Long-term functional course of Sjögren's disease-associated interstitial lung disease

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Shareable abstract (@ERSpublications)
Primary Sjögren's disease-associated interstitial lung disease bears a poor prognosis in the long term. A subgroup of patients has an accelerated pattern of lung function decline and a high risk of death. They are characterised by a low D_{LCO} at diagnosis. https://bit.ly/3UKViHP

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Abstract

Background Interstitial lung disease (ILD) is common in primary Sjögren's disease (pSD); its functional course is poorly known. Our aim was to characterise the long-term functional course and prognosis in patients with pSD-ILD. We determined the role of baseline demographic and clinical variables in the evolution of lung function and identified risk factors for death or transplantation.

Methods In a retrospective observational cohort study, patients with pSD and ILD were retrospectively identified from two French ILD centres. Forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (D_{LCO}) slopes were obtained from joint models. Latent class mixed models identified clusters of FVC and D_{LCO} trajectories.

Results We included 73 patients (63% women, mean age 63 years), with a median follow-up of 9.3 years. At baseline, mean FVC was 73±21% and D_{LCO} 51±16%. On average, FVC was stable, while there was an annual decline in D_{LCO} of 1% of the predicted value. Male sex, a pattern of usual interstitial pneumonia (UIP) or indeterminate for UIP on high-resolution computed tomography (HRCT), and features of fibrosis on HRCT, were associated with an accelerated decline in FVC and D_{LCO}.

Conclusion We identified clusters of lung function evolution. 1) Two FVC trajectories: patients with stable FVC (n=56, 78%); patients with FVC decline (n=16, 22%) of 2.4% per year, characterised by a low baseline D_{LCO} (39%) and a higher risk of death or transplantation (HR 52, 95% CI 10–273). 2) Three D_{LCO} trajectories: patients with stable D_{LCO} (n=44, 66%); patients with a slow decline in D_{LCO} (n=12, 18%) of 2.8% per year; patients with a rapid decline in D_{LCO} (n=11, 16%) of 4.8% per year, characterised by a low baseline D_{LCO} (41%) and a higher risk of death or transplantation (HR 156, 95% CI 18–1352).

Introduction

Sjögren's disease is an autoimmune epithelitis characterised by impaired function of exocrine glands and involvement of multiple organs, including the respiratory tract [1]. Pulmonary involvement includes parenchymal disease, airway abnormalities, lymphoproliferative disorders and, more rarely, vascular, muscular or pleural damage. Interstitial lung disease associated with primary Sjögren's disease (pSD-ILD), a common manifestation [2], can lead to acute or chronic respiratory failure and is associated with an increased mortality risk [3].

In recent years, a progressive pulmonary fibrosis (PPF) phenotype has been defined, characterised by an increase in respiratory symptoms, a decline in respiratory function and an increase in chest high-resolution computed tomography (HRCT) abnormalities, despite appropriate treatment, over a period of 1 to 2 years [4, 5]. This phenotype is typically observed in idiopathic pulmonary fibrosis patients, but can also be observed in other fibrotic lung disorders, such as ILD associated with connective tissue diseases (CTD-ILD), particularly systemic sclerosis (SSc) [6] and rheumatoid arthritis [7]. Patients with pSD-ILD are uncommon in published series of PPF. In the INBUILD trial, among 663 patients with PPF, seven had a diagnosis of pSD [8]. In a French series of 165 patients with PPF, 77 had a CTD, but only one had a pSD [9]. This low prevalence probably reflects the usually slow progression of ILD in these patients. Nevertheless, at present, very few studies have described the functional course of pSD-ILD. In a small series of pSD-ILD [10], five of 18 patients (28%) had a significant functional decline despite immunosuppressive therapy, over a mean follow-up of 38 months. In a recent cohort of 39 pSD-ILD patients [11], half of the patients had a progressive phenotype according to the INBUILD criteria [4], but in a time frame of 4.1 years, suggesting that pSD-ILD progression occurs over a long period of time.

The objectives of our study were to characterise the long-term functional course and prognosis of patients with pSD-ILD. We specifically identified risk factors for death or transplantation, and we determined the role of baseline clinical variables in the evolution of lung function.

Methods

Study design

This study was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine – Société de Pneumologie de Langue Française (CEPRO 2012-016). We included patients aged >18 years, diagnosed with pSD according to the American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) 2016 [12] and with ILD defined on HRCT managed between June 2002 and December 2020 in the pulmonology departments of Bichat Hospital, Paris, and Avicenne Hospital, Bobigny, two French reference centres for rare pulmonary diseases. We excluded patients with secondary Sjögren's disease and patients with exclusive bronchial or bronchiolar involvement, or isolated cystic disease. The flow chart of the study is presented in figure 1. No specific funding was obtained for this retrospective study.

