

Prevalence, incidence and mortality of interstitial lung disease in patients with Sjogren disease: data from the prospective observational “EMERGE” study

Andreina Manfredi^{a,b,*}, Caterina Vacchi^{c,1}, Stefania Cerri^{b,d}, Roberta Eufrosia Ledda^{e,f}, Roberto D’Amico^m, Fabrizio Luppi^{g,h}, Fabrizio Pancaldiⁱ, Giulia Cassone^c, Alessandra Rai^{a,b}, Dario Andrisani^d, Filippo Gozzi^d, Giovanni Della Casa^j, Lucia Dardani^b, Fabiola Atzeni^k, Athina Patsoura^d, Francesca Cozzini^{a,b}, Marco Sebastiani^{f,1}

^a University of Modena and Reggio Emilia, Department of Surgery, Medicine, Dentistry and Morphological Sciences with Transplant Surgery, Oncology and Regenerative Medicine Relevance, Italy

^b Rheumatology Unit, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy

^c Rheumatology Unit, AOU Policlinico di Modena, Modena, Italy

^d Respiratory Disease Unit and Center for Rare Lung Disease, AOU Policlinico di Modena, Modena, Italy

^e Radiology Unit, AOU Parma, Parma, Italy

^f Department of Medicine and Surgery, University of Parma, Parma, Italy

^g U.O.C. di Pneumologia, Fondazione IRCCS San Gerardo dei Tintori, 20900 Monza, Italy

^h School of Medicine and Surgery, Università degli Studi di Milano-Bicocca, 20100 Milan, Italy

ⁱ Department of Sciences and Methods for Engineering, University of Modena and Reggio Emilia, Modena, Italy

^j Radiology Unit, AOU Policlinico di Modena, Modena, Italy

^k University of Messina, Policlinico Gaetano Martino, Messina, Italy

^l Rheumatology Unit, AUSL Piacenza, Piacenza, Italy

^m Unit for Statistical and Methodological Support to Clinical, University of Modena and Reggio Emilia

ARTICLE INFO

Keywords:

Sjogren’s disease
Interstitial lung disease
Prevalence
Progressive pulmonary fibrosis
Survival

ABSTRACT

Background: Interstitial lung disease (ILD) is a severe pulmonary complication of Sjögren disease (SjD), but its prevalence, natural history and survival are not completely understood. Our study aimed to investigate prevalence, incidence, and mortality of SjD-ILD in a cohort of unselected consecutive SjD patients.

Methods: all consecutive SjD patients referred to our centre were enrolled in the study. A careful assessment for respiratory symptoms was periodically performed for each patient, and high-resolution computed tomography (HRCT) was requested in case of new-onset dyspnoea, persistent dry cough, or detection of velcro crackles by mean of electronic auscultation (VECTOR).

Findings: At enrolment, ILD was detected in 61/257 patients with a prevalence of 23.7 %. During a mean follow-up of 42.6 ± 14.6 months, 3 new cases of ILD were recorded, with an incidence of 0.41 new cases per 100 patients/year. Multivariate analysis showed a direct association between ILD and male sex, age at SjD diagnosis, and erythro-sedimentation rate >40 mm, and an inverse correlation with sicca syndrome. Nonspecific interstitial pneumonia was the most observed HRCT pattern, followed by usual interstitial pneumonia. During the follow-up, 21 patients (8.2 %) died, with a statistically significant difference between the overall survival of patients with ($66.5 \% \pm 11.7$) and without ILD ($88.4 \% \pm 5.5$) ($p < 0.001$). A fibrotic pattern was associated to a worse survival rate, while no difference was observed according to the radiologic pattern. Anti-SSA antibody was a protective factor for death, while the age at diagnosis of SjD, and the extent of ILD at HRCT were directly associated to an increased mortality.

* Corresponding author at: Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia & University of Modena and Reggio Emilia, Viale Risorgimento, 80, Reggio Emilia (RE), Italy.

E-mail address: andreina.manfredi@unimore.it (A. Manfredi).

¹ Andreina Manfredi and Caterina Vacchi equally contributed to the manuscript as co-first authors.

<https://doi.org/10.1016/j.semarthrit.2025.152886>

Interpretation: ILD can be identified in a high number of SjD patients, inducing a significant impairment in survival. The ILD extent, but not HRCT pattern of ILD, represents the main predictor of mortality. Therefore, careful monitoring, by a multidisciplinary team, should be ensured to all SjD-ILD patients.

Introduction

Interstitial lung disease (ILD) is recognized as a pulmonary complication of Sjögren's disease (SjD) [1], contributing to reduced quality of life and worsened disease prognosis, including increased morbidity and mortality [2–6]. However, the prevalence and natural history of SjD-associated ILD (SjD-ILD) remain not completely understood, mainly due to reliance on retrospective studies, which report highly variable ILD prevalence rates ranging from 6 % to 70 % [7]. A recent systematic review and meta-analysis, encompassing 8255 SjD patients, estimated an overall ILD prevalence of 23 % [7].

In some cases, the diagnosis of ILD precedes that of SjD. When this occurs, sicca symptoms are often mild, making difficult the early recognition of the underlying autoimmune rheumatic disorder (ARD) challenging and leading to delays in achieving a correct diagnostic definition [8,9]. Awareness of this possible clinical setting is mandatory for both pulmonologists and rheumatologists since detailed clinical history and specific tests may avoid misdiagnosis of autoimmune features.

Although pulmonary involvement significantly impacts mortality in SjD patients, specific survival data for SjD-ILD remain scarce. Through a prospective study, we aimed to provide a comprehensive and accurate characterization of SjD-ILD.

The primary objectives of our study were:

- To determine prevalence and incidence of ILD in a cohort of unselected consecutive SjD patients.
- To assess the two-year and overall survival of SjD patients with and without ILD

The secondary objectives were:

- To identify clinical and serological features associated with ILD in SjD
- To characterize radiological findings of SjD-ILD
- To evaluate the rate of ILD progression and potential prognostic factors for death.

Patients

Study population and eligibility criteria

Inclusion criteria: All consecutive patients aged 18 years or older, diagnosed with primary SjD [10] were included, from November 2019 to September 2022.

