Pleuroparenchymal fibroelastosis in systemic sclerosis: prevalence and prognostic impact

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Take-home message

We provide a thorough assessment of pleuroparenchymal fibroelastosis (PPFE) prevalence, severity and clinical impact in two large cohorts of scleroderma patients (Total N=359). PPFE was present in 18% of patients and independently predicted mortality.

Abstract

Interstitial lung disease (ILD) in systemic sclerosis (SSc) is a major cause of morbidity and mortality, mostly presenting as nonspecific interstitial pneumonia. Little is known about the prevalence of pleuroparenchymal fibroelastosis (PPFE), a specific entity affecting the visceral pleura and subpleural parenchyma. We set out to estimate PPFE prevalence in two large cohorts of SSc patients and to assess its impact on survival and functional decline.

A total of 359 SSc patients, derived from two referral centers in two different countries (UK and Italy), were included. The first available high-resolution computed tomography scan was independently evaluated by two radiologists blind to clinical information, to quantify ILD extent, freestanding bronchial abnormalities, and lobar percentage involvement of PPFE on a 4-point categorical scale. Discordant scores were adjudicated by a third scorer. PPFE extent was further classified as limited (≤2/18) or extensive (>2/18). Results were evaluated against functional decline and mortality.

The overall prevalence of PPFE in the combined SSc population was 18% (11% with extensive PPFE), with no substantial difference between the two cohorts. PPFE was significantly linked to free-standing bronchial abnormalities (61% vs 25% in PPFE vs no PPFE; p<0.0001) and to worse survival, independently of ILD severity or short-term lung function changes (HR 1.89, 95% CI 1.10-3.25; p=0.005).

In the current study, we provide an exhaustive description of PPFE prevalence and clinical impact in the largest cohort of SSc subjects published so far. PPFE presence should be carefully considered, due to its significant prognostic implications.

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Introduction

Systemic sclerosis (SSc, Scleroderma) is a rare, immune-mediated disorder, characterized by microvascular injury, circulating autoantibodies, and fibroblast activation, leading to fibrosis of the skin and visceral organs [1]. Lung involvement, including interstitial lung disease (ILD) and/or pulmonary hypertension, is the leading cause of morbidity and mortality [2]. ILD may range from subclinical to severe progressive lung fibrosis. Baseline functional impairment and short-term pulmonary function test (PFT) trends, along with ILD extent on high resolution computed tomography (HRCT), are currently the most informative prognostic tools in routine clinical practice [3,4]. Morphologically, nonspecific interstitial pneumonia (NSIP) is the most common pattern, while a usual interstitial pneumonia (UIP) pattern is seen in a minority. Little is known about prevalence and prognostic value of other parenchymal abnormalities [5]. In particular, no large-scale study has assessed presence and potential impact of pleuroparenchymal fibroelastosis (PPFE) in SSc.

PPFE is a specific clinical-pathological entity affecting the visceral pleura and the subpleural parenchyma with an upper-lobe predilection, characterized by elastin-rich intra-alveolar fibrosis and scattered fibroblastic foci [6]. Its pathogenesis is unclear, but the heterogeneous spectrum of clinical presentation and behavior suggests that it may represent the final expression of a variable interplay between immune dysregulation, environmental exposure and genetic predisposition [6]. PPFE can present as an idiopathic form, included in the latest ATS/ERS classification of idiopathic interstitial pneumonias [7], or in association with a variety of different conditions, including infection, lung and bone marrow transplantation and autoimmune diseases [8, 9]. Moreover, PPFE features are observed in association with other interstitial lung diseases, including idiopathic pulmonary fibrosis (IPF) [10, 11], hypersensitivity pneumonitis (HP) [12] and familial forms of pulmonary fibrosis [13].

The aims of the present study were to estimate the prevalence of PPFE in large unselected consecutive cohorts of SSc patients, to assess its potential impact on survival and functional decline, and to evaluate the correlation between PPFE and selected radiological/clinical features.