Data collection

Data were retrospectively collected from electronic files through a systematic chart review. Demographic and clinical items were sex, age of pSD and ILD onset, respiratory and extra-respiratory symptoms and vital status. For patients lost to follow-up, the survival status was checked with the French National Institute of Statistics and Economic Studies (INSEE) nominative registry. Laboratory data included the presence of autoantibodies, cryoglobulinaemia and serum protein electrophoresis.

Baseline lung HRCT was centrally reviewed by an experienced ILD radiologist, blinded to the clinical and pathological information. The analysis included the extent of elementary lesions, expressed as percentage of parenchyma affected [13]. The presence of fibrotic lesions (traction bronchiectasis and honeycombing) was identified. HRCT patterns were determined as recommended by the recent guidelines [14]: usual

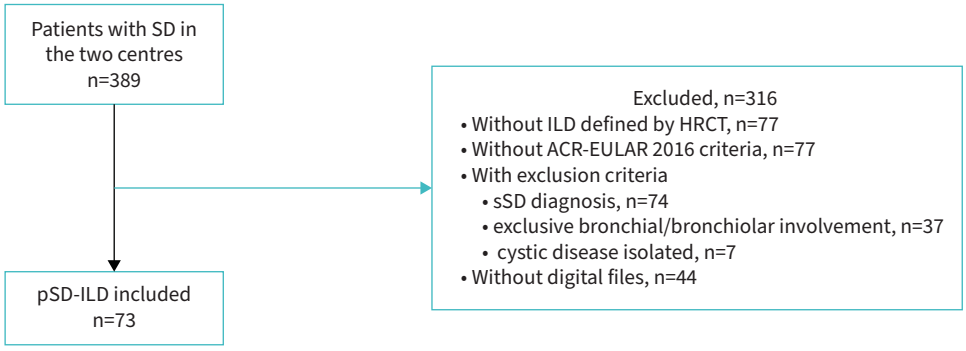

FIGURE 1 Flow chart of study population screening. SD: Sjögren's disease; ILD: interstitial lung disease; HRCT: high-resolution computed tomography; ACR-EULAR: American College of Rheumatology/European League Against Rheumatism; sSD: secondary Sjögren's disease; pSD: primary Sjögren's disease.

interstitial pneumonia (UIP), probable UIP, indeterminate for UIP and alternate diagnosis (including nonspecific interstitial pneumonia (NSIP), organising pneumonia (OP) (NSIP-OP), hypersensitivity pneumonitis (HP) [15] and lymphocytic interstitial pneumonia (LIP) [16]). For statistical analysis, we gathered UIP with probable UIP, and NSIP-OP with NSIP.

Patients underwent pulmonary function tests (PFTs) according to the established criteria for measurement of spirometry, lung volumes and diffusing capacity of the lungs for carbon monoxide (D_{LCO}) [17, 18]. Values were expressed as a percentage of predicted value (% pred). Data were collected from patients' charts at ILD onset and during follow-up. Lung function was considered abnormal when volumes were <80% pred or D_{LCO} was <70% pred. The GAP (Gender, Age, Physiology) index was calculated [19].

Statistical analysis

Descriptive analyses of patients' characteristics were completed using standard summary statistics for distributions. The primary outcome was transplant-free survival, *i.e.* the time from ILD diagnosis to death or lung transplantation. The association of predefined characteristics with the hazard risk of death or transplantation using Cox models was analysed. Longitudinal values of forced vital capacity (FVC) and D_{LCO} were analysed using mixed regression models and mean slopes of evolution of FVC and D_{LCO} were obtained from the joint models and expressed as % per year with their 95% confidence interval (CI). To identify distinct trajectories in the evolution of FVC and D_{LCO} after ILD onset, we used latent class joint mixed models. Details of the entire statistical analysis are given in supplementary material 1.

Results

Characteristics of patients at ILD onset

A total of 73 patients with pSD-ILD were included (figure 1). Clinical and biological baseline characteristics of the patients are summarised in table 1. Mean±SD age at ILD diagnosis was 62.7±14.3 years, 63% were female, and 33% were current or former smokers. Diagnosis of pSD and ILD were concomitant in 77% of patients. pSD preceded ILD onset in only six patients, while ILD preceded pSD for several years in 11 patients. Arthralgia or arthritis was the most common extra-respiratory manifestation (45%).

HRCT at ILD onset was available for all patients (n=73). Computed tomography abnormalities affected nearly 25% of the lung parenchyma on average at ILD onset (table 2). NSIP was the predominant HRCT pattern (28 patients, 38%).

Among the 73 pSD-ILD patients, 72 had PFT results at ILD onset available for analysis (table 2). A restrictive ventilatory defect was observed in 46 patients (66%). Mean±SD FVC was 73.4±21.4% pred. FVC values <80% and <50% pred were observed in 44 patients (61%) and 10 patients (14%), respectively. Severe D_{LCO} decrease (D_{LCO} <35% pred or cannot perform) was observed in 15 patients (21%). 25 patients (35%) were classified as stage II or III according to the GAP index (table 2).