Exclusion criteria: Patients with secondary forms of SjD and who did not provide informed consent were excluded from the study.

Patients affected by rheumatoid arthritis or other connective tissue diseases, including overlap syndromes, were not enrolled in the study.

A multidisciplinary team that has been actively working in our Centre for >15 years on both idiopathic pneumonias and ARDs potentially complicated by lung involvement. SjD-ILD patients enrolled in the current study were followed in a dedicated outpatient clinic by pulmonologists and rheumatologists who have extensive experience on clinical aspects and treatment of ILDs and ARDs.

Methods

Study design

At the enrolment, patients were classified in two groups according to the presence of ILD, diagnosed on chest high resolution computed tomography (HRCT).

If a diagnosis of ILD had not already been made at the time of enrolment, a HRCT was requested in presence of at least one of the following features:

- Dry cough for at least three months.
- New onset exertional dyspnoea.
- Velcro crackles at lung auscultation (even by mean of electronic auscultation, with additional support from software-based detection, VECTOR) [11].
- Suspicion of ILD on a chest X-ray regardless of the indications.

If a recent CT (performed for other reasons) was already available, a new HRCT was avoided to reduce radiation exposure.

Every six months, patients of non-ILD group were re-evaluated for lung involvement according to the above reported methods and, if indicated, underwent a chest HRCT. In case of a new diagnosis of ILD, pulmonary function tests (PFTs) were also performed. For ILD group, PFTs were repeated every six months, while chest HRCT was performed annually or when clinically indicated.

The study was conducted in accordance with the Declaration of Helsinki, and approved by or Ethics Committee of Area Vasta Emilia Nord, Modena (protocol code 108/2019 date of approval 2 April 2019).

Data collection

Demographic, clinical, and serological data

At enrolment, demographic, clinical, and serological data were recorded for each patient, including the age at disease onset, sex, smoking habit (current, past, or never), glandular and extra-glandular manifestations of SjD, other than signs and symptoms of pulmonary involvement (see Table 1). Ongoing therapy was recorded only for the

Table 1
Demographic, clinical and serologic features of SjD patients.

Females/Males	233/24	90.7/9.3 %
Smoking habit	45	17.5 %
Xerostomia	200	77.8 %
Xerophthalmia	195	75.9 %
Lymph node enlargement	55	21.4 %
Arthritis	93	36.2 %
Salivary gland swelling	39	15.2 %
Raynaud's phenomenon	56	21.8 %
Purpura	20	7.8 %
Antinuclear antibodies	199	77.4 %
Anti-Ro/SSA	168	65.4 %
Anti-La/SSB	78	30.4 %
Rheumatoid factor	103	40.1 %
Erythrocyte sedimentation rate ≥ 40 mmh	64	24.9 %
C4 reduction (<10 mg/dl)	20	7.8 %
Hypergammaglobulinemia	71	27.6 %
Cryoglobulins	20	7.8 %
Age at enrolment (years)	64.8 $\pm$ 12.6	
Age at SjD diagnosis (years)	57.8 $\pm$ 13.5	
SjD duration (months)	83.9 $\pm$ 78	

SjD - Sjögren disease.

ILD group.

For ILD group, the time of ILD onset and interval between the diagnosis of ILD and SjD were even recorded. SjD and ILD were considered concurrent when the two conditions were diagnosed within a period of 6 months.

For both groups, clinical, serological and therapeutic parameters were recorded at every visit. Results were reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Electronic auscultation – Vector system

VECTOR is a software able in detecting velcro crackles at lung auscultation of patients with interstitial pneumonia [11,12], and it has been validated in patients with connective tissue diseases, including SjD

[11,12]. The automatic detection of VELCRO crackles by VECTOR system demonstrated a diagnostic accuracy of 83.9 % for RA and 82.6 % for CTDs, with an overall sensitivity of >90 % [11–13].

For every patient, a search for velcro crackles by mean of VECTOR was performed before each visit.

Electronic auscultation was performed using a commercially available Littmann 3200™ (3M, USA) electronic stethoscope, connected via Bluetooth to a computer equipped with Zargis® StethAssist™ Heart and Lung Sound Software.

Auscultation was conducted in a low-noise environment, bilaterally on the posterior thorax, with the patient in a seated position. Recordings were obtained from at least three auscultatory sites per hemithorax, with preference given to the lung bases and mid-lung fields.

Audio recordings were analysed using VECTOR, a computer algorithm for the automatic recognition of lung sounds, developed by