Materials and methods

Two cohorts were included: one from the Royal Brompton Hospital Interstitial Lung Diseases Unit, London, UK (RBH cohort), the other from the rheumatological center of the Clinica Medica of University Hospital "Ospedali Riuniti", Ancona, Italy (Ancona cohort). Ethical approvals for this study of clinically indicated HRCT and pulmonary function data were obtained from the Institutional Ethics Committees of RBH and of "Ospedali Riuniti", respectively.

Patients and clinical information

Consecutive patients with a diagnosis of SSc according to recommended criteria [14], presenting to RBH between 1990 and 2011 and to Ancona between 2002 and 2014 were eligible for inclusion in the absence of the following exclusion criteria: 1) overlap with other connective tissue disease; 2) unavailability of the HRCT scan; 3) predominant radiological features suggestive of vasculopathy (Supplementary Materials).

Demographic factors and selected disease-related characteristics were collected for all SSc cases. These included: age, sex, smoking history, disease duration (defined as months from the onset of the first non-Raynaud's phenomenon clinical manifestation), cutaneous subset (limited/diffuse), serum autoantibodies, pulmonary hypertension (defined as a systolic pulmonary arterial pressure ≥ 40 mmHg by echocardiography and/or a mean pulmonary artery pressure ≥ 25 mmHg by right heart catheterization), previous and/or concomitant treatments (corticosteroids and/or immunosuppressant drugs). Treatment status was sub-categorized as either "intention to treat" (treatment instituted within 3

months of presentation or continuation of pre-existing treatment) or "intention to observe" (no therapy at 3 months of follow-up).

PFT measurements (expressed as absolute value and percent predicted) were recorded if performed within 6 months of chest HRCT. They included forced vital capacity (FVC), forced expiratory volume in 1s (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLco). The composite physiological index (CPI) was calculated using the formula: 91.0 - (0.65 x % predicted DLco) - (0.53 x % predicted FVC) + (0.34 x % predicted FEV_1).

The presence of either limited or extensive ILD involvement in SSc was defined according to the staging system proposed by Goh et al, based on integration of HRTC evaluation and FVC estimation (Supplementary materials) [3].

For the UK cohort, all sequential lung function tests, routinely collected and available from baseline until last visit or death were also analyzed. Trends were analyzed as continuous change and as categorical change in separate models. FVC and DLco changes were computed as the percent change relative to the absolute values at baseline. We did not record longitudinal lung function measurements in the Italian cohort, as most patients did not undergo routine PFTs on follow up.

HRCT analysis

HRCT scans were evaluated independently by two experienced radiologists, with a third scorer adjudicating discordant scores. Scorers assessed PPFE features and extent [13], total ILD extent as well as freestanding bronchial abnormalities [12, 15,16]. The extent of pleural surface involvement from PPFE in each lobe was evaluated on a 4-point categorical scale. PPFE extent was further classified as limited (≤2/18) or extensive (>2/18). Further details of the scoring methodology are provided in the Supplementary materials.

Statistical analysis

Analyses were performed using SAS (version 9.4). Group comparisons were made using Student's *t* test, Wilcoxon rank sum, χ^2 statistics and Fisher's exact test, as appropriate. Interobserver variation for visual score between radiologists was assessed using the weighted Kappa statistics.

Mortality and disease progression were quantified from the date of the first available HRCT up to March 2018. Univariable and multivariable Cox proportional hazard analysis was undertaken to investigate determinants of mortality. Multivariable models always included terms for age, sex, cohort, PPFE, Goh et al staging system or CPI, FVC, DLco, active treatment, pulmonary hypertension, body mass index (BMI) and smoking status. We considered the composite categorical decline (CCD) at two years, defined as either a decline in FVC of ≥ 10% or a decline in FVC of 5-9% in combination with a decline in DLco of ≥ 15%. This was included as time-dependent covariate in multivariable survival analysis.

The relationship between PPFE and the annual rate of decline in absolute FVC values (measured as millimeters per year) from the date of HRCT to the end of follow up, with all available FVC values included, was analyzed by using a random coefficient regression model (with random slopes and intercepts) that included sex and age as covariates.

