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Interstitial lung disease in primary Sjögren's syndrome: Risk factors for occurrence and radiographic progression

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Abstract. *Objectives:* The aim of this study is to investigate the characteristics of Primary Sjögren's syndrome (pSS) - interstitial lung disease (ILD) patients and compare them to those of pSS patients without ILD in the tertiary pSS-ILD cohort to evaluate potential risk factors for ILD occurrence and disease progression. *Methods:* Patients followed up who met the 2016 American College of Rheumatology-European League Against Rheumatism classification criteria for pSS were retrospectively analyzed. The patients were grouped as those with ILD and those without ILD according to medical records. High-resolution computed tomography (HRCT)/ thorax CT (TCT) results of all ILD patients were evaluated. Data on demographics, comorbidities, clinical characteristics and laboratory findings were collected. *Results:* A total of 378 pSS patients, including 60 with ILD and 318 without ILD were detected to have at least one obtainable HRCT/TCT and were included in the study. In the cohort of pSS patients with at least one HRCT or TCT, the frequency of ILD was 15.8%. In the ILD group, the most common HRCT pattern was NSIP, and the most common findings were ground glass opacities, traction bronchiectasis, and honeycombing. Logistic regression analysis showed that male gender (OR:2.90), being diagnosed with pSS over the age of 50(OR:4,24), smoking history (OR:2.38), elevated LDH(OR:3.27), elevated ESR(OR:2.51) and lymphopenia (OR:5.12) were related with development of ILD while being diagnosed with ILD after the age of 60 (OR:8.5) was related with radiographic progression. *Conclusion:* The study results provided a large spectrum view for pSS-ILD and pointed out several risk factors for ILD occurrence and radiographic progression.

Key words: Sjögren's disease, interstitial lung disease, progression

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by xerostomia and xerophthalmia caused by lymphocytic infiltration of exocrine glands. 30-40% of patients with pSS may have extra-glandular manifestations including lung involvement. (1). Lung involvement majorly comprises interstitial lung disease (ILD), small airway disease, and bronchus associated lymphoid tissue lymphoma (2).

Interstitial lung disease (ILD) is a serious pulmonary complication in patients with pSS with a cumulative incidence of 10% at 1st year after diagnosis, increasing to 20% in 5 years (3). Patients with pSS with ILD have a 5-year survival rate ranging from 84% to 87.3% (4, 5). However, in some cases, ILD can lead to fatal complications such as respiratory failure

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and secondary pulmonary hypertension, with a poor prognosis for survival and quality of life. Therefore, identification of patients with a risk to develop ILD and progress has foremost importance. While ILD develops years before the onset of pSS in 10-51% of patients, it begins concurrently with other systemic manifestations in approximately 10% of cases. In the remainder of the cases, ILD may develop late in the course of the disease. (6, 7).

High-resolution computed tomography (HRCT) is the gold-standard imaging tool for evaluating pSS-related pulmonary abnormalities due to its sensitivity for detecting even mildest parenchymal alterations, even in asymptomatic patients. However, it is a matter of debate in pSS whether routine HRCT screening is obligatory or not when relatively low incidence and better prognosis were considered in comparison to other connective tissue disorders (CTD) such as systemic sclerosis and inflammatory myositis. Therefore, detecting risk factors for development and progression of ILD gains further importance. Several reports identified a number of risk factors, yet, the topic can benefit further research when the scarcity of the data in the literature considered.

Here in this study, we respectively investigated characteristics of pSS-ILD patients and compare to pSS patients without ILD in our tertiary center CTD-ILD cohort to evaluate potential risk factors for ILD occurrence and disease progression.

Materials and methods

Patients followed up with pSS meeting the Rheumatology Clinic of Ankara City Hospital who met the 2016 American College of Rheumatology (ACR)–European League Against Rheumatism (EULAR) classification criteria for primary Sjögren's syndrome were retrospectively analyzed. pSS patients over 18 years of age with at least one obtainable HRCT or thorax CT (TCT) images were included in the study. Patients with secondary overlapping CTD's excluded. The patients were grouped as those with ILD and those without ILD according to medical records.