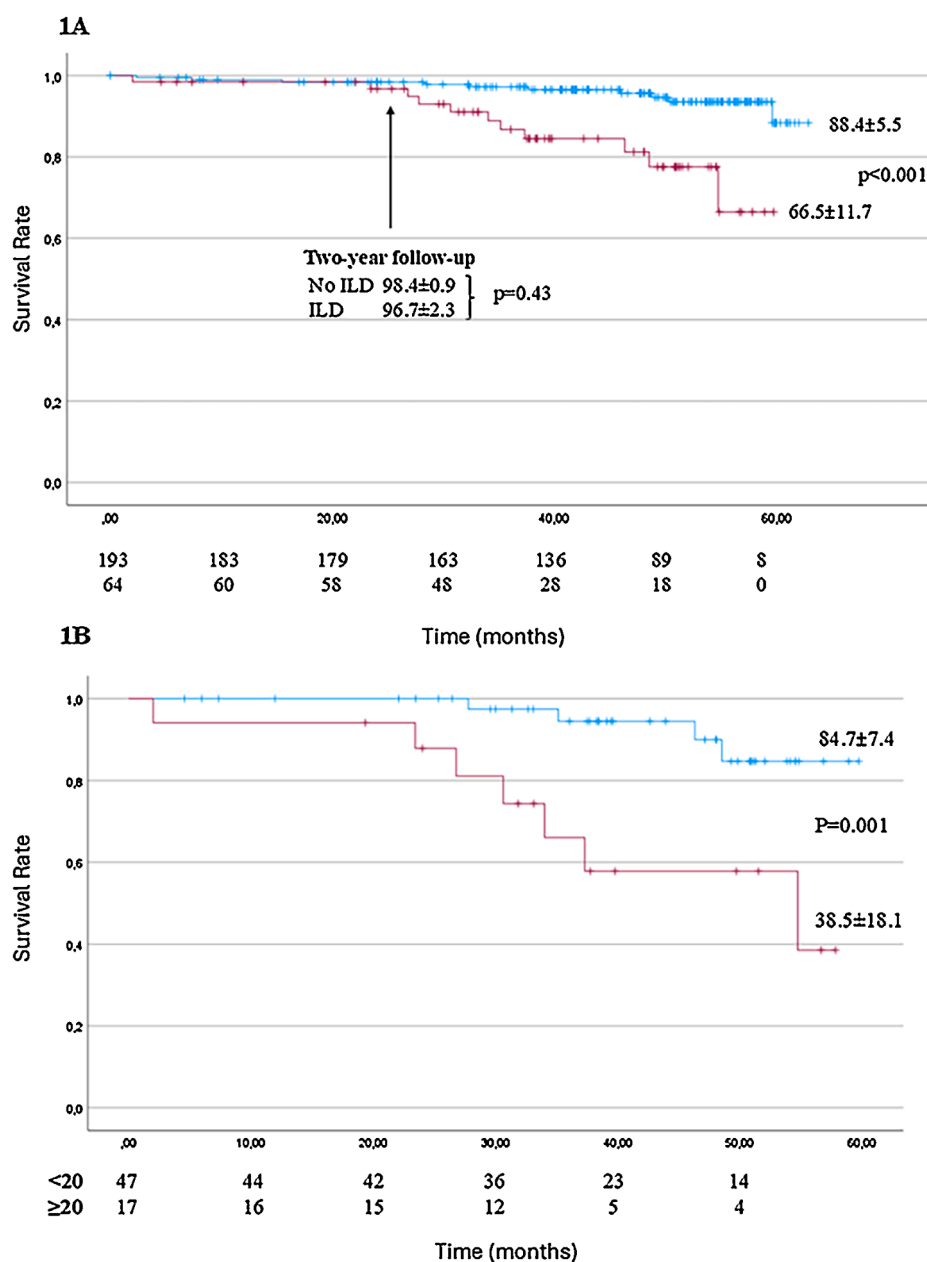


Fig. 1. Survival of patients enrolled in the study. 1.A. Survival of SjD patients with or without ILD. The overall survival for the two groups was 88.4 %±5.5 for non-ILD group (blue line), and 66.5 %±11.7 for ILD group (red line), $p < 0.001$. The two-year survival was 98.4 %±0.9 for non-ILD group and 96.7 %±2.3 for ILD group; $p = 0.43$. 1.B. Survival of SjD-ILD patients according to the extent of lung involvement. Overall survival of patients with an ILD extent of at least 20 % at CT was 38.5 %±18.1 (blue line) compared to a survival rate of 84.7 %±7.4 of patients with a lower ILD extent (red line); $p = 0.003$.

University of Modena [11,12].

Pulmonary function tests (PFTs)

Patients affected by ILD performed PFTs according to the international standards [14]. For each patient the percentage of forced vital capacity (FVC) and the percentage of single-breath diffusing capacity of the lung for carbon monoxide (DLCO) were recorded. All patients with a disproportionated low DLCO compared to FVC underwent to echocardiography for excluding a pulmonary hypertension.

Chest HRCT acquisition and evaluation

Regarding Chest HRCT, the whole chest volume was scanned during one deep inspiratory breath-hold with the patient lying in supine position. Reconstruction parameters for lung images were slice thickness ≤ 2 mm; window width 1500 Hounsfield Unit (HU); and window level -700 HU.

HRCT scans were blindly assessed by two chest radiologists with >5 years of experience for the study of ILD. In case of fibrotic ILD, the extent of fibrosis was reported as percentage of parenchymal involved as per visual assessment.

ILD patterns were defined according to the Fleischner Society White Paper statement on the diagnosis of idiopathic pulmonary fibrosis (IPF) and included usual interstitial pneumonia (UIP), (Fig. 1), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP) and other patterns. The extension of lung involvement at HRCT was evaluated according to Goh et al. [14–17]

Evaluation of ILD progression

A progression of ILD was defined according to the enrolment criteria of the INBUILD study [18]. Fibrotic disease progression was confirmed at HRCT if any of the following changes were observed at follow-up: increased extent or severity of traction bronchiectasis or reticular abnormalities, appearance of new ground-glass opacity with traction bronchiectasis, new onset or increased honeycombing and lobar volume loss.

Statistical analysis

Clinical features were reported as dichotomic or ordinal parameters. p value <0.05 is considered statistically significant. Continuous variables were reported as mean and standard deviation or median and interquartile ranges (IQR) when appropriate, while categorical variables were reported as absolute numbers and percentages and differences between the medians were determined using Mann-Whitney test for unpaired samples. Changes of continuous variables over time were analysed by mean of Wilcoxon's test for paired samples. Categorical variables were analysed by chi square test or Fisher's exact test when appropriate. To define the possible predictive factors of death only baseline values were considered. Multivariate Cox regression was performed to analyse the effect of the baseline features of the patients on development of progression of lung disease and death, while survival and cumulative survival rates were computed by the Kaplan-Meier method.

Results

Baseline features, prevalence and incidence

We enrolled 257 SjD patients: 233 females and 24 males (90.7 % and 9.3 %, respectively). Mean age at enrolment was 64.8 ± 12.6 years, with a SjD duration of 83.9 ± 78 months. The follow-up duration was 43.1 ± 14.7 months. Details of the clinical and serological data are shown in Table 1.

At baseline, including patients with a known diagnosis and those

with a diagnosis made after the first assessment, ILD was recorded in 61 patients, with a prevalence of 23.7 %. During follow-up, three new cases of ILD were diagnosed in 196 patients, with an incidence of 0.41 new cases per 100 patients/year. The intervals between SjD and ILD in the three patients with incident ILD were 14, 19, and 204 months, respectively.

Among eleven ILD patients diagnosed by screening, velcro crackles were the main indication for chest HRCT in 6 cases, new-onset dyspnoea in 2, and cough in 3.