Treatment

Treatments received during the study period are shown in supplementary table S1. 55 patients (75%) received at least one immunosuppressive agent (IS) with a median of two different ISs (range 1–5), either jointly or sequentially. ISs were combined with systemic corticosteroids in 91% of patients. Eight patients (11%) received an antifibrotic drug, all after several lines of IS.

Survival analysis

Median follow-up was 9.3 years from ILD diagnosis (range 1.7–17.2). An acute exacerbation (AE) was diagnosed in nine patients (5 women, mean±SD age 69.6±11.6 years), 4±3.3 years after ILD onset. Eight patients received immunosuppressive treatments prior to AE. An infection (rhinovirus) was documented in two patients. Of the 73 participants, 29 (40%) died during follow-up, and four patients (5%) underwent lung transplantation 3.4±1.9 years after ILD onset. The 10-year survival was 63% (95% CI 52–78), and the 10-year transplant-free survival was 61% (95% CI 50–75) (figure 2).

Causes of death were as follows: respiratory failure (n=11, including an AE in five patients), complications after lung transplant (n=2), sepsis (n=4), pulmonary hypertension (n=1), cardiovascular disease (n=4) and colon cancer (n=1). The cause of death was unknown in six patients.

Parameters at diagnosis associated with transplant-free survival (table 3)

In multivariate analysis, an indeterminate HRCT pattern, the initial extent of lesions on HRCT and a GAP stage II or III were significantly associated with an increased risk of death or transplantation. On HRCT, the "other pattern" category (LIP, OP and HP) was associated with a lower risk of mortality or transplantation.

TABLE 1 Clinical and biological characteristics of patients at ILD onset (n=73)

Demographic and clinical features	
Female	46 (63)
Age at ILD diagnosis years	62.7±14.3
Age at pSD diagnosis years	63.0±14.7
Smoking status	
Never-smoker	49 (67)
Current or former smoker	24 (33)
mMRC dyspnoea scale	
0	10 (14)
1	27 (37)
2	27 (37)
3	9 (12)
4	0
Cough	50 (68)
Bronchorrhoea	12 (16)
Arthralgia	33 (45)
Myalgia	15 (21)
Gastro-oesophageal reflux	21 (29)
Raynaud's phenomenon	17 (23)
Purpura	5 (7)
Peripheral neuropathy	12 (16)
Tubulointerstitial nephritis, interstitial cystitis	2 (3)
Laboratory findings	
ANA[#] (+)	51 (70)
RF[¶] (+)	22 (30)
Anti-CCP (+)	5 (7)
Gammaglobulin $g \cdot L^{-1}$ (n=62)	16.1±8.3
Hypergammaglobulinaemia, n/N (%)	33/65 (51)
Monoclonal gammopathy, n/N (%)	8/65 (12)
Cryoglobulinaemia, n/N (%)	5/31 (16)
Sjögren's disease criteria[+]	
Anti-Ro/SSA (+)	51 (70)
52 kDa	18 (25)
60 kDa	7 (10)
52 and 60 kDa	12 (16)
Undifferentiated	14 (19)
Salivary gland biopsy, n/N (%)	
Focus score ⩾1	58/68 (85)
Schirmer's test ⩽5 mm/5 min	52/61 (85)
Unstimulated whole saliva flow rate ⩽0.1 $mL \cdot min^{-1}$	10/48
Anti-Ro/SSA (+) and focus score ⩾1, n/N (%)	36/68 (53)

Data are presented as mean±SD or n (%) unless indicated otherwise. ILD: interstitial lung disease; pSD: primary Sjögren's disease; mMRC: modified Medical Research Council; ANA: antinuclear antibodies; RF: rheumatoid factor; anti-CCP: anti-citrullinated protein. [#]: positive for ANA titres ⩾1:160; [¶]: positive RF >20 $IU \cdot mL^{-1}$; [+]: Sjögren's disease criteria according to American College of Rheumatology/European League Against Rheumatism 2016.

Clinical and serological variables were not statistically significant in univariate analysis (supplementary table S2).

Annual decline of FVC and D_{LCO} in the overall population

The analysis of lung function tests evolution is shown in table 4. There were 72 patients with FVC measurements available for analysis. The median number of FVC measurements was eight per patient (range 1–20). FVC in the overall population was stable on average. However, a UIP pattern and presence of fibrosis on HRCT were associated with a decline of FVC, while female sex, other HRCT patterns (OP, LIP, HP) and absence of lung fibrosis on HRCT were associated with improved FVC during follow-up.

There were 67 patients with D_{LCO} measurements available for analysis. The median of D_{LCO} measurements was seven per patient (range 1–20). D_{LCO} declined at a mean rate of 1.0% pred per year (95% CI 0.7–1.3%) in the overall population. Male sex, a UIP or an indeterminate HRCT pattern, and the presence of fibrosis on HRCT were associated with an accelerated D_{LCO} decline.