Data on demographics, comorbidities, clinical characteristics, treatment history and laboratory findings were collected. In addition, serologic markers, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, leukopenia, lymphopenia, platelet count, rheumatoid factor (RF), complement (C) 3, C4, immunoglobulin (Ig) G levels, kidney and liver function tests at the time of first visit were recorded. Most patients lacked obtainable initial pulmonary functional test (PFT) results therefore last obtainable PFT results were collected in patients with ILD. PFTs results were expressed as percentages of the predicted value for each parameter, with forced vital capacity (FVC), volume of air exhaled in 1 second of forced expiration (FEV1), FEV1/FVC, and diffusing capacity of the lung for carbon monoxide (DL_{CO}) noted. The EULAR Sjögren's syndrome disease activity index (ESSDAI) scores at the time of initial visit for all patients were calculated. Lung involvement was excluded from the scoring in the calculation of ESSDAI.

Functional status and oxygen need of ILD patients were staged according to idiopathic pulmonary fibrosis (IPF) scoring stages of which are as follows: Stage 1; recently diagnosed without oxygen need, stage 2 ;needing oxygen with activity, but not at rest, stage 3; needing oxygen 24 hours a day, with activity, at rest and during sleep, stage 4; advanced oxygen needs (needing high-flow oxygen or when a lightweight, portable delivery system is unable to meet a patient's needs).

Assessment of radiographic characteristics and progression

HRCT/TCT results of all ILD patients were evaluated by single researcher with at least 2 years of experience in the field. Radiographic features indicative of ILD included ground glass opacities, irregular interseptal thickening, increased reticular density, traction bronchiectasis, honeycombing, consolidations, and cystic formations. Radiographic patterns were defined in accordance with the American Thoracic Society/European Respiratory Society IIP classification, as non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), and organizing pneumonia (OP) (8). First ever obtainable scan with features of ILD was recorded as initial scan and the last ever obtainable as the final scan. In case of presence of a secondary pulmonary condition at the time of the scan such as, pulmonary thromboembolism, infection, alveolar hemorrhage or pulmonary edema, the initial and final scans were replaced by another one deemed suitable by the researchers. Inflammatory lesions such as glass-gound opacities

and consolidations were considered to be related with ILD only after it was reassured that any other causes were excluded at the time of scan, via medical records.

Percentage of affected lung parenchyma in the initial and final scans was evaluated by the method described by Goh et al. (9). Regression and progression were decided in presence of a percentage difference greater than 5%. For LIP patients in addition to parenchymal changes, increases in number and/or size of the cysts were also considered progression (10). Accordingly, ILD patients were grouped with progression and without progression (regression and stable disease).

The study was carried out in accordance with the Helsinki declaration with the approval of the Ankara City Hospital ethics committee (E1-23-3550).

Statistical analyses

Statistical Package for the Social Sciences (SPSS) v22 were used for statistical analyses (IBM Corp., Armonk, NY). Normality of continuous variables were analyzed both visually by plots and histograms, and analytically by Kolmogorov-Smirnoff test. Continuous variables with normal distribution were presented by mean ± standard deviations (SD) and otherwise by median (interquartile range [IQR]). Categorical variables were presented by numbers (percentages). Continuous variables were compared between groups either with student t test or Mann-Whitney-U test, and within groups either by paired samples t test or Wilcoxon test according to normality. Categorical variables between groups were compared by x^2 test and within groups by McNemar test. For the multivariate analyses significantly different parameters between groups were further entered into the logistic regression analysis. Hoshmer-Lemeshow goodness of fit was used to assess model fit. 5% type 1 error was used to infer statistical significance in all analyses.

Results

A total of 2,127 patients were detected to have an ICD-10 code for Sjögren's syndrome (M35.0) recorded in the hospital database. Among those a total of 378 pSS patients, including 60 with ILD and 318 without ILD were detected to have at least one obtainable HRCT/TCT and were included in the study. Clinical characteristics and demographics were presented in Table 1. Patients with ILD were predominantly male, older and diagnosed with pSS in an older age. Smoking history was more frequent in patients with ILD. When comorbid diseases were evaluated coronary artery disease, chronic kidney disease and malignancies were more frequent in ILD patients. pSS manifestations were similar between patients with and without ILD, except for lymphoma which was more frequent in ILD group. ESSDAI scores at the initial admission to our clinic was indifferent, mortality was more frequent in ILD patients. Patients with ILD patients were more frequently received azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CTX) and rituximab (RTX) treatments more frequently than those without. 3 ILD patients were receiving an antifibrotic agent and 4 were under long term oxygen therapy.