Comparison of SjD patients with and without ILD

To define the clinical and serological features associated with ILD in SjD, we compared 64 SjD-ILD patients (including prevalent and incident cases) and SjD patients without ILD (see Table 2 for details).

The female/male ratio in ILD group was 3.27/1, which was significantly lower than that observed in the non-ILD group. Moreover, patients in the ILD group were older at SjD diagnosis, showed higher values of erythrocytation rate (ERS), and a lower prevalence of antinuclear antibodies (ANA) than those in the non-ILD group. As expected, in the ILD group the frequency of smokers was significantly higher than in patients without ILD. No difference was reported for sicca symptoms, namely eye and mouth dryness (Table 2).

Multivariate logistic regression was performed to assess possible associations between SjD features and ILD using a model including sex, smoking habit, ANA, mean age at SjD diagnosis, and mean SjD duration. The analysis showed that male sex, $ERS > 40$ mm, and age at the time of SjD diagnosis were significantly associated with ILD. Even when ANA was replaced with anti-SSA antibodies in the model, the association did not change.

Radiologic and functional features of SjD-ILD

The radiological and functional features of SjD-ILD are summarized in Table 3.

Among the ILD group, 26 patients (40.6 % of total SjD-ILD) showed a NSIP pattern, UIP (definite or probable) was reported in 20 (31.3 %), OP in 3 (4.7 %), and LIP in 11 (17.2 %). In 4 cases, the ILD pattern was not classifiable.

Globally, 42/64 patients (65.6 %) showed fibrotic ILD. Other than patients with UIP, 21 with NSIP (80.8 % of NSIP) and 1 with a non-classifiable pattern were classified as fibrotic.

Conversely, 22 subjects (34.4 %) presented with non-fibrotic ILD; of them, 19.2 % had NSIP (five cases), all subjects had LIP and OP patterns, and three had a non-classifiable ILD pattern.

An extent of > 20 % was observed in 26.6 % of patients, while the median extent of lung involvement at enrolment (or at diagnosis for incident cases) was 15 % (IQR 10, 25).

About functional data the mean baseline predicted FVC was 98.2 ± 20.8 %, while the mean baseline predicted DLCO was 56.0 ± 18.6 %.

Treatment of SjD-ILD

At enrolment, 17 patients (26.6 %) with SjD-ILD were treated with an immunosuppressant, namely mycophenolate mofetil (CellCept), which was prescribed in 14 subjects (21.9 %), rituximab in 2 (3.1 %), azathioprine (Imuran) in only one (1.6 %), glucocorticoids were prescribed in 43 patients (67.2 %), a dose ≤ 5 mg in 39 (60.9 %), and a dose higher than 5 mg daily in 4 (6.3 %). Four (6.3 %) patients were already treated with nintedanib.

Comparison according to time of ILD occurrence

In 18/64 cases (28.1 %), ILD was diagnosed within one year of the diagnosis of SjD, while in 22 (34.4 %) patients, ILD was diagnosed later than one year after SjD. In 24 patients (37.5 %), the diagnosis of ILD

Table 2

Comparison between SjD patients with and without ILD and associated factors with ILD.

	ILD* (%) 64/257 (24.9)	No ILD (%) 193/257 (75.1)	Univariate			Multivariate		
			OR	CI95%	P	OR	CI95%	p
Male gender	15 (23.4)	9 (4.7)	6.26	2.58–15.15	<0.01	7.43	2.41–22.91	<0.01
Smoking	21 (32.8)	24 (12.4)	3.38	1.72–6.63	<0.01	1.49	0.63–3.51	0.36
Antinuclear antibodies	39 (60.9)	161 (83.4)	0.31	0.17–0.58	<0.01	0.52	.024–1.14	0.10
Anti-Ro/SSA	32 (50.0)	136 (70.5)	0.42	0.23–0.75	<0.01			
Anti-La/SSB	12 (18.8)	66 (34.2)	0.44	0.22–0.89	0.02			
Rheumatoid factor	28 (43.7)	75 (38.9)	1.26	0.70–2.26	0.45			
Erythrocytation rate ≥ 40 mmh	23 (35.9)	41 (21.2)	2.09	1.09–4.00	0.03	2.34	1.12–4.90	0.02
Reduced C4	9 (14.1)	11 (5.7)	2.47	0.94–6.46	0.09			
Hypergammaglobulinemia	22 (34.4)	49 (25.4)	1.48	0.79–2.79	0.24			
Xerostomia	48 (75.0)	160 (82.9)	0.62	0.31–1.22	0.17			
Xerophthalmia	46 (71.9)	158 (81.9)	0.57	0.29–1.09	0.09			
Salivary gland swelling	9 (14.1)	30 (15.5)	0.89	0.40–1.99	0.84			
Arthritis	26 (40.6)	67 (34.7)	1.29	0.72–2.30	0.45			
Raynaud's phenomenon	14 (21.9)	42 (21.8)	1.01	0.51–1.99	0.98			
Purpura	3 (4.7)	17 (8.8)	0.51	0.14–1.80	0.42			
lymph nodes enlargement	12 (18.7)	40 (20.7)	1.14	0.57–2.28	0.71			
Mean age at SjD diagnosis (years)	64.8 $\pm$ 13.2	55.5 $\pm$ 12.8	1.06	1.03–1.09	<0.01	1.05	1.01–1.08	<0.01
Mean SjD duration (months)	55.9 $\pm$ 69.1	93.2 $\pm$ 78.7	0.99	0.99–1.00	<0.01	1.00	0.99–1.00	0.47
Mean age at enrolment	69.4 $\pm$ 11.7	63.2 $\pm$ 12.6			<0.01			
Cough at enrolment	42 (65.6)	23 (11.9)	13.48	6.79–26.79	<0.01			
Dyspnoea at enrolment	48 (75.0)	23 (11.9)	21.78	10.51–45.16	<0.01			
Velcro-crackles at enrolment	53 (82.8)	48 (24.9)	15.41	7.26–32.69	<0.01			

SjD: Sjogren Disease; ILD: interstitial lung disease.

Table 3

Functional and radiologic features of SjD-ILD.

