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Factors for progressive pulmonary fibrosis in connective tissue disease-related interstitial lung disease

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Abstract

Background: Progressive fibrosis can occur in connective tissue disease (CTD)-related interstitial lung disease (ILD) and make the prognosis worse.

Objectives: This study aimed to investigate factors related to progressive pulmonary fibrosis (PPF) phenotype in CTD-ILDs.

Design: Medical records of patients diagnosed as CTD and ILD at a single, tertiary hospital in South Korea were retrospectively reviewed.

Methods: Patients whose lung functions were followed up for more than a year were included in analysis. PPF was defined as forced vital capacity (FVC) declined ⩾10% or diffusion capacity of carbon monoxide (DLco) ⩾15%.

Results: Of 110 patients with CTD-ILD, 24.5% progressed into PPF. Rheumatoid arthritis (RA) and Sjogren's disease accounted for more than 63% of PPF. Compositions of CTD type were similar between PPF and non-PPF. Clinical characteristics and proportion of usual interstitial pneumonia (UIP) pattern on chest images were also similar between PPF and non-PPF. Approximately 10% of patients in both groups were treated with anti-fibrotic agents. Use of systemic steroids and/or other immunomodulating agents lowered the risk of developing PPF in CTD-ILD patients after adjusting for gender-age-physiology score and smoking status (adjusted odds ratio: 0.25, 95% confidence interval: 0.07–0.85).

Conclusion: About a quarter of CTD-ILD progressed into PPF. The use of immunomodulating agents lowered the risk of developing PPF. To improve outcomes of patients, future studies need to detect patients at higher risk for PPF earlier and set up clinical guidelines for treatment strategies in the process of PPF.

Keywords: connective tissue disease, interstitial lung disease, progressive fibrosis, risk factors

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Introduction

Connective tissue disease (CTD) is a systemic autoimmune disease characterized by immune-mediated organ dysfunction. Interstitial lung disease (ILD) is one of the most serious pulmonary involvements of CTDs.[1] Approximately 20% of ILDs reported in Europe and the United States are associated with CTD.[2] Progressive, irreversible lung function loss can be developed and deterioration of lung function will resultantly cause symptoms.[3] Although the prevalence and clinical outcome of CTD-associated ILDs can vary, they are known to increase morbidity and mortality.[1,4] Moreover, it can remain silent in the early phases, and ILD might be the first manifestation of CTD, so that it can precede a diagnosis of CTD by years.[5,6] Accompanied ILD in CTD represents variable clinical impact and severity. Up to 40% of patients with CTD-ILDs can develop a progressive fibrosing phenotype.[2] Although systemic sclerosis (SSc) is known to be the most common autoimmune disease accompanied by

ILD,[6] relative prevalence of those who develop progressive fibrotic ILD (PF-ILD) is the highest in rheumatoid arthritis (RA), followed by that in SSc. Thus, both CTDs take up more than 70% of PF-ILD in CTD-ILDs.[2]

Irrespective of the underlying type of ILDs, PF-ILD shares common pathogenetic pathways resembling idiopathic pulmonary fibrosis (IPF). Various triggers can initiate and exaggerate cascades of inflammatory and fibrosis pathways, leading to self-sustained pulmonary fibrosis.[7–9] The main treatment of CTDs lies in their immunologic background. Several types of immunomodulating agents have been used. However, there is no universally agreed clinical guidance for patients with CTD-ILDs, especially when they are suspected to develop progressive fibrosis. Even if PF-ILD in CTD shows poor clinical course such as worsening respiratory symptoms, decline of lung function, deteriorating quality of life, and early mortality,[8–10] united diagnostic criteria are lacking. Recently, patients previously classified into PF-ILD have been redefined as progressive pulmonary fibrosis (PPF).[11] This study aimed to compare clinical features of PPF and non-PPF with spirometry-based criteria and identify risk factors for PPF in CTD-ILDs.

Methods

Study population

Medical records of patients diagnosed with both CTD and ILD in Seoul Saint Mary's Hospital between January 2019 and May 2022 were retrospectively reviewed. Among 124 patients with CTD-ILD, 110 patients whose lung function was measured at least once since baseline measurement with a year interval were included in the analysis. Diagnosis of CTD was based on relevant criteria for all patients by rheumatology specialists such as the American College of Rheumatology classification criteria for RA,[12] SSc,[13] and Sjogren.[14] Judgement on combined ILD was made by a multidisciplinary discussion of pulmonologists, rheumatologists, and radiologists.