The laboratory parameters of patients with and without ILD were presented in Table 2. Lymphopenia and anti-La/SS-B positivity were more frequent in patients with ILD (p=0.001, p=0.039, respectively). Elevated ESR, CRP and lactate dehydrogenase (LDH) levels were more frequently observed in patients with ILD (p=0.001, p=0.034, p<0.001, respectively). We observed no statistically significant differences in rates of antinuclear antibody (ANA) positivity in immunofluorescence assay, serum rheumatoid factor and anti-SSA/Ro positivity. Rates of hypergammaglobulinemia and hypocomplementemia were similar.

Age at diagnosis of pSS with ILD was 58,86 ± 11,93 years (Table 3). ILD onset was identified to be concurrent with pSS diagnosis in 27 (45%) patients and developed after pSS diagnosis in 27 (45%), whereas in 6 (10%) patients the onset was prior to pSS diagnosis. The most common pulmonary symptom was dyspnea (73,3%), and the most common pulmonary involvement pattern was NSIP (36,7%). When IPF severity scores were evaluated, the patients were most frequently stage 1 (65,5%) (Table 3). PFT results could be obtained for 34 patients and results were presented in Table 3.

Initial HRCT/TCT scans were evaluated in all ILD patients. In 41 patients a final scan was also obtainable. Properties of initial and final scans were presented in Table 4. The mean duration between two scans was 25.92±17.54 months. While the percentage of lung involvement at the time of

Table 1. Demographic and clinical characteristics of pSS patients with and without ILD

	pSS with ILD (n = 60)	pSS without ILD (n = 318)	*p*
Female, n (%)	43(71.6)	284(89.3)	**<0.001**
Age, year, mean ±SD	63.16±11.13	55.53±10.79	**<0.001**
Age at pSS diagnosis, year, mean ±SD	56±13.4	49.94±11.29	**<0.001**
Disease duration, months, median (IQR)	72(84)	48(60)	0.184
Comorbidities, n(%)			
Diabetes mellitus	8(13.3)	40(12.6)	0.872
Hypertension	29(48.3)	128(40.3)	0.244
Coronary artery disease	9(15.0)	18(5.7)	**0.010**
Chronic kidney disease	5(8.3)	4(1.3)	**0.001**
Hypothyroidism	7(11.7)	53(16.7)	0.331
COPD/Asthma	11(18.3)	34(10.7)	0.094
Malignancy	7(11.7)*	10(3.1)**	**0.003**
Ever smokers, n(%)	18(30)	50(15.7)	**0.008**
Xerostomia, n(%)	52(86.7)	295(92.8)	0.114
Xerophthalmia, n(%)	48(80)	274(86.2)	0.218
Raynaud's phenomenon, n (%)	4(6.7)	18(5.7)	0.760
Arthritis, n(%)	6(10)	60(18.9)	0.097
Parotid enlargement, n(%)	1(1.7)	16(5)	0.249
Positive Schirmer's test, n(%)	45(83.3)	224(73.7)	0.131
Positive salivary gland biopsy, n(%)	22(64.7)	116(70.7)	0.487
Lymphadenopathy, n(%)	8(13.3)	23(7.2)	0.114
Lymphoma, n(%)	2(3.3)	0(0)	**0.025**
CNS involvement, n(%)	1(1.7)	6(1.9)	0.908
PNS involvement, n(%)	2(3.3)	7(2.2)	0.639
Kidney involvement, n(%)	2(3.3)	2(0.6)	0.120
Medication and other treatments, ever, n(%)	60(100)	304(95,6)	0.098
Hydroxychloroquine	5(8.3)	12(3,8)	0.118
Methotrexate	25(41.7)	13(4,1)	**<0.001**
Azathioprine	13(21.7)	4(1,3)	**<0.001**
Mycophenolate mofetil	5(8.3)	0	**<0.001**
Cyclophosphamide	3(5)	0	**0.004**
Rituximab	3(5)	0	
Antifibrotic	4(6.7)	0	
LTOT			
ESSDAI, median(IQR)	1(4)	0(2)	0.259
Mortality, n(%)	7(11.7)	0(0)	**0.001**