TABLE 2 HRCT and pulmonary function test baseline characteristics of patients at ILD onset (n=73)

HRCT findings	
Ground glass opacities	69 (95)
Reticular opacities	64 (88)
Traction bronchiectasis	57 (78)
Honeycombing	30 (41)
Consolidations	23 (32)
Parenchymal nodules/micronodules	22 (30)
Mosaic perfusion	10 (14)
Cysts	18 (25)
ILD extent %	24.5±13.0
HRCT pattern	
NSIP[#]	28 (38)
UIP[¶]	13 (18)
OP	5 (7)
LIP	5 (7)
HP	2 (3)
Indeterminate for UIP	20 (27)
Baseline pulmonary function	
TLC % pred (n=70)	72.3±15.9
TLC <80% pred, n/N (%)	46/70 (66)
FVC % pred (n=72)	73.4±21.4
FVC <50% pred, n/N (%)	10/72 (14)
D_{LCO} % pred (n=67)	51.0±16.3
K_{CO} % pred (n=61)[+]	78.3±17.3
D_{LCO} <70% pred, n/N (%)	62/71 (87)
D_{LCO} <35% pred, or unfeasible, n/N (%)	15/71 (21)
FEV_1/FVC <70%, n/N (%)	14/72 (19)
FEV_1 % pred (n=70)	76.3±22.1
GAP stage, n/N (%)	
I	46/71 (65)
II	19/71 (27)
III	6/71 (8)

Data are presented as mean±SD or n (%) unless indicated otherwise. HRCT: high-resolution computed tomography; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; OP: organising pneumonia; LIP: lymphocytic interstitial pneumonia; HP: hypersensitivity pneumonitis; % pred: % of the predicted value; TLC: total lung capacity; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; K_{CO}: D_{LCO}/alveolar volume; FEV_1: forced expiratory volume in 1 s; GAP: Gender, Age, Physiology. [#]: NSIP (n=26) and OP-NSIP (n=2) were gathered; [¶]: UIP (n=9) and probable UIP (n=4) were gathered; [+]: D_{LCO} values were not available for six patients (because of respiratory limitation in four patients; not available, n=2).

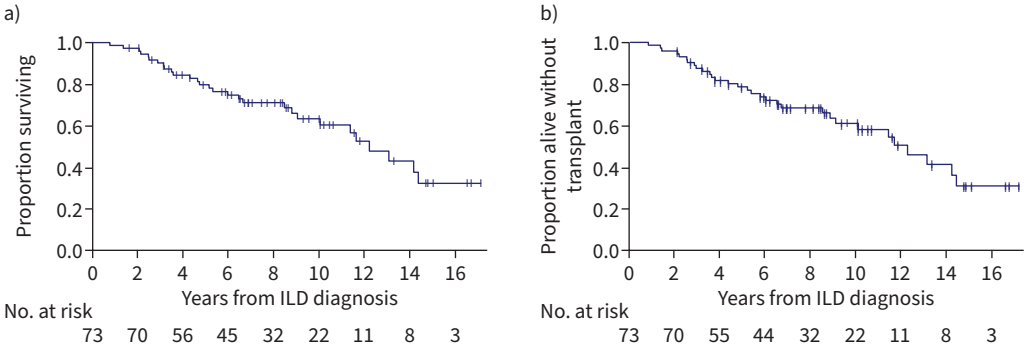

FIGURE 2 Survival estimates were performed using the Kaplan–Meier method. a) Overall survival; b) transplant-free survival. Survival was counted from ILD diagnosis to death in the overall survival (a), and death or lung transplantation whichever occurred first in the transplant-free survival (b). ILD: interstitial lung disease.

TABLE 3 Association of baseline factors with transplant-free survival

Variable	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Female sex	0.50 (0.23–1.05)	0.067	0.61 (0.21–1.78)	0.35
ILD pattern				
NSIP	1 (ref)		1 (ref)	
UIP	0.59 (0.20–1.79)	0.34	1.06 (0.31–3.61)	0.92
Other[#]	0.18 (0.038–0.90)	0.038	0.11 (0.018–0.68)	0.020
Indeterminate for UIP	1.41 (0.60–3.31)	0.41	2.94 (1.08–8.01)	0.036
ILD initial extent, per 1% up to 30%[¶]	1.05 (1.00–1.10)	0.070	1.09 (1.02–1.16)	0.009
GAP stage II–III	3.20 (1.51–6.79)	0.004	3.53 (1.11–11.3)	0.035

Results are for a multivariable model, pooled over imputed datasets. HR: hazard ratio; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; GAP: Gender, Age, Physiology. [#]: other pattern includes lymphocytic interstitial pneumonia n=5, organising pneumonia n=5 and hypersensitivity pneumonitis n=2. [¶]: linear effect up to 30%, then a constant effect.