Results

Of the initial 705 patients screened, 261 were excluded as the chest HRCT was not available for assessment. However, no differences in ILD severity were seen between patients included in the study and those excluded because of unavailable HRCT (Supplementary Material). Of the remaining 444 patients, 45 were excluded because of overlap with other connective tissue diseases and 40 due to the presence of predominant vasculopathy features on HRCT. A total of 359 patients were included in the present study, of which 228 from RBH and 131 from Ancona (Figure 1).

Demographic and clinical characteristics of the combined cohort and by center are summarized in Table 1. The mean age was 53.6 (±13.2) years, and the majority of patients were females (76.8%) and nonsmokers (58%), without significant differences according to cohort. Disease duration was similar in the two cohorts (74.9 ± 85.6 and 62.8 ± 86.5 months), the limited cutaneous subtype was more frequent than the diffuse in both cohorts, and no substantial difference was detected in anti-topoisomerase antibody frequency. Lung involvement was significantly worse in the UK cohort, as documented by worse lung function parameters, higher mean CPI, greater ILD extent on HRCT, more frequent extensive ILD stage [3], prevalence of pulmonary hypertension, and higher proportion of subjects on "intention to treat" (Table 1). Median follow up time was 6.7 years in UK cohort and 8.6 years in the Italian cohort. With reference to radiological features other than PPFE, the prevalence of emphysema was approximately 15%, with no substantial difference between subgroups. Freestanding bronchial abnormalities were overall present in up to one third of the study population (32%), with a higher proportion in the Italian cohort (respectively 38% and 28%).

Prevalence of PPFE and associations with selected features

PPFE was detected in 65 of 359 SSc patients (PPFE+ 18.1%), of whom 41 (11.4%) had extensive PPFE The prevalence of PPFE, overall and by extent (limited/extensive) was similar in the two cohorts (Table 2). Interobserver agreement for the presence of PPFE was good (weighted kappa statistics: 0.67). A comparison of demographic, clinical and radiological characteristics according to the presence of PPFE is shown in Table 3. Age, sex, smoking status, cutaneous subtype, anti-topoisomerase antibody frequency, active treatment and presence of PH did not differ between PPFE+ and PPFE- subgroups. PPFE was associated with a trend towards longer disease duration, a slightly lower mean ILD extent at HRCT, and more severe functional impairment (in FVC and DLco predicted values), although these differences did not reach statistical significance.

Body mass index (BMI) was significantly lower in PPFE+ compared to PPFE- patients (21.2 ± 3.53 and 25.3 ± 4.91, respectively). The prevalence of freestanding bronchial abnormalities was markedly higher in patients with PPFE compared to those without (61% in PPFE+ group vs 25% in PPFE- group, $p < 0.0001$).There was no statistical difference in the prevalence of emphysema according to PPFE presence (14% in patients with and without PPFE).

Prognostic impact of PPFE

Data on survival were available for 344 patients (PPFE- subgroup=281; PPFE+ subgroup=63). As no difference was observed in the prevalence of PPFE or in its severity according to centre, the analysis of the relationship between PPFE and survival was performed using the combined cohorts, although cohorts were adjusted for in the multivariable analysis. The presence of PPFE on HRCT was significantly associated with increased mortality on univariable analysis (HR: 1.56, 95% CI 1.02-2.40; p=0.04) (Figure 1 and Supplementary Table 2S). There were 28 deaths in PPFE+ subgroup (44%) and 92 in PPFE- subgroup (32%). Multivariable analyses are reported in Table 4, providing a base model, adjusted for age, sex, cohort, and Goh staging system, and a full model, including also active treatment, pulmonary hypertension, BMI and smoking status. The association, if anything, was stronger in both models (HR 1.79, 95% CI 1.16-2.78;p=0.009 in base model; HR 1.89, 95% CI 1.10-3.25; p=0.02 in full model) (Table 4). In order to assess whether the relationship with PPFE was influenced by short term lung function changes, the full model also included the CCD variable, with no change in the association between PPFE and survival (Table 4). When CPI was used in a separate multivariable model, the association between PPFE and survival remained significant (HR 1.60, 95% CI 1.03-2.50; p=0.04).

With regard to the severity of PPFE, we observed a trend towards a worse survival both in patients with limited and with extensive PPFE, compared to PPFE- patients, although in view of the small numbers

in each subgroup (Table 2S), this did not reach statistical significance both on univariable and multivariable analyses.