Clinical data collected

Detailed demographics, smoking status, and comorbid conditions were reviewed through medical records. We defined the time of ILD diagnosis when they visited pulmonary department for ILD for the first time. Chest computed tomography (CT) was taken for all patients. Radiologic classification of ILD was made based on typical chest CT findings.[15] Seoul St. Mary's Hospital has three experienced chest radiologists, and all chest CT scans were interpreted by these three radiologists. Pulmonary function tests were performed using standard equipment in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.[16,17] Percents of predicted values were calculated using an equation adjusted for the Korean population.[18,19] Lung volume was measured by body plethysmography carried out according to the relevant guidelines.[20] Exercise capacity was assessed by 6 min walking distance (6MWD). Blood samples were collected at stable disease status on a regular outpatient clinic follow-up. Most results were obtained at baseline visit. Autoantibodies such as anti-nuclear antibody (ANA) were also checked. Comorbid conditions and lists of administered medications, including antifibrotics (pirfenidone or nintedanib) and immunomodulating agents were investigated by reviewing electronic medical records from rheumatology and pulmonology department.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental File).

Definition of PPF

We combined diagnostic criteria for PPF of two recent clinical trials and clinical practice guidelines.[11] In the INBUILD trial,[21] non-IPF ILD patients were included. Those who met one of the following conditions were classified into progressive fibrosing ILD (PF-ILD): (1) relative decline of FVC greater than 10% during 2 years of follow-up; or (2) at least two of the following: (a) decline of FVC from 5% to 10%, (b) worsening of symptom, and (c) increasing extent of fibrosis. On the other hand, TRAIL1 study[22] enrolled RA-ILD patients. Those who met either of the following conditions were classified into PF-ILD: (1) relative decline of FVC more than 10%, or (2) FVC declined from 5% to 10% and diffusing capacity of carbon monoxide (DLco) declined more than 15%. Recent guidelines used absolute change of lung function to define physiologic aspect of PPF. Thus, we modified these criteria and defined PPF when they satisfied either absolute decline rate of FVC $\geq$ 10% or DLco $\geq$ 15% during follow-up.

Statistical analysis

All data are presented as numbers (%) for categorical variables and median with interquartile range (IQR) for continuous variables. Student's *t*-test and Chi-square test were used to analyze continuous and categorical variables, respectively. The risk of progression to PPF during the follow-up period was analyzed using logistic regression analysis. Covariates including gender-age-physiology (GAP) index and smoking status were adjusted in the multivariable analysis. All tests were two-sided. $p < 0.05$ was taken to indicate statistical significance. All analyses were performed using STATA software version 16 (StataCorp, College Station, TX, USA).

Results

Prevalence of PPF and comparison of baseline characteristics depending on PPF

Of 110 patients with CTD-ILD, 27 (24.5%) were classified into PPF. Annual decline rate of FVC was -5.73 ± 0.99 *versus* $0.60 \pm 0.58\%$ of predicted value and that of DLco was -6.29 ± 1.20 *versus* $1.47 \pm 0.69\%$ of predicted value for PPF *versus* non-PPF ($p < 0.001$ for both).

Among 27 patients with PPF, RA was the most frequent type of CTD (33%), followed by Sjogren's disease, SSc, and myositis sequentially (30%, 18%, and 15%, respectively) (Figure 1). On the other hand, in the non-PPF group, Sjogren's disease ranked the first (28.9%), followed by SSc and RA (26.5% and 24.1%, respectively), although the composition of the type of CTD was not significantly different between PPF and non-PPF ($p = 0.784$).

Mean age at diagnosis of CTD and ILD was older in the PPF group. Time interval between CTD and ILD diagnosis was shorter in the PPF group. However, there was no clinical significance. Usual interstitial pneumonia (UIP) pattern on chest CT scan was more common in the PPF group (40.7% *versus*.32.5%; $p = 0.436$). Among non-UIP patterns, non-specific interstitial pneumonia (NSIP) was the most common one in both groups (Table 1). Only 11% and 12% of PPF and non-PPF groups were prescribed antifibrotics. Both systemic steroid and non-steroid immunomodulating agents were used more frequently in the non-PPF group (Table 2).