In joint mixed models, a current value of D_{LCO} was found associated with death (HR 1.94, 95% CI 1.31–2.88) for a 10% lower D_{LCO}. There was less evidence of an association for current FVC values (HR 1.18, 95% CI 0.95–1.47) for a 10% lower FVC.

Characteristics of patients and survival according to the FVC trajectory

We aimed at identifying patients with a physiological progression phenotype. Joint latent class mixed model identified two different trajectories of FVC (figure 3a). Trajectory 1 ("Progressive FVC") comprised 16 patients (22%) with apparent linear decrease of FVC over time, at a rate of 2.4% per year. Trajectory 2 ("Stable FVC") comprised 56 patients (78%) and showed limited FVC variation over time. Adjusted for other prognostic factors (HRCT pattern, ILD initial extent, GAP index), trajectory 1 was highly associated with death or transplantation (HR 52.3, 95% CI 10.0–273) compared to trajectory 2 (figure 3b). One individual with no FVC measurement was excluded from this analysis. A description of patients in those trajectories is given in supplementary table S3.

TABLE 4 Annual decline of FVC and D_{LCO} during the follow-up

	FVC % predicted		D_{LCO} % predicted	
	Slope (95% CI)	p-value[#]	Slope (95% CI)	p-value[#]
All patients	−0.2 (−0.5–0.2)		−1.0 (−1.3– −0.7)	
Sex		<0.001		<0.001
Male	−0.3 (−0.7–0.2)		−2.2 (−2.7– −1.6)	
Female	1.4 (1.2–1.7)		−1.1 (−1.3– −0.8)	
ILD pattern		<0.001		0.002
NSIP	0.4 (0.0–0.7)		−0.8 (−1.1– −0.4)	
UIP	−0.8 (−1.2– −0.3)		−1.8 (−2.2– −1.3)	
Other[¶]	1.0 (0.4–1.5)		−1.0 (−1.4– −0.5)	
Indeterminate for UIP	−0.1 (−0.7–0.5)		−1.5 (−2.0– −1.0)	
Fibrosis at initial HRCT		<0.001		<0.001
Yes	−0.5 (−0.7– −0.2)		−1.7 (−2.2– −1.3)	
No	0.9 (0.1–1.6)		0.6 (0.2–1.0)	
GAP stage		0.41		0.057
I	−0.1 (−0.5–0.2)		−0.7 (−1.0– −0.4)	
II–III	0.1 (−0.4–0.6)		−1.3 (−1.7– −0.8)	

Data presented are the slopes obtained from joint models (and 95% CI) expressed as % predicted per year; positive slopes indicate an average increase, and negative slopes an average decrease over time. FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; GAP: Gender, Age, Physiology. [#]: interaction test for the comparison of slopes; [¶]: other pattern includes lymphocytic interstitial pneumonia (LIP) n=5, organising pneumonia (OP) n=5 and hypersensitivity pneumonitis (HP) n=2.

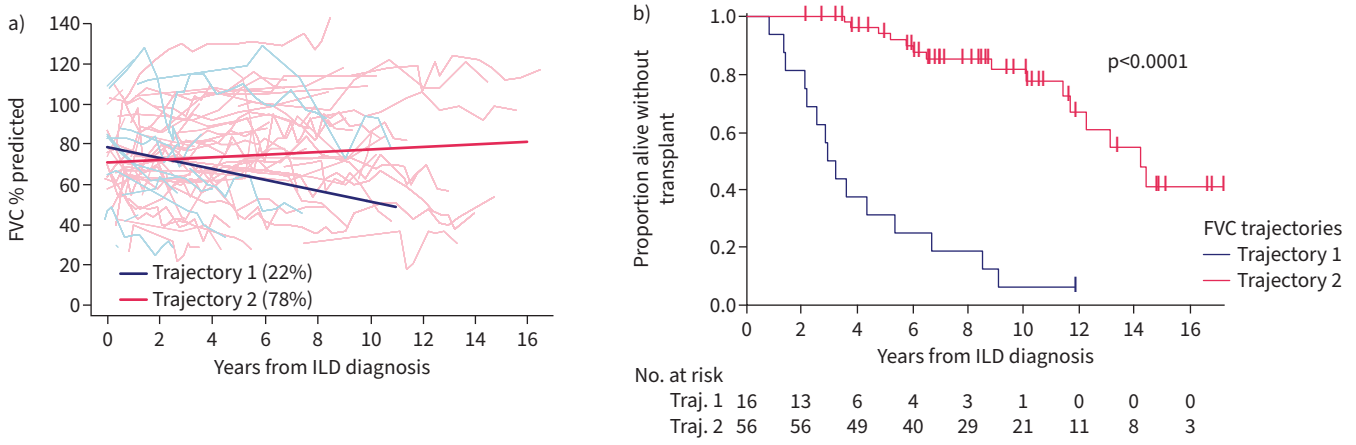

FIGURE 3 a) Trajectories of evolution of longitudinal FVC over follow-up; b) observed survival without transplantation according to the FVC trajectory. FVC: forced vital capacity; ILD: interstitial lung disease; Traj: trajectory.