In the UK cohort alone, we analyzed the relationship between PPFE and the adjusted annual rate of decline in absolute FVC values. A trend towards higher decline in absolute FVC values (66 ml/year vs 44 ml/year, p=0.08) was detected, although only of borderline significance. This did not change after adjusting for disease extent or "intention to treat" (data not shown).

Discussion

The present study provides a detailed assessment of PPFE prevalence, associations and clinical impact in a large cohort of SSc patients, derived from two referral centers in two different countries. PPFE was present in approximately 18% of patients, and was an independent predictor of worse prognosis.

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Interestingly, the prevalence of PPFE was essentially the same in the two populations, despite a significant difference in ILD severity. The UK population was derived from a tertiary ILD referral center and thus characterized by more severe ILD compared to the Italian cohort, which was retrieved from a rheumatology referral center for SSc, less selected in terms of pulmonary involvement. This suggests that the genesis and progression of PPFE in SSc is not necessarily linked to the progression of the background ILD pattern and may have alternative explanations. Interestingly, we observed a strong association between PPFE and freestanding bronchial abnormalities, although this link remains to be explained.

These results are in line with a previous Japanese study evaluating prevalence and prognosis of radiological PPFE lesions in a cohort of patients with CTD-ILDs (n = 113), including 14 subjects with SSc. The overall prevalence of PPFE in the whole CTD population was 19%, with the highest peak in the SSc subgroup (43%) and survival analysis in a multivariable model showed that PPFE presence

was a significant risk factor for mortality due to respiratory causes [9]. We also found that the presence of PPFE features is independently associated with an excess mortality risk by 77% on multivariable analysis that included age, Goh et al staging system (or CPI in separate models), BMI, progressive functional decline (CCD at 2 years), intention to treat and pulmonary hypertension. Potential determinants of a worse survival may include direct mechanisms, such as the marked functional restriction in these patients and/or more rapid lung function decline, as well as indirect/systemic effects, such as a reduced BMI and/or higher susceptibility to infections. A more rapid rate of lung function decline is a further pathological mechanism that might be linked to a higher mortality, as we observed a trend bordering on statistical significance towards a greater rate of decline in FVC in patients with PPFE. However, as longitudinal lung function was only available for the UK cohort, further studies are needed to assess the link between PPFE and lung function decline in different populations. We find a strong association with low BMI in PPFE+ subjects, with BMI predictive of worse survival on univariable analysis in our cohort. Although the association was no longer significant on multivariable analysis, a low BMI may well be contributing to the poor survival in this cohort. A low or decreasing BMI is known to be an independent predictor of increased mortality in patients with IPF [17-20].

With reference to the higher susceptibility to infections in these patients, it is worth underlining the strong association between PPFE and freestanding bronchiectasis, found in both our cohorts. The higher prevalence of freestanding bronchial abnormalities in subjects with PPFE (33.7% vs 1.1%, $p<0.0001$) is consistent with findings in a large IPF cohort (N=274) [10]. The strong link between PPFE and freestanding bronchiectasis supports the hypothesis that PPFE might represent an aberrant fibrosing immune response to repeated infections and inhaled antigens. In the paper by Reddy et al, over half of PPFE patients reported recurrent infections, including allergic bronchopulmonary aspergillosis, and aspergilloma [13], and Piciucchi et al. documented a PPFE case of a patient who

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tested positive for Aspergillus precipitins [21]. Moreover, no significant association was found between PPFE and smoking history, confirming previous observations [12].

We did not observe increased mortality in extensive PPFE, compared to limited PPFE, despite the fact that the extensive PPFE has been linked to higher mortality in IPF and HP [10,12]. This is possibly due to the the low number of observations, or to a different interaction operating in SSc-ILD patients.