*3 breast, 2 lung, 2 lymphoma; **2 breast, 3 thyroid, 3 over, 1 brain, 1 oral cavity. Abbreviations: pSS: primary Sjögren's syndrome, ILD: interstitial lung disease, COPD: chronic obstructive pulmonary disease, CNS: central nervous system, PNS:peripheral nervous system, LTOT: long-term oxygen therapy ESSDAI: EULAR Sjögrens syndrome disease activity index.

initial scan was median (IQR) 10 (12.5) and it was increased to 15 (21.25) at the final scan (p=0.180). In HRCT, at the time of diagnosis, the most common findings were ground glass opacities (71.1%), traction bronchiectasis (35%) and honeycombing (30%). In controls after treatment the rate of ground glass decreased to 56.1%, traction bronchiectasis to 29.3% and honeycombing to 31.1%. The ground glass opacities were the only HRCT finding that showed statistically significant improvement during follow-up (p:0.031). While the ILD was considered to be stable in 39% of the patients radiologically, progression was observed in 31.7% and regression in 29.3%.

Table 2. Laboratory findings of pSS patients with and without ILD

	pSS with ILD (n = 60)	pSS without ILD (n =318)	*p*
Anemia, n(%)	13(22)	48(15.1)	0.184
Lymphopenia, n(%)	13(22)	24(7.5)	**0.001**
Leukopenia, n(%)	2(3.4)	11(3.5)	1.000
Thrombocytopenia, n(%)	2(3.4)	12(3.8)	1.000
RF positivity, n(%)	18(30)	95(30.4)	0.945
ANA-IFA positivity, n(%)	50(83.3)	257(80.8)	0.647
Anti-Ro/SS-A positivity, n(%)	28(46.7)	168(52.8)	0.381
Anti-La/SS-B positivity, n(%)	25(41.7)	90(28.3)	**0.039**
Anti-Ro52 positivity, n(%)	31(51.7)	138(43.4)	0.237
Anti-RNP positivity, n(%)	3(5.1)	11(3.5)	0.467
Anti-centromere positivity, n(%)	3(5.1)	11(3.5)	0.468
Elevated ESR, n(%)	33(55)	101(31.9)	**0.001**
Elevated CRP, n(%)	25(41.7)	89(28)	**0.034**
Elevated LDH, n(%)	25(48.1)	49(17.2)	**0.000**
Hypocomplementemia, n(%)	8(15.1)	24(8.1)	0.105
Hypergammaglobulinemia, n(%)	12(24.5)	53(18)	0.280

Abbreviations: pSS: primary Sjögren's syndrome, ILD: interstitial lung disease, RF: rheumatoid factor, ANA-IFA: antinuclear antibody immunofluorescence assay, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: lactate dehydrogenase.

The 41 ILD patients with a follow-up scan was regrouped as patients with radiographic progression and patients without (regression and/or stable disease), and clinical characteristics were compared (Table 5). Patients with progression in final scan had older age, older age at pSS diagnosis and older age at ILD diagnosis. Remaining disease features demographics and laboratory properties were similar, except that malignancies and mortality were more frequent in progressing patients.

Potential factors to be related with ILD development and progression were evaluated by logistic regression analysis and shown in Table 6. Male gender, being diagnosed with pSS over the age of 50, ever smoking history, elevated LDH, elevated ESR and lymphopenia was significantly related with the development of ILD in patients with pSS. When progression considered only being over age of 60 at the time of ILD diagnosis was significantly related with radiographic progression.

Discussion

Our results demonstrated that in our cohort of pSS pateints with at least one HRCT or TCT, the frequency of ILD was 15.8%. The majority of patients were diagnosed with ILD involvement either concomitantly or after the diagnosis of pSS with a median duration of 2 years between pSS and ILD diagnosis. The most common HRCT pattern was NSIP and the most common findings were ground glass opacities, traction bronchiectasis and honeycombing. Affected lung parenchyma percentage increased during follow up yet without significance. Rate of only ground glass opacities were decreased significantly during the follow-up. IPF severity scale and PFT results indicated majority of patients mildly affected from ILD. Among 41 patients with follow-up scans, 13 were determined to be progressed radiographically and 7 mortalities observed in the study were all in the progressing patient subgroup. Male gender, being diagnosed with pSS over the age of 50, smoking history, elevated LDH, elevated ESR and lymphopenia were related with development of ILD while being diagnosed with ILD after the age of 60 was related with radiographic progression.