FVC % at enrolment	98.2 $\pm$ 20.8
DLCO % at enrolment	56.0 $\pm$ 18.6
Fibrosing ILD pattern	42 (65.6 %)
UIP	20 (31.3 %)
NSIP	26 (40.6 %)
LIP	11 (17.2 %)
Other	7 (10.9 %)
Extent > 20 %	17 (26.6 %)

Legend SjD: Sjogren Disease; ILD: interstitial lung disease; FVC: predicted forced vital capacity; DLCO: single-breath diffusing capacity of the lung for carbon monoxide; UIP: usual interstitial pneumonia; NSIP: non specific interstitial pneumonia; LIP: lymphocytic interstitial pneumonia.

preceded that of SjD for at least six months (non-sicca onset SjD).

Patients with non-sicca onset SjD showed no difference in pulmonary involvement, namely radiologic patterns, ILD extent, and lung function when compared with patients developing ILD after SjD diagnosis. In contrast, non-sicca onset SjD patients were older and had a significantly lower prevalence of anti-SSA and anti-SSB antibodies than SjD-ILD subjects with a later diagnosis of ILD. However, a careful investigation of sicca symptoms revealed a high unreported prevalence of eye and mouth dryness. Schirmer's test was positive in all cases, and a minor salivary gland biopsy confirmed the presence of typical sialadenitis [8, 10].

Data are summarized in Table 4.

ILD progression and potential prognostic factors

Forty-three patients with SjD-ILD had at least 24 months of follow-up, and ILD progression was evaluated according to the INBUILD criteria [18]. In this regard, progression of fibrotic alterations on chest HRCT was recorded in 32.8 % of ILD patients within 24 months of enrolment; in the same period of time, a relative decline of at least 10 % of FVC was observed in 31.8 % of cases. Globally, including also worsening symptoms, progressive fibrosing ILD was observed in 30/42 fibrosing SjD-ILD patients (69.8 %). No parameters were predictive of ILD progression.

Table 4

Comparison of SjD-ILD patients according to the time of ILD diagnosis.

	Preceding SjD	Concurrent/ following SjD	p
Nr (%)	31 (48.4)	33 (51.6)	
Male sex	9 (29)	6 (18.2)	0.31
Smoking	14 (45.2)	7 (21.2)	0.06
ANA	15 (48.4)	24 (72.7)	0.07
Anti-Ro/SSA	6 (19.4)	26 (78.8)	<0.01
Anti-La/SSB	1 (3.2)	11 (33.3)	<0.01
Rheumatoid factor	11 (35.5)	17 (51.5)	0.14
Erythrocytation rate ≥ 40 mmh	7 (22.6)	16 (48.5)	0.10
Reduced C4	3 (9.7)	6 (18.2)	0.20
Hypergammaglobulinemia	9 (31)	13 (39.4)	0.41
Xerostomia	24 (77.4)	24 (72.7)	0.66
Xerophthalmia	21 (67.7)	25 (75.8)	0.48
Salivary gland swelling	2 (6.5)	7 (21.2)	0.15
Arthritis	10 (32.3)	16 (48.5)	0.21
Raynaud's phenomenon	9 (31)	5 (15.2)	0.23
Purpura	0 (0)	3 (9.1)	0.24
Lymph node enlargement	5 (16.1)	7 (21.2)	0.65
Mean age at SjD diagnosis (years)	71.3 $\pm$ 10.0	58.7 $\pm$ 13.1	<0.01
Mean disease duration at enrolment (months)	15.7 $\pm$ 16.6	93.6 $\pm$ 78.2	<0.01
Mean age at enrolment	72.5 $\pm$ 9.6	66.5 $\pm$ 12.8	0.07
Cough at enrolment	23 (69.7)	19 (57.6)	0.13
Dyspnoea at enrolment	28 (84.8)	20 (60.6)	0.02
Velcro-crackles at enrolment	31 (100)	22 (66.7)	<0.01
FVC at baseline	98.7 $\pm$ 21.9	97.7 $\pm$ 20.5	0.85
DLCO at baseline	55.7 $\pm$ 16.1	55.8 $\pm$ 22.2	0.95
ILD extension	17.7 $\pm$ 12.1	14.7 $\pm$ 9.6	0.18
Fibrosing pattern	7 (22.6)	15 (45.5)	0.07
UIP pattern	19 (61.3)	25 (75.8)	0.28

SjD: Sjogren Disease; ILD: interstitial lung disease; Nr: number; ANA: Antinuclear antibodies; FVC: predicted forced vital capacity; DLCO: single-breath diffusing capacity of the lung for carbon monoxide; UIP: usual interstitial pneumonia.

Mortality and potential prognostic factors

During the follow-up (43.1 $\pm$ 14.7 months), 21 patients (8.2 %) died, 11 (17.2 %) in the ILD and 10 (5.2 %) in non-ILD group ($p < 0.01$).

The two-year survival rates were 96.7 ± 2.3 and 98.4 ± 0.9 for patients with SjD with and without ILD, respectively, without a significant difference between the two populations ($p = 0.43$).

A statistically significant difference in survival between the two groups was recorded at the end of follow-up, and the overall survival was 88.4 ± 5.5 and 66.5 ± 11.7 for the non-ILD and ILD group, respectively ($p < 0.001$; see Fig. 1). The estimated mean survival time was 53.4 ± 1.7 and 60.8 ± 0.6 months, respectively for ILD and non-ILD group.

SjD-ILD patients with a fibrotic pattern had a survival rate of 53.7 ± 14.0 , with an estimated survival time of 50.1 ± 2.3 months, worse than the whole cohort. None of the patients with a non-fibrosing pattern died during the observation period; therefore, no formal statistical test was performed to compare the fibrosing and non-fibrosing groups.

The two most frequent radiologic patterns, namely UIP and NSIP, were associated with a significantly more severe prognosis than the other patterns, without significant differences among them. The survival rates were 48.0 ± 3.8 and 51.9 ± 2.3 for UIP and NSIP, respectively ($p = 0.19$), while the survival rate of patients with other ILD patterns was 93.8 ± 6.1 , which was not different from that observed in the non-ILD group.