A few death events occurred in our cohorts: four in the non-PPF group and one in the PPF group. Of five death cases, three died from acute exacerbation of ILD and two died from sepsis and pneumonia.

Comparison of lung function and laboratory test results depending on PPF

Table 3 shows baseline value of spirometry, lung volume measurement, and blood tests. The PPF

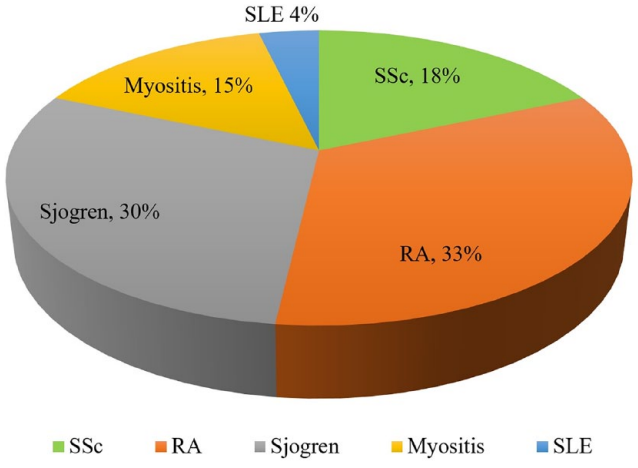

Figure 1. Types of CTD in PPF.
CTD, connective tissue disease; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Table 1. Comparison of clinical characteristics between non-PPF and PPF groups.

Clinical features	Non-PPF	PPF	*p* Value
Patients, *n*	83 (75.5)	27 (24.5)	
Age (years)	61.7 ± 12.0	63.7 ± 16.6	0.564
Female sex	70 (84.3)	21 (77.8)	0.433
Age at CTD diagnosis	53.1 ± 12.9	55.9 ± 16.5	0.355
Age at ILD diagnosis	57.6 ± 12.0	58.5 ± 14.9	0.749
Mean time interval between CTD and ILD diagnosis	4.5 ± 7.2	2.6 ± 5.6	0.207
Smoking status, former smoker	9 (10.8)	4 (14.8)	0.579
Comorbid condition			
Hypertension	20 (24.1)	6 (22.2)	0.842
Diabetes mellitus	10 (12.1)	5 (18.5)	0.395
Cardiovascular disease (CAD or CHF)	28 (33.7)	7 (25.9)	0.449
Gastroesophageal reflux disease	7 (8.4)	2 (7.4)	0.866
Pulmonary tuberculosis	4 (4.8)	4 (14.8)	0.082
Airway disease (COPD or asthma)	3 (3.6)	2 (7.4)	0.411
Radiologic pattern of ILD			
UIP	27 (32.5)	11 (40.7)	0.436
Non-UIP	56 (67.5)	16 (59.3)	
NSIP	45 (54.2)	13 (48.2)	
OP	9 (10.8)	2 (7.4)	
LIP	1 (1.2)	1 (3.7)	
Unclassifiable	1 (1.2)	0 (0)	

Data are presented as *n* (%) or median (IQR).
CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; LIP, lymphoid interstitial pneumonia; MCTD, mixed-connective tissue disease; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PM, polymyositis; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

group had higher baseline lung volume and diffusing capacity than the non-PPF group. Airflow limitation index [forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio] and index of air-trapping [residual capacity (RV)/total lung capacity (TLC)] were not significantly different between PPF and non-PPF groups.

Results of ANA were available for 103 patients. Positive ANA test was more frequent in the non-PPF group. However, there was no significant difference in ANA titer. Other autoimmune biomarkers for CTD were not significantly different between PPF and non-PPF groups either.

Factors associated with progression to PPF

To identify factors related to the development of PPF in CTD-ILD patients, univariate analysis and multivariate analysis were performed sequentially. Of clinic-laboratory variables, the use of systemic steroids or other immunomodulating agents was the only factor that could reduce the risk for PPF [adjusted odds ratio (OR): 0.25, 95% confidence interval (CI): 0.07–0.85] (Table 4).