Patients belonging to the "Progressive FVC" trajectory with a poorer prognosis had a lower initial D_{LCO} (39.3% *versus* 52.2%; p=0.013) but a similar initial FVC, more myalgias (44% *versus* 14%; p=0.027) and tended to be older at ILD diagnosis (67.7 *versus* 61 years; p=0.097). We also observed numerically more patients with a UIP pattern and less patients with "other" patterns (25% *versus* 14% and 6% *versus* 20% respectively) in trajectory 1. There were no differences regarding biological findings, presence of fibrosis or ILD extent on HRCT.

Characteristics of patients and survival according to the D_{LCO} trajectory

Clustering of D_{LCO} trajectories using a similar approach identified three groups of patients with different trajectories (figure 4a) among the 67 participants with D_{LCO} measurements. The most frequent one (n=44, 66%), trajectory A ("Stable D_{LCO}"), comprised patients with stable D_{LCO} over time. Trajectory B (n=11, 16%) comprised patients with lower D_{LCO} at diagnosis and a rapid decline of D_{LCO} during follow-up at a rate of 4.8% per year ("Low D_{LCO}, rapid decline"). The last cluster (n=12, 18%), trajectory C, had higher D_{LCO} at ILD diagnosis than the other groups, and a decrease at a yearly rate of 2.8% ("High D_{LCO}, slow decline").

In the joint model, adjusted for other prognostic variables (HRCT pattern, ILD initial extent, GAP index) and compared to trajectory A, the "Low D_{LCO}, rapid decline" group (trajectory B) was associated with a

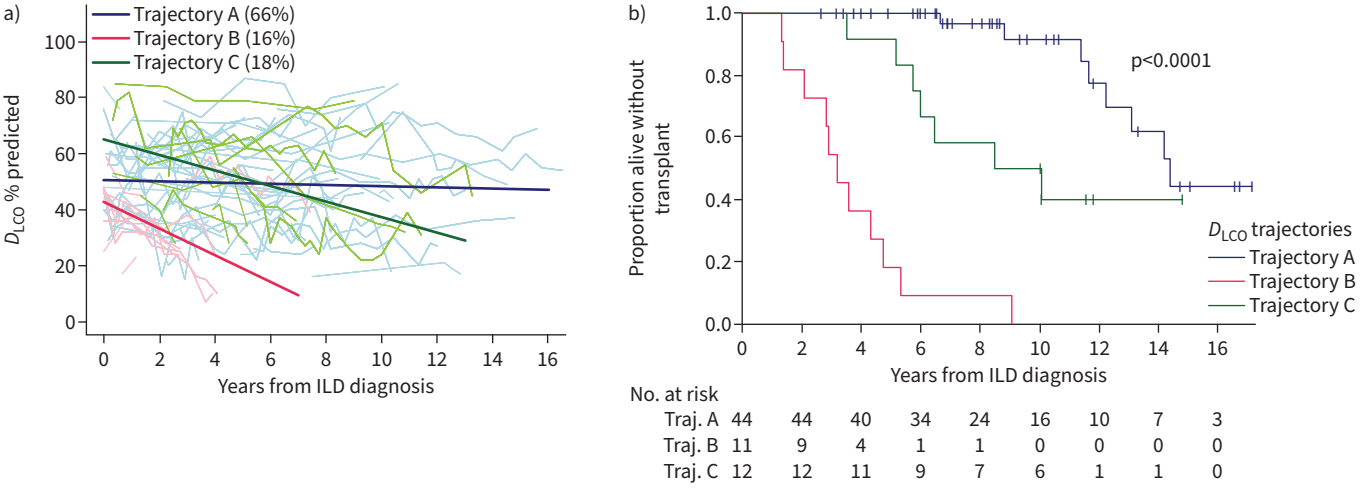

FIGURE 4 a) Trajectories of evolution of longitudinal D_{LCO} over follow-up; b) observed survival without transplantation according to the D_{LCO} trajectory. D_{LCO}: diffusing capacity of the lungs for carbon monoxide; ILD: interstitial lung disease; Traj: trajectory.

high risk of death or transplantation (HR 156.0, 95% CI 18.0–1352). A similar trend was observed for the "High D_{LCO}, slow decline" group (trajectory C) (HR 4.56, 95% CI 0.59–35.5) (figure 4b). A description of patients in those trajectories is given in supplementary table S4. Patients belonging to the worst prognosis group ("Low D_{LCO}, rapid decline" group, trajectory B) had a lower baseline D_{LCO} (41.0% *versus* 51.6% and 58%). There were no significant differences regarding the other parameters, although patients in the group with a better prognosis tended to be more females, younger at ILD diagnosis, with an increased prevalence of "other" HRCT patterns (n=10, *versus* n=2 in trajectories 2 and 3).