Evidence regarding the prevalence of ILD in patients with pSS is controversial. Previous studies reported that the prevalence of pSS-ILD ranged from 1.01% to 78.61%, depending on ethnicity, study

Table 3. ILD associated characteristics of pSS patients with ILD.

	n=60
Age at diagnosis of ILD, year, mean±SD	58.86±11.93
Time between ILD and pSS, months, median(IQR)	24 (72)
Time of ILD onset (n, %)	
Before pSS onset	6(10)
Concomitant with pSS	27(45)
After pSS onset	27(45)
Pulmonary symptoms (n, %)	
Dyspnea	44(73.3)
Dry cough	34(56.7)
Productive cough	8(13)
Fever	1(1.7)
Recurrent pulmonary infections	3(5)
HRCT/TCT scan pattern (n, %)	
NSIP	22(36.7)
UIP	11(18.3)
LIP	15(25)
OP	2(3.3)
Indeterminate	10(16.7)
Pulmonary function test parameters, mean±SD	
FEV1 (%)	87.31±12.81
FEVC (%)	86.73±16.18
FEV1/FVC (%)	91.73±17.22
DL_{CO}-corr(%)	56.78±13.25
IPF stage, n (%)	
Stage 1	38(65.5)
Stage 2	14(24.1)
Stage 3	4(6.9)
Stage 4	2(3.4)

Abbreviations: pSS: primary Sjögren's syndrome, ILD: interstitial lung disease, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, LIP: lymphocytic interstitial pneumonia, OP: organizing pneumonia, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, DLCO: diffusion capacity for carbon monoxide, IPF: idiopathic pulmonary fibrosis.

design, and diagnostic options (11-18). In 2015, the EULAR Sjögren's Syndrome Task Group conducted a systematic literature review to characterize pSS-related lung involvement and found an overall prevalence of 16% of bronchial or parenchymal lung disease (19). In a recent meta-analysis of ILD, its prevalence in pSS patients was found to be 13% (12). Earlier studies performing CT scans in asymptomatic pSS patients showed that up to 65% of subjects detected lung abnormalities, including features of ILD (20, 21). However, in most studies, HRCT is performed only in patients with clinically suspected lung involvement, and asymptomatic patients are generally excluded. Therefore, it is very difficult to clearly state the prevalence of pSS-ILD. In our cohort, the frequency of pSS-ILD was found to be 15.8% among pateints with at least one HRCT or TCT.

The most common HRCT pattern in the cohort was NSIP (36.7%), followed by LIP (25%) and UIP (18.3%). According to most research the most common radiological pattern in pSS-ILD is NSIP, followed by UIP, OP, and LIP (22, 23). A study of the published cases with histopathology revealed that 45% were NSIP, 16% were UIP, 15% were LIP, 7% were OP, and 17% were other diseases (19). HRCT findings are crucial in the diagnosis of ILD. Previous research has discovered that ground glass and non-septal linear opacities are more common in pSS patients' HRCT scans (24-26). Another study found that linear opacities, ground glass opacities, and parenchymal micronodules/nodules were the most prevalent aberrations (27). In our study the most common abnormalities were ground glass opacities, traction bronchiectasis, and honeycombing. Yet, we did not evaluate pulmonary nodules/micronodules. Among these structural anomalies observed in HRCT, especially ground glass opacities were observed to decrease with treatment. This suggests that the response to treatment may be higher in patients with pSS with ILD with predominant inflammatory lesions such as ground glass opacities than patients with fibrotic changes such as honeycombing and traction bronchiectasis.

It has been reported that 10-51% of patients developed ILD years before the onset of pSS and pSS-ILD developed concomitant with other systemic manifestations in approximately 10% of cases. (6). In the remainder of the cases, ILD develops late in the course of the disease (7). In one study, lung involvement was observed as the first symptom of pSS in 21.21% of patients, similar to other studies (13, 23, 27). Another prospective study found that ILD was the primary symptom in 16.88% of pSS patients, with no autoantibody positive (17). In our study, ILD occurred frequently concomitant or after pSS diagnosis. The median (IQR) interval between PSS diagnosis and ILD was 24(72) months. It can be speculated that such diversity may imply at least two pathogenetically separate subsets of pSS-ILD patients: In the first group the underlying mechanism may be long-term subclinical local damage to the pulmonary airways and parenchyma associated with pSS, and in the second group it may be an