The study had limitations. Although the CT appearance of PPFE has been defined [13], tissue corroboration was lacking in our cohorts. However, as the histological distinction between a UIP and NSIP pattern does not change management in SSc-ILD [25,26], tissue biopsy is no longer performed in these patients. Thus, PPFE can be identified in SSc patients only by means of HRCT, and, therefore, our observations are applicable to routine clinical practice with PPFE identified with observed good inter-observer agreement. Selection bias must be acknowledged, as patients were evaluated at two national tertiary referral centers, and were, therefore, likely to have more severe pulmonary involvement than in unselected cohorts. Furthermore, there were differences in patient characteristics between the two centers. However, the presence of PPFE was not related to ILD severity, and, importantly, the linkage between PPFE and mortality was independent of ILD severity, the distinction between intention to treat and intention to observe, and the referral centre. Given these observations and the fact that the full spectrum of ILD severity was well-represented in the study cohort, we believe that our findings are likely to be generalizable.

A further potential bias is related to the exclusion of subjects with predominant features suggestive of vasculopathy at HRCT. In the absence of standardized radiological criteria, we adopted the features used to describe SSc-associated pulmonary veno-occlusive disease, including the presence of both centrilobular ground glass opacities and non-subpleural interlobular septal thickening [27, 28]. As indirect confirmation of the reliability of this definition in identifying vascular rather than interstitial changes, a reduction in DLCO with preserved lung volumes was observed in this excluded subgroup.

Lastly, due to the retrospective nature of this study, information on serological status was missing for many patients, and standardized data on the frequency of respiratory infections and other clinical features was not available.

In conclusion, the increasing awareness of PPFE among specialists over recent years has led to an increase in its identification in both idiopathic and secondary contexts, suggesting that it is not as rare as previously thought. In the current study, we describe PPFE prevalence, extent and clinical impact in the largest cohort of SSc subjects published so far. Our results indicate that its presence should be carefully considered, due to its significant prognostic implications. Owing to the absence of effective tailored treatments, the identification of PPFE does not currently alter management of this subgroup of SSc patients, but greater awareness, surveillance and careful prevention of infections is recommended. Further studies are needed to better define the pathogenesis and optimal management of PPFE.

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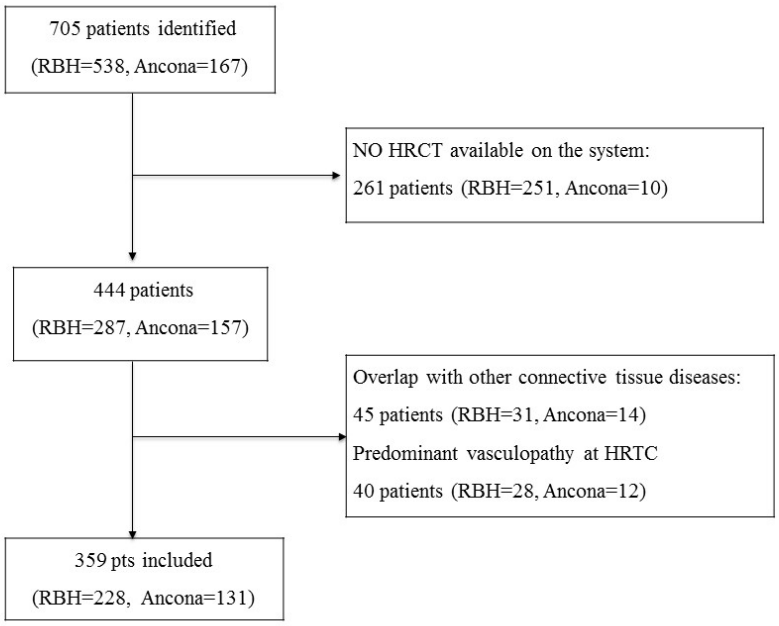
Figure 1. Flow-chart of cohort selection