Finally, patients with an ILD extent of at least 20 % at HRCT had an overall survival rate of 38.5 ± 18.1 and an estimated survival time of 44.2 ± 4.2 months compared to a survival rate of 84.7 ± 7.4 and an estimated survival time of 56.9 ± 1.3 months of patients with a lower ILD extent ($p = 0.003$).

At univariate analysis, among patients with ILD, the presence of anti-SSA was a protective factor for mortality (HR 0.19; CI95 % 0.04–0.87; $p = 0.03$), while the age at diagnosis of SjD (HR 1.09; CI95 % 1.02–1.17; $p = 0.01$) and the extent of ILD on HRCT (HR 1.06; CI95 % 1.02–1.10; $p = 0.001$) were directly associated with an increased risk of death. In a model including the extent of lung involvement on HRCT, anti-SSA antibodies, and age at SjD diagnosis, only the ILD extent remained associated with an increased risk of death (Table 5).

Discussion

To our knowledge, this is the first prospective study aimed to evaluate clinical history, epidemiological data, and survival outcomes of patients with ILD within a cohort of consecutive, unselected SjD patients. Additionally, we characterized SjD-ILD by assessing its clinical behaviour over a long observation period (> 3 years).

In our study, the prevalence of ILD was 23.7 %. Data on the prevalence of ILD in patients with SjD are largely variable. In 2020, a meta-analysis reported a prevalence of 13 % [19], whereas Berardicurti reported a pooled prevalence of 23 % [7]. The latter meta-analysis included patients predominantly diagnosed by HRCT, which might explain the higher prevalence of ILD in our and other recent studies. Moreover, in our cohort, all patients were systematically screened for potential lung involvement; in some cases, ILD was diagnosed when the patients were still asymptomatic. In contrast, the lack of routine screening in other studies may have underestimated the prevalence in patients with slow disease progression or remaining asymptomatic for a long period. Moreover, our findings underscore the importance of including patients with lung involvement preceding glandular manifestations of SjD, when estimating the prevalence of ILD in SjD [20].

Table 5
Cox regression multivariate analysis.

Predictive factors of mortality in SjD-ILD patients				
	Hazard ratio	95.0% CI		Sign.
ILD extent (%)	1.05	1.01	1.09	0.02
Age at SjD diagnosis	1.05	0.98	1.14	0.18
Anti-Ro/SSA antibodies	0.42	0.07	2.46	0.34

SjD: Sjogren Disease; ILD: interstitial lung disease.

In our population, this subgroup exhibited clinical and pulmonary characteristics similar to those of patients who developed ILD after SjD diagnosis, except for a lower frequency of anti-SSA/SSB antibodies. Therefore, a close collaboration with pulmonologists may improve the awareness of autoimmune systemic diseases and enhance the identification of patients with “occult SjD”.

Our study was designed before the ACR/CHEST and ERS/EULAR recommendations were published. At that time, specific risk factors for ILD in SjD had not yet been defined, and there was no consensus on ILD screening strategies for patients with ARDs. Moreover, the risk factors proposed by the two recent recommendations do not fully overlap, further emphasizing the complexity and relevance of this issue.

In designing this study, we decided to include the entire SjD population to better intercept the early occurrence or presence of ILD.

Previously [11,21], we emphasized the key role of velcro crackles when considering other clinical signs suggestive of ILD. This approach is consistent with recent ACR/CHEST guidelines for the screening and monitoring of ILD in ARDs as well as with other recent publications [22]. Our study further corroborates the significance of velcro crackles as a valuable screening tool, since it was detected in over 80 % of ILD cases compared to < 25 % of patients without ILD.

In our cohort, three new cases of ILD were identified during a follow-up period of > 3 years, yielding an incidence rate of 0.41 new cases per 100 patient-years. These findings suggest that ILD frequently develops early in the course of the disease, with 65.6 % of all cases being diagnosed within the first year of SjD diagnosis. However, > 34 % of the cases were diagnosed later, emphasizing the importance of regular screening. Systematic assessments for velcro crackles, along with monitoring respiratory symptoms such as cough and dyspnea, can aid in the early identification of incident cases. Nevertheless, our results did not identify a specific subset of patients with SjD at a higher risk for ILD, except for elderly males with elevated ESR, as suggested in previous reports [7]. In any case, as mentioned above, screening should just be performed during the patient's initial assessment, given the high percentage of ILD diagnoses in the early stages of the disease.

Consistent with other studies [23,24], NSIP was the most prevalent radiologic pattern, observed in 40.6 % of cases, whereas UIP was noted in > 30 % of cases. In recent years, the prevalence of UIP in SjD has been described with increasing prevalence, with a recent meta-analysis reporting frequencies of 52 % (95 % CI: 41–64) and 44 % (95 % CI: 32–55) for NSIP and UIP, respectively [7].

As already suggested [25,26], the HRCT pattern is not associated with different disease progression and prognosis, and SjD-ILD appears to be characterized by a high prevalence of fibrotic radiologic patterns (> 60 % of cases) [27,28]. Notably, no difference in radiologic patterns or extent was observed between patients in whom the diagnosis of ILD preceded that of SjD and the other ILD group.

LIP has historically been associated with SjD, though data on its prevalence remain limited [29]. Data from our study allowed us to observe the prevalence of LIP patterns in 17.2 % of patients with SjD-ILD.

Fibrotic ILD has a significant impact on survival, particularly in patients with UIP and NSIP patterns [2,30]. Fibrosis at baseline, but not progression according to the INBUILD criteria (18), was correlated with the risk of death, with an estimated mean survival time of approximately 4 years, comparable to that reported for IPF. In addition to fibrosis, the extent of ILD on HRCT [15] was the only factor associated with an increased risk of mortality, suggesting that the detection of fibrosis could affect prognosis more than the radiological ILD pattern [31]. The absence of deaths in the non-fibrotic ILD group did not allow calculation of the risk of death associated with fibrosis.

An interesting finding from our study was the low mortality rate in the two years following enrolment, both in patients with and without ILD. However, over a longer follow-up period, the difference in mortality between the two groups became significant. Unlike IPF, SjD-ILD is typically diagnosed when patients are asymptomatic, which may

partially explain the initial low mortality rate. Conversely, we cannot rule out the possibility that SjD-ILD progresses more slowly than IPF does. Understanding the natural course of SjD-ILD is critical for optimizing patient management, particularly when antifibrotic treatments are considered.