Out of the 110 CTD-ILD patients, organizing pneumonia (OP) pattern was observed in 11 (10%) patients. Excluding the patients with the OP pattern, which tends to respond well to steroids and immunosuppressive therapy, we re-analyzed the risk factors for PPF in the 99 (90%) patients presenting with signs of chronic ILD. Analysis excluding the OP pattern yielded consistent results, with the use of systemic steroids or other immunomodulating agents being the only factor that could reduce the risk for PPF (adjusted OR: 0.20, 95% CI: 0.05–0.73). For the UIP pattern, even after adjusting for the GAP score and smoking, the OR increased, but it was not statistically significant (adjusted OR: 2.00, 95% CI: 0.70–5.72) (Supplemental Table S1).

Table 2. Comparison of disease-specific medications between non-PPF and PPF groups.

Medications	Non-PPF	PPF	*p* Value
Antifibrotics	10 (12.1)	3 (11.1)	0.896
Pirfenidone	8 (9.6)	3 (11.1)	0.825
Nintedanib	2 (2.4)	0 (0)	0.416
Systemic steroid	74 (89.2)	20 (74.1)	0.053
Other Immunomodulating agent	51 (61.5)	13 (48.2)	0.224
AZA	35 (42.2)	10 (37.0)	0.638
MMF	20 (24.1)	4 (14.8)	0.310
Cyclophosphamide	10 (12.1)	0 (0)	0.059
Tacrolimus	3 (3.6)	2 (7.4)	0.411

AZA, azathioprine; MMF, mycophenolate mofetil; PPF, progressive pulmonary fibrosis.

Discussion

Most patients in our cohort of CTD-ILD exhibited well-preserved lung function at baseline. However, a quarter of patients progressed into

Table 3. Comparison of spirometry and laboratory test results.

Clinical features	Non-PPF	PPF	*p*-Value
Spirometry			
FVC, L	2.39 ± 0.74	2.69 ± 0.53	0.017
FVC, % of predicted value	71.5 ± 16.0	84.9 ± 17.4	0.001
FEV_1, L	1.89 ± 0.60	2.91 ± 3.89	0.005
FEV_1, % of predicted value	72.3 ± 16.4	88.9 ± 20.8	<0.001
FEV_1/FVC ratio	79.5 ± 7.8	81.0 ± 6.9	0.559
DLco, mL/mmHg/min (n = 106)	11.2 ± 4.0	13.7 ± 3.9	0.008
DLco, % of predicted value	58.3 ± 17.7	75.4 ± 17.3	<0.001
Lung volume parameters (n = 101)			
TLC, L	3.58 ± 1.11	4.02 ± 0.66	0.016
TLC, % of predicted value	73.7 ± 19.1	85.0 ± 12.7	0.001

(Continued)

Table 3. (Continued)

Clinical features	Non-PPF	PPF	*p*-Value
VC, L	2.38 ± 0.83	2.76 ± 0.53	0.011
VC, % of predicted value	77.7 ± 19.6	92.6 ± 18.8	0.002
RV/TLC ratio	32.3 ± 8.2	31.4 ± 6.8	0.762
6MWD, m (only available in 11)	458.3 ± 108.5	360.0 ± 42.4	0.156
Biomarkers			
ANA, positivity (*n* = 103)	72 (91.1)	20 (83.3)	0.278
Titer	1083.8 ± 1010.3	1181.0 ± 1151.9	0.966
ANCA, positivity (*n* = 59)	11 (22.9)	4 (36.4)	0.356
RF (*n* = 106)	38 (46.9)	11 (44.0)	0.798
Anti-dsDNA (*n* = 79)	1 (1.6)	1 (5.9)	0.321
Anti-CCP (*n* = 85)	21 (31.3)	7 (38.9)	0.545
Anti-Ro (*n* = 80)	36 (56.3)	10 (62.5)	0.651
Anti-La (*n* = 77)	7 (11.5)	2 (12.5)	0.910
Anti-Scl70 (*n* = 78)	18 (29.0)	3 (18.8)	0.408
ESR (*n* = 106)	24.0 ± 18.7	26.6 ± 20.6	0.581
KL-6 (only available in 7)	924.4 ± 541.0	865.6 ± 0	0.617
GAP index	2.29 ± 1.36	1.74 ± 1.10	0.066

ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-CCP, anti-cyclic citrullinated peptide antibody; anti-dsDNA, anti-double stranded deoxyribonucleic acid (DNA); DLco, diffusing capacity of carbon monoxide; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; GAP, gender-age-physiology; IC, inspiratory capacity; KL-6, Krebs von den Lungen-6; PPF, progressive pulmonary fibrosis; RF, rheumatoid factor; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

PPF. Of various physiologic, radiologic, and laboratory aspects, only the use of immunomodulating agents lowered the risk of developing PPF after adjusting for age, lung function, and smoking status. Considering that PPF may be a part of the natural course of CTD-ILD, our findings emphasize the importance of treating the inflammatory background of CTD-ILD, as such treatment could effectively reduce the risk of PPF.