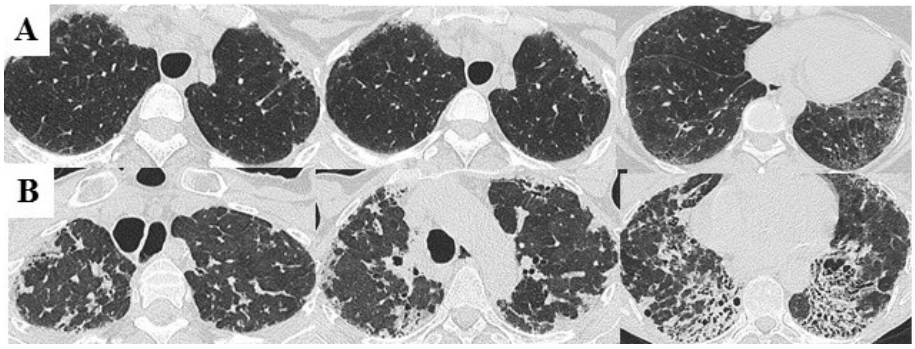


Figure 2 A-B. Axial CT images showing limited (A) and extensive (B) features of pleuraparenchymal fibroleastosis (PPFE). Fig. 2A highlights limited pleural and parenchymal aggregations of fibrous tissue in the upper lobes, and separate interstitial abnormalities in the lower lobes. Fig 2B shows extensive subpleural, parenchymal and airways-centered PPFE features in the upper and lower lobes. A fibrotic NSIP pattern can be also observed in the lower lobes.

Characteristics	**Whole cohort (n=359)**	**RBH cohort (n=228)**	**Ancona cohort (n=131)**	***P***
Age, years	53.6 ± 13.2	53.2 ± 12.5	54.3± 14.4	0.4
Sex, no. male/no. female	83/276	58/170	25/106	0.1
Smoking status, no./ no. assessed (%) (n=325)				
Never smokers	189 (58)	124/217 (57)	65/108 (60)	0.3
Ever- smokers	136 (42)	93/217 (43)	43/108 (40)	
Duration of systemic disease, median months	70.5 ± 85.9	74.9 ± 85.6	62.8 ± 86.5	0.2
Limited cutaneous SSc/diffuse cutaneous SSc, no (n=241)	158/83	67/43	91/40	0.06
Antitopoisomerase antibody positive/ no. assessed (%)	158/312 (50)	88/185 (48)	70/131 (53)	0.3
Active treatment at baseline/ no. assessed (%) (n=317)	167/317 (53)	146/186 (78)	21/131 (16)	<.0001
Presence of PH, no. (%) (n=336)√	73/336 (21)	66/205 (32)	7/131(5)	<.0001
Pulmonary function test at baseline, % predicted (n=319)	(n=319)	(n=226)	(n=93)	
FEV1	75.6 ± 21.6	71.6 ± 20.5	86.5 ± 21.2	< .0001
FVC	78.9 ± 23.4	74.6 ± 22.1	89.6 ± 23.2	<.0001
DLco	50.8 ± 19.5	45.4 ± 17.3	64.1 ± 17.9	<.0001
Kco	72.4 ± 18.8	69.2 ± 18.7	80.2 ± 16.8	<.0001
Limited/extensive ILD disease* (n= 347)	156/191	85/143	71/48	<.0001
CPI (n=300)	42.7 ± 16.9	46.6 ± 15.4	31.9 ± 16.1	<.0001
ILD average extent on HRCT	29.2 ± 13.2	32.8 ± 30.2	22.8 ± 18.7	<.0001
Extent < 5 percentage (n, %)	70/359 (19)	23/228 (10)	47/131 (36)	
Radiological features				
Any emphysema no(%)	51 (14)	35 (15)	16 (12)	0.4
-Trivial	22 (6)	13 (6)	9 (7)	
-Moderate/severe	29 (8)	22 (9)	7 (5)	
Any freestanding bronchial abnormalities no. (%)	114 (32)	64 (28)	50 (38)	0.04
-Bronchial dilatation	79 (22)	43 (19)	36 (27)	0.05
-Bronchial wall thickening	70 (19)	38 (17)	32 (24)	0.07

Table 1. Demographic, clinical and radiological characteristics of the whole cohort and by center

Values are reported as mean ± SD as Number (%), as appropriate.

√ 34 diagnosed byright heart catheterization (mean pulmonary artery pressure ≥25 mmHg), 39 by echocardiogram (estimated pulmonary artery systolic pressure ≥40 mmHg) by echocardiogram.