This study has both strengths and limitations. In our opinion, the main strength of our study is its longitudinal design, which can capture the clinical behaviour of SjD-ILD. All patients were regularly evaluated for ILD occurrence, supporting the hypothesis that also if chest HRCT was not used for screening, the prevalence data can be sufficiently reliable. Another important point is that all patients with ILD were followed up in a tertiary centre with multidisciplinary outpatient visits performed by experienced pulmonologists and rheumatologists, as well as the involvement of expert thoracic radiologists. This approach allowed us to regularly evaluate disease progression and prompt therapeutic changes when required. Finally, the long follow-up period allowed us to obtain data regarding long-term survival. This is an important point since a shorter follow-up would not have shown the real impact of lung disease on the life expectancy of these patients. On the other side, the main limitation of our study was the monocentric cohort, which can be affected by selection bias related to the high sensitivity of pulmonologists in the early diagnosis of lung-dominant SjD. Second, not all chest CT images were acquired and reconstructed using a high-resolution protocol, limiting the accuracy of the evaluation. Additionally, most patients had a long-standing history of ILD at the time of enrolment. Therefore, in some cases, the data included in the present study capture only a segment of the full disease course. Finally, the mean value of DLCO was lower than expected because of the intrinsic feature of the adopted plethysmograph. However, all patients with a disproportionately low value of DLCO compared to FVC underwent echocardiography to screen for pulmonary hypertension.

Interestingly, the absence of deaths in the non-fibrotic ILD group did not allow us to calculate the hazard ratio of mortality related to the presence of lung fibrosis; however, we had the opportunity to observe that the presence of fibrotic ILD is the most important prognostic factor for this population.

In conclusion, ILD is a frequent extra-glandular manifestation of SjD, involving >20 % of patients and severely affecting their life expectancy. Since ILD represents an early manifestation of SjD in many cases, sometimes preceding the clinical onset of sicca syndrome, both rheumatologists and pulmonologists should be aware of the importance of early diagnosis of this condition.

Panel: research in context

Evidence before this study

We searched MEDLINE from database inception to May 31, 2025 using the following search terms for interstitial lung disease (ILD) related to Sjogren disease (SjD) (Sjogren (syndrome* OR disease*) AND (interstitial lung disease) AND ((prevalence) OR (incidence) OR (progression) OR (survival))). Articles were eligible for inclusion if they reported data on epidemiology, clinical course or survival of patients with SjD-ILD. ILD has a prevalence varying from 6 % to 70 % in retrospective studies, with very few data on the evolution over time of SjD-ILD, including the rate of progression of lung disease and death. Nevertheless, SjD-ILD seems to have a rate of progression similar to other rheumatic diseases, namely rheumatoid arthritis, but factors associated to higher risk of progression and death are still unknown.

Added value of this study

This is the first prospective study aiming to evaluate both prevalence and incidence of ILD in SjD, and to assess its prognostic impact on survival. ILD was diagnosed in >20 % of SjD patients with an incidence rate of 0.41 new cases per 100 patients/year. Moreover, it was associated

with a high mortality rate, significantly higher of that of SjD patients without lung involvement, supporting the need for routine screening in SjD. Notably, fibrotic ILD, regardless of radiologic pattern or progressive pulmonary fibrosis phenotype, was predictive of mortality.

Implications for practice or policy and future research

The significant prognostic impact of ILD in SjD highlights the need for increased clinical awareness among rheumatologists and pulmonologists. SjD should be actively considered in the diagnostic work-up of newly identified ILDs. On the other side, the search for respiratory symptoms and lung auscultation should be routinely performed by rheumatologist in SjD patients. Early referral to multidisciplinary teams may facilitate timely diagnosis, optimize therapeutic strategies, and potentially improve outcomes. Future research should focus on defining tailored management pathways and therapeutic targets for this high-risk subgroup.

Funding

No funding has been used for this study.

Author contributions

Conceptualization, AM, CV, MS; methodology, investigation, SC, REL, FL; resources, C.V. and S.C.; data curation, GC, AR, DA; writing—original draft, SC, REL, FL, FP, GC, AR, DA, FG, GDC, LD, FA, AP, FC; writing—review & editing, AM, CV, MS; supervision, M.S. All authors provided critical feedback and helped shape the research, analysis and manuscript.

** all authors had full access to all the data in the study; Caterina Vacchi and Andreina Manfredi had final responsibility for the decision to submit for publication.*

Data sharing

Anonymized data of the study will be available by request to the corresponding author.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andreina Manfredi reports was provided by University of Modena and Reggio Emilia. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We acknowledge Erica Keeling for her support in data management.

References

- [1] Ramos-Casals M, Baer AN, Brito-Zerón M, del P, Hammitt KM, Bouillot C, Retamozo S, et al. 2023 International Rome consensus for the nomenclature of Sjögren disease. *Nat Rev Rheumatol* 2025;21(7):426–37. Jul 10.
- [2] Saluja P, Marco JL, Gautam N, Chhakchhuak CL, Gardner GC, Gupta N. Clinical course and outcomes in patients with Sjögren's associated interstitial lung disease. *Semin Respir Crit Care Med*. 2025;46(3):281–7.
- [3] Luppi F, Sebastiani M, Sverzellati N, Cavazza A, Salvarani C, Manfredi A. Lung complications of Sjogren syndrome. *Eur Respir Rev* 2020;29(157):200021. Sep 30 Available from: <http://err.ersjournals.com/lookup/doi/10.1183/16000617.0021-2020>.
- [4] Flament T, Bigot A, Chaigne B, Henique H, Diot E, Marchand-Adam S. Pulmonary manifestations of Sjögren's syndrome. *Eur Respir Rev* 2016;25(140):110–23.
- [5] Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjogren syndrome. *Chest* 2006;130(5):1489–95.