Table 4. HRCT findings of pSS patients with ILD and temporal changes

	pSS with ILD		
	Initial HRCT/TCT (n = 60)	**Final HRCT/TCT at follow-up (n:41)**	**p**
HRCT/TCT findings (n, %)	43(71.7)	23(56.1)	**0.031**
Ground glass opacities	21(35)	12(29.3)	1.000
Traction bronchiectasis	18(30)	14(31.1)	0.500
Honeycombing	17(28.3)	11(26.8)	1.000
Cysts	17(28.3)	11(26.8)	1.000
Irregular interseptal thickening	17(30.4)	11(26.8)	1.000
Increased reticular density Consolidation	5(8.3)	4(9.8)	1.000
Percentage of lung paryncheme involved, median (IQR)	10 (12.5)	15 (21.25)	0.180
The time interval between the initial and final scans, months, median(IQR)	23(24.5)		
Radiographic prognosis, n(%)			
Stable	16(39)		
Progression	13(31.7)		
Regression	12(29.3)		

Abbreviations: pSS: primary Sjögren's syndrome, ILD: interstitial lung disease, HRCT: high resolution computed tomography, TCT: thorax computed tomography.

Table 5. Characteristics of patients with and without radiographic progression

	pSS with ILD with progression(n=13)	**pSS with ILD without progression(n = 28)**	***p***
Female, n (%)	10(76.9)	20(71.4)	0.712
Age, year, mean±SD	70.5±5.8	63.28±8.73	**0.003**
Age at pSS diagnosis, year, mean±SD	64.54±9.01	53.11±13.23	**0.008**
Age at diagnosis of ILD, year, mean±SD	68.25±6.29	59.42±10.62	**0.001**
Disease duration, months, median (IQR)	70.15(60)	94.03(84)	0.255
Comorbidities, n(%)			
Diabetes mellitus	2(15.4)	2(7.1)	0.579
Hypertension	8(61.5)	11(39.3)	0.184
Coronary artery disease	2(15.4)	3(10.7)	0.645
Chronic kidney disease	0(0)	2(7.1)	1.000
Hypothyroidism	2(15.4)	4(14.3)	1.000
COPD/Asthma	4(30.8)	6(21.4)	0.698
Malignancy	4(30.8)	1(3.6)	**0.028**
Ever smokers, n (%)	4(30.8)	7(25)	0.698
Xerostomia, n (%)	13(100)	22(78.6)	0.071
Xerophthalmia, n (%)	10(76.9)	23(82.1)	0.695
Raynaud's phenomenon, n (%)	0(0)1	1(3.6)	1.000
Arthritis, n (%)	2(15.4)	3(10.7)	0.645
Parotid enlargement, n (%)	0(0)	1(3.6)	1.000
Positive Schirmer's test, n(%)	12(100)	20(74.1)	0.052
Positive salivary gland biopsy, n(%)	4(57.1)	12(70.6)	0.525
Lymphadenopathy, n (%)	2(15.4)	3(10.7)	0.645
Lymphoma, n (%)	1(7.7)	1(3.6)	0.539
ESSDAI, median(IQR)	3.69(3)	2.36(4)	0.251

(*Continued*)

	pSS with ILD with progression(n=13)	pSS with ILD without progression(n = 28)	*p*
Anemia, n(%)	4(30.8)	6(21.4)	*0.698*
Lymphopenia, n(%)	3(23.1)	5(17.9)	*0.692*
Leukopenia, n(%)	0(0)	2(7.1)	*1.000*
RF positivity, n(%)	4(30.8)	7(25)	*0.719*
ANA-IFA positivity, n(%)	12(92.3)	24(85.7)	*0.548*
Anti-Ro/SS-A positivity, n(%)	6(46.2)	13(46.4)	*0.987*
Anti-La/SS-B positivity, n(%)	6(46.2)	13(46.4)	*0.987*
Anti-Ro52 positivity, n(%)	7(53.8)	14(50)	*0.819*
Anti-RNP positivity, n(%)	1(7.7)	1(3.6)	*0.539*
Anti-centromere positivity, n(%)	0(0)	1(3.6)	*1.000*
Elevated ESR, n(%)	10(76.9)	15(53.6)	*0.154*
Elevated CRP, n(%)	7(53.8)	12(42.9)	*0.511*
Elevated LDH, n(%)	7(70)	10(38.5)	0.090
Hypocomplementemia, n(%)	3(23.1)	2(83)	*0.321*
Hypergammaglobulinemia, n(%)	3(27.3)	9(39.1)	*0.705*
HRCT/TCT pattern (n, %)			*0.738*
NSIP	5(38.5)	9(32.1)	
UIP	3(23.1)	6(21.4)	
LIP	4(40)	6(21.4)	
OP	0(0)	2(7.1)	
Indeterminate	1(7.7)	5(17.9)	
Pulmonary functiontest parameters, mean±SD			*0.189*
FEV1 (%)	85±8.1	91±9.6	*0.105*
FEVC (%)	87.2±20.5	88.42±16.7	*0.194*
FEV1/FVC (%)	102.7±25.7	93.8±15.17	*0.314*
DL_{CO}-corr(%)	50.75±10.8	52.28±13.30	
Percentage of lung involvement, mean±SD	13±8.5	17.8±9.5	0.699
Mortality, n (%)	7(84.6)	0 (0)	**0.033**