* According to Goh et al staging system [3]

CPI: composite physiological index; DLco: Diffusion capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HRCT: high resolution computed tomography; Kco: transfer coefficient of the lung for carbon monoxide ILD: interstitial lung disease; PH: arterial pulmonary hypertension (defined as PASP≥40 mmHg on echocardiogram and/or ≥25 mmHg on right heart catheterization); SSc: scleroderma

Characteristics	Whole cohort (n=359)	RBH cohort (n=228)	Ancona cohort (n=131)	*P*
PPFE	65 (18.1)	42 (18.4)	23 (17.5)	0.8
Limited	24 (6.7)	16 (7.0)	8 (6.1)	
Extensive	41 (11.4)	26 (11.4)	15 (11.4)	

Table 2. PPFE prevalence and extent in the whole cohort and by center

PPFE: pleuroparenchymal fibroelastosis

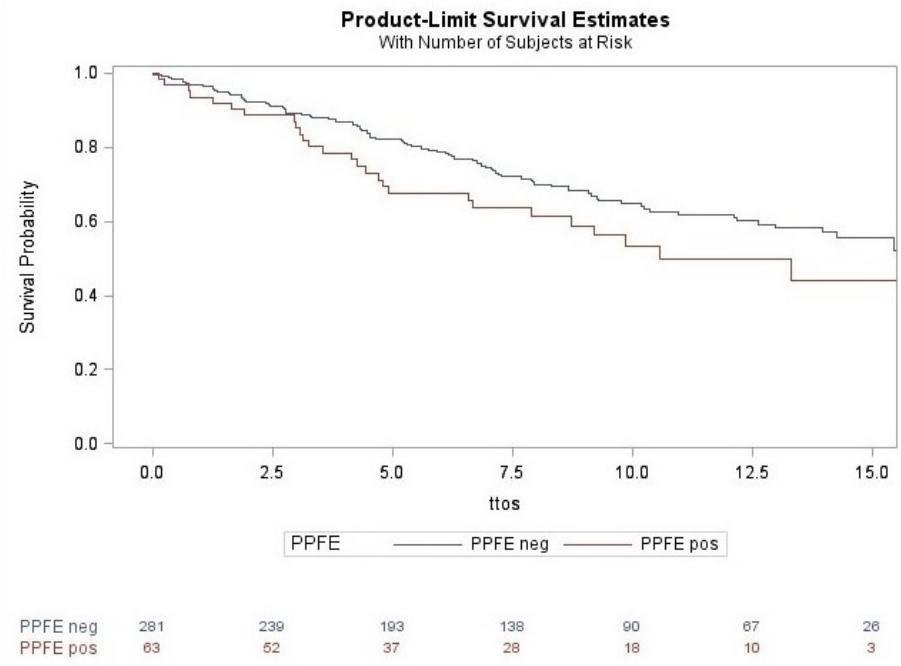
Characteristics	Patients with PPFE (n=65)	Patients without PPFE (n=294)	*P*

Table 3. Demographic, clinical and radiological characteristics according to PPFE presence.

Age, years	54.3 ± 11.5	53.4 ± 13.5	0.6
Sex, no. male/no. female	10/55	73/221	0.1
Smoking status, no. (n=315)	(n=56)	(n=259)	
Never smokers	33 (59)	146 (49)	0.6
Ever- smokers	23 (41)	113 (43)	
Body mass index (n=328)	21.2 ± 3.52	25.3 ± 4.91	<.0001
Duration of systemic disease, mean months	87.3 ± 89.2	66.8 ± 89.2	0.08
Limited cutaneous SSc/ no. assessed (%) (n=241)	25/40 (62)	133/201 (66)	0.6
Antitopoisomerase antibody positive/ no. assessed (%) (n=316)	28/57 (50)	130/259 (50)	0.3
"Intention to treat"/ no. assessed (%)(n=317)	30/59 (50)	137/258 (53)	0.7
Presence of PH, no./ no. assessed (%) (n=336)	15/61 (25)	58/275 (21)	0.6
Pulmonary function test at baseline, % predicted (n=319)	(n=59)	(n=260)	
FVC	74.5 ± 24.6	80.0 ± 23.1	0.1
DLco	47.6 ± 17.3	51.5 ± 19.8	0.1
Kco	72.9 ± 19.9	72.3 ± 18.6	0.8
ILD average extent on HRCT	26.9 ± 21.3	29.7 ± 22.7	0.3
Radiological features			
Any emphysema no. (%)	9 (14)	42 (14)	0.9
Any freestanding bronchial abnormalities no. (%)	40 (61)	74 (25)	<.0001
-Bronchial dilatation	31 (48)	48 (16)	<.0001
-Bronchial wall thickening	27 (42)	43 (14)	<.0001