Discussion

In our cohort of 73 patients with pSD-ILD, managed in two French reference centres for rare pulmonary diseases, we found that, in contrast to the common perception, pSD-ILD bears a poor prognosis in the long term, with a subgroup of patients experiencing a rapid FVC and/or D_{LCO} decline. These findings provide important information on the course of disease in pSD-ILD seen in reference centres and identify specific phenotypes of progression that may help clinical decision-making in these situations.

The main characteristics of our cohort were close to previous cohorts of pSD-ILD, including a mean age at ILD onset of 63 years [10, 20–22], a predominance of NSIP pattern [20–23] and a low prevalence of extra-respiratory symptoms [21, 22] or biological activity [22, 23]. Our cohort includes a large proportion of men (2 females/1 male) compared with the usual sex ratio for pSD. Male sex has been identified as a risk factor for ILD in pSD and in other CTD [22]. This over-representation of males in pSD-ILD cohorts is variable but common [11, 24, 25].

In our study, pSD-ILD has a severe prognosis. The 10-year survival rate was estimated at 63% over a median follow-up of 9.3 years. Half of deaths could be attributed to pulmonary progression. The majority of patients received systemic corticosteroids and immunosuppressants, in line with the EULAR 2020 recommendations for the management of Sjögren's disease [26]. In previous pSD-ILD cohorts, the 10 year survival rate was estimated to be around 80% [20, 25]. This difference in prognosis could be explained by a shorter follow-up period in previous studies (median follow-up of 6 years) and by the recruitment of our cohort, from two pulmonology departments where severe patients are preferentially referred.

The extent of lesions on baseline HRCT and the GAP index were identified as independent prognostic factors for survival in our cohort. These results are consistent with previous studies. Chen *et al.* [27] and Xu *et al.* [28] showed that an extensive lung involvement was associated with worse survival, while Enomoto *et al.* [24] showed that the extent of reticular abnormalities on HRCT was independently associated with prognosis. The GAP index is a prognostic score based on sex, age, baseline FVC and D_{LCO} values, which was initially validated for patients with idiopathic pulmonary fibrosis [19], then for other ILD, including CTD-ILD [29]. We confirmed that a GAP stage II or III was an independent predictor of poor prognosis in pSD-ILD. This score is potentially interesting because it is easily applicable in clinical practice.

We found no difference in transplant-free survival between NSIP and UIP HRCT pattern. Although UIP is known to be associated with an increased mortality risk in rheumatoid arthritis-associated interstitial lung disease (RA-ILD) [30], the data in pSD-ILD cohorts are heterogeneous. Several studies found no difference in prognosis between UIP and NSIP [24, 25]. In a Korean cohort of 62 pSD-ILD [31], UIP was a risk factor for mortality compared with non-UIP, with a HR of 4.58 (95% CI 1.17–17.98). Interestingly, an indeterminate pattern for UIP was common in our cohort, affecting 27% of the patients, and was associated with a poor prognosis. Outside from pSD, Chung *et al.* [32] previously described the high prevalence of histological UIP (54%) in patients with an indeterminate for UIP HRCT pattern. Whether a significant proportion of indeterminate HRCT pattern could be histological UIP in pSD patients is unknown.

Our study provides the longest longitudinal follow-up of FVC and D_{LCO} in a cohort of pSD-ILD. The majority of patients had impaired PFTs at ILD onset, with mean FVC 73.4% pred and mean D_{LCO} 49% pred. In our study, a UIP pattern was characterised by an increased annual decline of FVC and D_{LCO}, compared to other patterns. A UIP pattern is a well-documented predictor of PFT deterioration in other CTD-ILD [33, 34] and in cohorts of PPF [9]. In recent cohorts of pSD-ILD, Zhang *et al.* [35] identified a UIP pattern as being associated with ILD progression, defined by a decrease in absolute FVC of 10% and/or a decline in absolute D_{LCO} of 15% at 6 months. Similarly, Kim *et al.* [31] showed a higher decline rate in D_{LCO} and a tendency for a higher decline in FVC in patients with a UIP pattern. Other previous series of pSD-ILD noted the same trend [10, 21]. Interestingly, we observed that an alternative pattern as OP, LIP or HP was associated with a better prognosis in our study, probably linked to the steroid response usually observed in patients with those patterns [36, 37].

