589	0.249
Sex, female	0.540	0.246-1.185	0.124	0.473	0.210-1.063	0.069
Smoked, yes	1.501	0.696-3.239	0.301			
BMI (<18 kg/m^2)	1.941	0.873-4.315	0.104			
Idiopathic, yes	0.721	0.337-1.544	0.399			
CTD, yes	0.236	0.055-1.021	0.053			
Dust exposure, yes	2.014	0.605-5.036	0.135			
Post-HSCT, yes	3.921	1.527-10.07	0.004	3.799	1.386-10.41	0.009
Family history, yes	1.097	0.327-3.677	0.881			
Flat chest index (<0.57)	1.950	0.882-4.313	0.099			
KL-6 (>500 U/mL)	1.589	0.736-3.431	0.238			
SP-D (>110 ng/mL)	2.226	0.919-5.393	0.076			
FVC %pred (<70%)	3.652	1.617-8.248	0.002	3.044	1.342-6.904	0.007
DLco %pred (<80%)	2.240	0.301-16.66	0.431			

Abbreviations: PPFE, pleuroparenchymal fibroelastosis; HSCT, hematopoietic stem cell transplantation; CTD, connective tissue disease; IQR, interquartile range; BMI, body mass index; CT, computed tomography; UIP, usual interstitial pneumonia; KL-6, Krebs von den Lungen-6; SP-D, Surfactant protein D; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of the lung for carbon monoxide; CI, confidence interval.

patients with idiopathic PPFE were similar to those of patients with secondary PPFE, post-HSCT PPFE was significantly associated with a poor survival.

The influence of the PPFE etiology on the survival has not been fully investigated. To date, two studies have compared idiopathic and secondary PPFE. Oda et al. reported no marked differences in the clinical characteristics or outcomes of patients with idiopathic versus secondary PPFE. However, their cohort included only one patient with post-HSCT PPFE (25). Ikegami et al. assessed the clinical, radiological, and pathological findings of patients with PPFE who underwent lung transplantation. They reported similar pathological findings in the idiopathic and secondary PPFE groups (26). However, they could not evaluate mortality because all of their patients were lung transplant recipients. Previous studies on the prognostic factors of PPFE have included a mixed population of idiopathic and secondary PPFE, and the number of patients with secondary PPFE has been relatively small (24, 27). In addition, the factors associated with a poor prognosis in patients with secondary PPFE have not been sufficiently examined. To our knowledge, this is the first study to show the prognostic significance of the underlying diseases and conditions in PPFE.

PPFE is a rare late post-transplant complication after HSCT, and the incidence of PPFE among HSCT recipients is reported to be 0.28%-1.5%. Patients who develop pneumonia more than three months after HSCT are at particularly high risk for PPFE (6, 28, 29). Our cohort had a slightly higher number of post-HSCT patients than the other cohorts because we were a joint team of pulmonologists and hematologists and had more opportunities to see patients with pulmonary complications after HSCT. To our knowledge, relevant literature does not include any data on the survival of patients with post-HSCT PPFE. To assess the prognosis of post-HSCT PPFE in a greater number of patients, we searched for cases of post-HSCT PPFE that were published and/or freely available on the Internet from 2011 to 2021. A total of 14 publications were identified from our database search, 7 of which (n=20) were eligible for inclusion in the prognostic analysis (6, 28, 30-34). The characteristics of the 20 patients are summarized

in the Supplemental Table. Most patients were young (median age, 38 years old). Ten patients (50%) had chronic graft-versus-host disease (GVHD). The median time from HSCT to the PPFE diagnosis was 54 (range, 38-107) months. The median survival time was 37 (range, 23-66) months, which was shorter than that of patients with idiopathic PPFE (96 months–11 years) (10, 27). Although several advances in HSCT practice have reduced the overall incidence of infectious pulmonary complications, the incidence of noninfectious pulmonary complications continues to increase. PPFE has been recognized as a major cause of morbidity and mortality after HSCT (35). Thus, early consideration of lung transplantation and close monitoring of disease progression are required in patients with post-HSCT PPFE (36).

Several limitations associated with the present study warrant mention, including its single-center, retrospective cohort design and relatively small study population. Our cohort did not include patients with chronic or recurrent bronchopulmonary infection, short telomeres due to mutations in genes encoding the telomerase complex, hypersensitivity pneumonitis, or lung transplant recipients (11). The survival time of patients with post-HSCT PPFE depends on the timing of the PPFE diagnosis, as a late diagnosis will lead to a shorter survival time. The prognosis of hematological malignancies and the therapies that were given to the patients also influence the survival of post-HSCT PPFE. To minimize selection bias, we reviewed the relevant literature to identify post-HSCT PPFE cases. This helped us understand the clinical and prognostic significance of post-HSCT PPFE.

In conclusion, the prognosis of patients with PPFE is strongly influenced by underlying diseases or conditions. Among patients with PPFE, those with post-HSCT PPFE showed a poorer prognosis, while those with CTD showed a better prognosis. Although the clinical course and prognosis of PPFE vary, physicians should closely monitor disease progression and consider lung transplantation in patients with post-HSCT PPFE. Further studies are needed to elucidate the mechanisms responsible for PPFE progression.

Conflict of Interest: Each author declares no commercial associations (e.g. consultancies, stock ownership, equity interest, patent /licensing arrangement) that might pose a conflict of interest in connection with the submitted article.

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