There has been no unified definition for PPF. Therefore, trials and cohorts used their own criteria to define PPF. Recently, ATS/ERS formed a joint committee with the Japanese Respiratory Society (JRS) and Asociación Latinoamericana de Tórax (ALAT) to clarify the concept of PPF and suggested criteria for defining it based on physiologic and radiological aspects.[11] ILD patients who met at least two of the following three criteria could regarded as PPF: (1) decline of absolute value of FVC more than 5% or DLco declined more than 10%, (2) worsening of symptoms, and (3) radiological evidence of disease progression. However, radiologic progression is not easily applicable in real practice yet because there is large inter-observer variability in interpreting HRCT scans. In addition, an objective, well-validated quantitative assessment tool for defining progressive fibrotic phenotype on CT scan is not applicable yet.

Table 4. Predictors of PPF with multivariable logistic regression.

Clinical features	Crude OR (95% CI)	*p* Value	Adjusted OR (95% CI)*	*p* Value
Time interval between CTD and ILD diagnosis	0.95 (0.88–1.03)	0.205	0.95 (0.88–1.03)	0.221
UIP pattern	1.43 (0.58–3.49)	0.437	2.11 (0.76–5.86)	0.152
ANA positivity	0.49 (0.13–1.83)	0.286	0.46 (0.12–1.77)	0.259
RF positivity	0.89 (0.36–2.19)	0.798	0.92 (0.37–2.32)	0.865
ANCA	1.92 (0.47–7.80)	0.361	2.05 (0.47–8.83)	0.337
Cardiac disease (HTN, IHD, CHF)	0.69 (0.26–1.82)	0.451	0.86 (0.31–2.37)	0.765
GERD	0.87 (0.17–4.46)	0.866	0.83 (0.16–4.43)	0.830
Antifibrotics	0.91 (0.23–3.59)	0.896	1.32 (0.31–5.61)	0.709
Systemic steroid	0.35 (0.12–1.05)	0.061	0.39 (0.13–1.20)	0.102
Immunomodulating agents other than steroid	0.58 (0.24–1.40)	0.226	0.65 (0.27–1.61)	0.353
Immunomodulating agent (either steroid or others)	0.22 (0.07–0.74)	0.014	0.25 (0.07–0.85)	0.026

*Adjusted for GAP score and smoking status
ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CHF, congestive heart failure; CI, confidence interval; CTD, connective tissue disease; GERD, gastroesophageal reflux disease; HTN, hypertension; IHD, ischemic heart disease; ILD, interstitial lung disease; OR, odds ratio; PPF, progressive pulmonary fibrosis; RF, rheumatoid factor; UIP, usual interstitial pneumonia.

A few years ago, the ILD guideline from the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society suggested that a decline ⩾10% in FVC or ⩾15% in DLco in the first 6–12 months was a risk factor for adverse outcome.[23] Our modified criteria for PPF were in line with previous study[24] and the prevalence of PPF in CTD-ILD cohort was 24.5%. Accompanied ILD is a leading cause of death in CTD patients. Progressive fibrosis of ILD is also associated with high mortality.[25,26] Presence of radiologic UIP patterns has been reported to be associated with progression of ILD and high mortality.[27,28] In this study, UIP pattern on chest CT was not related to the development of PPF. However, it is difficult to exclude the possibility of PPF only based on the absence of UIP because chest CT manifestations may vary depending on the underlying cause of ILDs.

To date, reliable biomarkers to predict disease progression in CTD-ILD are also lacking. Some studies have shown that Krebs von den Lungen-6 protein (KL-6) is associated with a higher rate of disease progression not only in patients with IPF, but also in those with CTD-ILDs.[29–32] Although KL-6 has been introduced recently as a prognostic marker for ILD, it has not been widely used in Korea until recently. Its values were only available for seven patients in our study.