Values are reported as mean ± SD as Number (%), as appropriate. DLco: Diffusion capacity of the lung for carbon monoxide; FVC: forced vital capacity; Kco: transfer coefficient of the lung for carbon monoxide; HRCT: high resolution computed tomography; ILD: interstitial lung disease; Kco: PH: arterial pulmonary hypertension (defined as PASP≥40 mmHg on echocardiogram and/or ≥25 mmHg on right heart catheterization); PPFE: pleuroparenchymal fibroelastosis; SSc: scleroderma

Figure 3. Survival comparison between patients with and without PPFE in the whole cohort (n=344)



		Base Model[a]		Full Model[b]	
Characteristic	**N**	**HR**	**95%CI**	**HR**	**95%CI**
PPFE (yes)	332	1.79	1.16-2.78	1.89	1.10-3.25
Age (yrs)	332	1.04	1.02-1.06	1.05	1.03-1.07
Sex (Female)	332	1.57	1.05-2.33	1.71	1.05-2.77
Cohort (Italian)	332	0.43	0.26-0.69	0.57	0.21-0.53
FVC % pred (per 1% increase)	306	0.97	0.96-0.98	1.00	0.98-1.01
DLco % pred (per 1% increase)	304	0.94	0.93-0.96	0.95	0.92-0.97
ILD extent at HRCT (per 1% increase)	344	1.02	1.01-1.03	1.01	0.99-1.03
Goh et al staging system (extensive)	332	2.15	1.42-3.26	2.38	1.29-4.40
CPI (per unit increase)	288	1.05	1.03-1.06	1.05	1.03-1.08
CCD at 2 years[c] (yes)	332	4.14	2.85-6.00	5.95	3.56-8.78
Active treatment (yes)	296	1.24	0.69-2.21	1.71	0.83-3.49
Pulmonary hypertension (yes)	309	2.78	1.85-4.24	3.07	1.93-4.89
Smoking status (ever)	284	1.09	0.72-1.63	0.99	0.62-1.61
BMI (per kg/m^2)	306	0.95	0.90-0.99	0.96	0.92-1.01

Table 4. Mortality in SSc patients according to selected covariates, expressed as hazard ratios (HR) with 95% confidence intervals (CI)

DLco: carbon monoxide diffusion capacity; FVC: forced vital capacity; HR:hazard ratio; HRCT: high resolution computed tomography; ILD: interstitial lung disease; PH: arterial pulmonary hypertension (defined as PASP≥40 mmHg on echocardiogram and/or ≥25 mmHg on right heart catheterization); PPFE: pleuroparenchymal fibroelastosis; SSc: scleroderma.

[a] HR adjusted for age, sex, cohort, and Goh staging (except for ILD extent at HRCT and CPI))
[b] HR adjusted for all the characteristics listed in the table, except for ILD extent at HRCT, FVC%, DLco%, and CPI(N=227). For ILD extent at HRCT and, in a separate model CPI, HR adjusted for all the characteristics listed in the table except for Goh staging , DLco% and FVC% (N=216).

[c] time-dependent covariate

Figure legend

Figure 1. Flow-chart of case inclusion in study

Figure 2 A-B. Axial HRCT images showing limited (A) and extensive (B) features of pleuroparenchymal fibroleastosis (PPFE). Fig. 2A highlights limited pleural and parenchymal aggregations of fibrous tissue in the upper lobes, and interstitial abnormalities in the lower lobes. Fig 2B shows extensive subpleural, parenchymal and airway-centered PPFE features in the upper lobe as well in the lower lobes

Figure 3. Survival comparison between patients with and without PPFE in the whole cohort (n=344)