- [6] Pang R, Ma X, Guo H, Qi X. Meta-analysis of mortality-associated factors in primary Sjögren's syndrome patients with interstitial lung disease. *Clin Rheumatol* 2025;44(1):23–31. Jan 21.
- [7] Berardicurti O, Marino A, Genovali I, Navarini L, D'Andrea S, Currado D, et al. Interstitial lung disease and pulmonary damage in primary Sjögren's syndrome: a systematic review and meta-analysis. *J Clin Med* 2023;12(7):2586. Mar 29.
- [8] Manfredi A, Sebastiani M, Cerri S, Cassone G, Bellini P, Della Casa G, et al. Prevalence and characterization of non-sicca onset primary Sjögren syndrome with interstitial lung involvement. *Clin Rheumatol* 2017;36(6):1261–8. Jun 21.
- [9] Gao H, Zou Y, Zhang X, He J, Zhang J, Sun Y, et al. Interstitial lung disease in non-sicca onset primary Sjögren's syndrome: a large-scale case-control study. *Int J Rheum Dis* 2018;21(7):1423–9. Jul 2.
- [10] Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League against rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017;69(1):35–45. Jan 26 Available from: <https://onlinelibrary.wiley.com/doi/10.1002/art.39859>.
- [11] Manfredi A, Cassone G, Vacchi C, Pancaldi F, Della Casa G, Cerri S, et al. Usefulness of digital velcro crackles detection in identification of interstitial lung disease in patients with connective tissue diseases. *Arch Rheumatol* 2020. Jun 25.
- [12] Manfredi A, Cassone G, Cerri S, Venerito V, Fedele AL, Trevisani M, et al. Diagnostic accuracy of a velcro sound detector (VECTOR) for interstitial lung disease in rheumatoid arthritis patients: the InSPIRe validation study (InTERStitial pneumonia in rheumatoid ArThritis with an electronic device). *BMC Pulm Med* 2019;19(1):111. Dec 20.
- [13] Pancaldi F, Sebastiani M, Cassone G, Luppi F, Cerri S, Della Casa G, et al. Analysis of pulmonary sounds for the diagnosis of interstitial lung diseases secondary to rheumatoid arthritis. *Comput Biol Med* 2018;96:91–7. May 1.
- [14] Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J* 2022;60(1):2101499. Jul 13.
- [15] Goh NS, Desai SR, Veeraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008;177(11):1248–54. Jun 1.
- [16] Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med* 2018;6(2):138–53. Feb.
- [17] Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198(5):e44–68. Sep 1.
- [18] Flaherty KR, Brown KK, Wells AU, Clerisme-Beatty E, Collard HR, Cottin V, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. *BMJ Open Respir Res* 2017;4(1):e000212. Sep 17.
- [19] He C, Chen Z, Liu S, Chen H, Zhang F. Prevalence and risk factors of interstitial lung disease in patients with primary Sjögren's syndrome: a systematic review and meta-analysis. *Int J Rheum Dis* 2020;23(8):1009–18. Aug 26.
- [20] Brito-Zerón P, Theander E, Baldini C, Seror R, Retamozo S, Quartuccio L, et al. Early diagnosis of primary Sjögren's syndrome: EULAR-SS task force clinical recommendations. *Expert Rev Clin Immunol* 2016;12(2):137–56. Feb 22.
- [21] Sgalla G, Walsh SLF, Sverzellati N, Fletcher S, Cerri S, Dimitrov B, et al. "Velcro-type" crackles predict specific radiologic features of fibrotic interstitial lung disease. *BMC Pulm Med* 2018;18(1):103. Dec 18.
- [22] Johnson SR, Bernstein EJ, Bolster MB, Chung JH, Danoff SK, George MD, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the screening and monitoring of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Care Res* 2024;76(8):1070–82. Aug 8.
- [23] Konak HE, Atalar E, Hezer H, Ulucaköy RK, Erdoğan EK, Babaoglu H, et al. Interstitial lung disease in primary sjögren's syndrome: risk factors for occurrence and radiographic progression. *Sarcoidosis Vasculitis Diffuse Lung Dis* 2024;41(3).
- [24] Huang Y, Qiu Y, Xie Z, Zhang F, Zhang Y, Guan M, et al. Risk factors and prognosis of interstitial lung disease for primary Sjögren syndrome patients: a retrospective case-control study. *Clin Rheumatol* 2023;42(11):3033–41. Nov 8.
- [25] Manfredi A, Venerito V, Cazzato M, Sambataro G, Zanini U, Gozzi F, et al. Pulmonary progressive fibrosis in rheumatoid arthritis and primary Sjogren syndrome: similarities and differences. *J Clin Med* 2024;13(21):6508. Oct 30.
- [26] Manfredi A, Sambataro G, Rai A, Cerri S, Sambataro D, Vacchi C, et al. Prevalence of progressive fibrosing interstitial lung disease in patients with primary Sjogren syndrome. *J Pers Med* 2024;14(7):708. Jul 1.
- [27] Manfredi A, Vacchi C, Della Casa G, Cerri S, Cassone G, Di Cecco G, et al. Fibrosing interstitial lung disease in primary Sjogren syndrome. *Joint Bone Spine* 2021;88(6):105237. Dec.
- [28] Chen YH, Lee TJ, Hsieh HJ, Hsieh SC, Wang HC, Chang YC, et al. Clinical outcomes and risk factors of progressive pulmonary fibrosis in primary Sjögren's syndrome-associated interstitial lung disease. *BMC Pulm Med* 2023;23(1):268. Jul 19.
- [29] Gonçalves CM, Cordeiro LR, de Andrade CAF, de Carvalho JF. Lymphocytic interstitial pneumonia associated with Sjögren Syndrome: case-based review. *Curr Rheumatol Rev* 2023;19(1):1–6. Feb.
- [30] Koh JH, Park Y, Lee J, Jeon H, Moon SJ, Kim YH, et al. Long-term outcome of interstitial lung disease in patients with primary Sjögren's syndrome: a retrospective observational study. *Korean J Intern Med* 2025;40(1):148–59. Jan 1.
- [31] Humphries SM, Adegunsoye A, Demoruelle MK, Wei Kam ML, Amigues I, Bang TJ, et al. Quantitative CT scan analysis in rheumatoid arthritis-related interstitial lung disease. *Chest* 2025;167(5):1428–39. May.