Otherwise, lower FVC is thought a predictor of mortality in patients with PF-ILDs, including RA-ILD[28,33] and SSc-ILD.[34,35] However, in this study, even in patients with good lung functions at CTD-related ILD diagnosis, they progressed to PPF. This suggests that caution is needed on possibility of PPF regardless of physiological lung function parameters. The most widely used tool for predicting prognosis of ILDs is the GAP model originally developed to predict mortality in patients with IPF based on gender, age, FVC, and DLco of % of predicted value.[36] However, it showed inconsistent predictive performance in CTD-ILD.[37–39] In our study, GAP score was not

significantly different between PPF and non-PPF groups. It was rather higher in the non-PPF group. Composite predictive tool for disease progression in CTD-ILDs is also needed.

Although immunomodulating agents are the first consideration to treat CTD-ILD, there is growing evidence of benefits of antifibrotic agents such as pirfenidone and nintedanib on outcomes of ILDs other than IPF. Nintedanib in PF-ILD could slow the annual rate of FVC decline over 52 weeks by 58% of relative reduction in a study that included 25.6% of autoimmune ILD.[21,40] In terms of pirfenidone, it could reduce the decline rate of FVC by 84% in unclassifiable ILD patients compared to placebo group at week 24.[41] Although early termination of trial due to slow recruitment which underpowered the effect, pirfenidone meaningfully slowed down the rate of decline of FVC in 231 patients with RA-ILD.[22] Therefore, when progressive fibrosis is developed despite immunomodulatory therapy in non-IPF ILDs, antifibrotic therapy, and/or combination with immunomodulatory therapy will be recommended.[42] However, to date, standard treatment and appropriate timing for initiation of antifibrotic agents have not been established yet. They usually depend on clinician's own decision. Moreover, there is a cost issue when using antifibrotics in the PPF group of CTD-ILD in Korea. In this study, antifibrotic agents were prescribed only for about 10% of patients. Neither pirfenidone nor nintedanib for treating patients with PPF in non-IPF ILD was covered by the National Health Insurance. It might make clinicians not to initiate antifibrotics in these patients.

In our study, lung volume parameters were relatively preserved at baseline and the PPF group had better lung function parameters than the non-PPF group. Low lung function is known as a risk factor for poor outcomes in ILD.[2] However, findings of this study suggest that patients who have well-preserved lung function diagnosis can progress into PPF. This warns us to pay attention to even those with good lung function and suggests the need for further efforts to find out risk factors for PPF beyond lung function.

Limitations

This study has several limitations that should be considered. First, this was a retrospective study of a single center. Second, PPF was only defined based on lung function values. Third, treatment strategies were dependent on clinician's decision. Dose of immunomodulating agents might go up and down depending on the disease status. This made us not aware of clinical deterioration that was not severe enough to lead to hospitalization. Fourth, we could not assess the effect of antifibrotics on the risk for PPF because a small number of patients used antifibrotics. Fifth, we were unable to discover or develop new biomarkers related to the progression of PPF due to the nature of retrospective study. Sixth, each CTD has specific factors related to ILD progression (such as autoantibody positivity or high titer in the particular CTD) and radiologic patterns vary for each CTD. However, due to the limited number of patients with each CTD-ILD, it was challenging to conduct a subgroup analysis on the risk of PPF progression based on the presence of certain radiologic patterns or a specific CTD subgroup. Lastly, study period was not long enough to analyze risk for long-term outcomes such as mortality.

Conclusion

Approximately a quarter of patients with CTD-ILD progressed into PPF. The use of immunomodulating agents based on inflammatory background of systemic autoimmune disease reduced the risk for PPF. Fundamental treatment strategies focusing on pathogenesis of the disease itself might slow down disease progression involving lung manifestation in patients with CTD-ILD. Pulmonary fibrosis is a pathologic process with an adverse impact on prognosis. Based on growing evidence of antifibrotic therapy and biologics on PPF, early detection of those who are at risk for developing PPF and appropriate standards for treatment and initiation of PPF in non-IPF ILDs will be needed.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, the Catholic University of Korea (KC22RISI0501). Informed consent was waived because of retrospective nature and patient information was de-identified and anonymized throughout the study.

Consent for the publication

Not applicable.

Author contributions

Kyuhwan Kim: Conceptualization; Investigation; Project administration; Writing – review & editing.

Jongmin Lee: Conceptualization; Investigation; Project administration; Supervision; Writing – review & editing.

Yong Suk Jo: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supplemental material

Supplemental material for this article is available online.

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