In addition, we observed that men had a higher mean annual decline in FVC and D_{LCO} than women. In a cohort of 359 CTD-ILD patients, including eight with pSD-ILD [38], male sex was associated with a decrease in FVC and D_{LCO}. These results have not yet been shown in cohorts of pSD-ILD, but the studies of functional evolution included few men (n=2 in Roca *et al.* [21]). On the other hand, in the study of Zhang *et al.* [35] male sex was associated with UIP pattern, itself associated with a decline in FVC and D_{LCO}. Further large-scale studies are required to determine whether male sex or UIP pattern, or both independently, are at risk of functional decline in pSD-ILD.

We used mixed latent class models to identify patients with an accelerated decline of lung function. Although stable FVC and D_{LCO} trajectories include the greatest number of patients, the respiratory function of some patients described a rapidly progressive decline in FVC or D_{LCO}, leading to a very high risk of mortality or transplantation (HR 4.56–156 depending on trajectories). FVC and D_{LCO} declines are predictive of mortality in PPF cohorts [9], SSc-ILD [39], RA-ILD [40] and in a recent cohort of 62 pSD-ILD [31] where non-survivors showed a higher decline rate in FVC and D_{LCO} than survivors.

A lower baseline D_{LCO} (≈40%) was associated with FVC and D_{LCO} decline trajectories compared to stable trajectories. Moreover, we observed that a current value of D_{LCO} was associated with an increased risk of death for a 10% lower D_{LCO}. These results indicate that D_{LCO}, at baseline and during follow-up, is highly associated with prognosis. A low baseline D_{LCO} has already been shown as an independent predictor of disease progression and mortality in other CTD-ILD [30, 34]. In pSD-ILD cohorts, Roca *et al.* [21] showed that PFT deterioration was more commonly encountered in patients with lower baseline D_{LCO} (47% *versus* 64% pred; p<0.05), and Kim *et al.* [31] showed that non-survivors had a lower initial D_{LCO} than survivors (49% *versus* 62% pred, p=0.04). In contrast, in a recent retrospective study, Chen *et al.* [41] did not identify D_{LCO} at baseline as being associated with progression.

D_{LCO} is a global reflection of the respiratory system, including vascular abnormalities. In our cohort, 31 patients had echographic pulmonary hypertension (defined by systolic pulmonary artery pressure >35 mmHg) during follow-up, nine were documented by right heart catheterisation. Unlike D_{LCO}, FVC was not associated with FVC and D_{LCO} decline trajectories. Baseline FVC was comparable between trajectories, and risk for death or transplantation between current FVC for a 10% lower FVC was not significant. Similar findings have been observed in pSD-ILD cohorts [11, 21, 35].

Myalgia was the only clinical parameter significantly more present in patients with an accelerated decline of FVC. The relationship between myalgia and respiratory function was not previously identified in pSD-ILD cohorts. In the study of Roca *et al.* [21], progressors had no more myalgia than non-progressors, but myalgia was poorly represented in the cohort (n=3). Although we excluded all secondary Sjögren's disease with the data we had, it may be that some of our patients with anti-SSA 52 kDa had an underlying occult idiopathic inflammatory myositis instead of pSD that could explain the muscle involvement.

This study has several limitations related to its retrospective design. Although the study was bicentric, our cohort is drawn from two pneumology departments operating as ILD reference centres which possibly gather the most severe pSD-ILD. Nevertheless, there was a long follow-up with few missing data for FVC or D_{LCO}, still allowing robust statistical analysis. Our study focused on the functional evolution, and we did not assess HRCT changes nor the evolution of respiratory symptoms, although these are important elements for the definition of PPF. We also did not perform trajectories of other Sjögren's variables. Similarly, our data did not allow for a detailed analysis of the effect of treatment on lung function decline. The EULAR Sjögren's syndrome disease activity index (ESSDAI) score was not included in our analysis, even though a high ESSDAI score at diagnosis is known to be associated with a higher risk of mortality [42]. Retrospective calculation of this score is difficult, notably due to missing data on certain extrapulmonary involvement. Finally, due to the retrospective nature of our study with missing data, the exact prevalence of pulmonary hypertension at diagnosis was not assessed, an important consideration in view of our results. Despite these limitations, this is one of the few studies to predict longitudinal change in PFTs using easily attainable predictor variables in a pSD-ILD population.

In summary, in this retrospective cohort of pSD-ILD, we have identified parameters associated with a poor prognosis (death or transplantation) in patients with pSD-ILD: a high extent of lesions on the initial HRCT, a low D_{LCO}, a GAP stage II or III, and a high annual rate of decline of FVC and D_{LCO}. Furthermore, although the general pattern of evolution of lung function is characterised by a relative stability, parameters are associated with functional decline: male sex, patterns of UIP and indeterminate for UIP and features of fibrosis on HRCT baseline. Finally, we have identified a subgroup of patients with an accelerated pattern of lung function decline and high risk of death who are characterised by a low D_{LCO} at

diagnosis. These data should be considered for future prospective studies. If the results are confirmed, those patients should be managed carefully and the focus of a specific attention for clinical decision-making.

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