Abbreviations: pSS: primary Sjögren's syndrome, ILD: interstitial lung disease, COPD: chronic obstructive pulmonary disease, CNS: central nervous system, PNS:peripheral nervous system, ESSDAI: EULAR Sjögrens syndrome disease activity index, RF: rheumatoid factor, ANA-IFA: antinuclear antibody immunofluorescence assay, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: lactate dehydrogenase, HRCT: high resolution computed tomography, TCT: thorax computed tomography, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, LIP: lymphocytic interstitial pneumonia, OP: organizing pneumonia, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, DL_{CO}: diffusion capacity for carbon monoxide, IPF: idiopathic pulmonary fibrosis.

Table 6. Factors significantly related with ILD occurrence and progression according to logistic regression analyses

	OR (95% CI)	*p*
ILD development		
Gender, male	2.90 (1.23-6.8)	**0.014**
Age at pSS diagnosis > 50 years	4.24 (1.33-13.5)	**0.015**
Ever smoking history	2.38 (1.05-5.34)	**0.036**
Elevated LDH	3.27 (1.60-6.68)	**0.001**
Elevated ESR	2.51 (1.27-4.96)	**0.008**
Lymphopenia	5.12 (1.83-14.26)	**0.002**
Radiographic progression		
Age at diagnosis of ILD > 60 year	7.74 (1.30-45.94)	**0.024**

Abbreviations: ILD: interstitial lung disease, pSS: primary Sjögren's disease, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate.

immunologic dysregulation that primarily targets the lung before other manifestations of pSS occur.

Our results suggest male gender, being diagnosed with pSS over the age of 50, smoking history, elevated LDH, elevated ESR and lymphopenia may be associated with development of ILD in pSS patients. Numerous observational studies have attempted to find demographic, clinical, and serological factors that may be associated with the development of ILD, as well as ILD-related risk factors, however, the results are sometimes conflicting. In a study, pSS patients associated with ILD were more likely to be male, elderly, and smokers compared to pSS patients without ILD (15). In a meta-analysis, the only variables found to be statistically associated with ILD were elder age, male gender, and high CRP. pSS-ILD patients were 9.25 years older than pSS patients without ILD, with a mean difference of 9.25 years across six studies. Furthermore, with an OR of 1.92, ILD was related with male gender (12). It has also been reported that the diagnosis of pSS has increased in the years since the onset of ILD (7). Moreover, a retrospective analysis of 15 LIP cases revealed that the prevalence of anti-Ro60, anti-Ro52, anti- SSB autoantibodies, and hypergammaglobulinemia were higher in the LIP patients (28). In this study, anti-SSB antibody was detected more frequently in pSS-ILD patients than in non-ILD patients, although it was not identified as a risk factor for ILD development in the regression analysis. Furthermore, previous investigations that were similar to ours showed elevated LDH and lymphopenia as independent risk factors for the development of ILD (26, 27, 29). All these data imply that in elder, male patients, in patients with an older age at the time of pSS diagnosis and in pateints with laboratory features such as elevated LDH, elevated ESR and lymphopenia more cautious approach should be taken regarding ILD development.

It has also been a matter of interest that whether there are factors to predict progression in pSS-ILD. It has been reported that male gender, non-siccan onset, reticular pattern on HRCT, greater levels of baseline LDH, and lower FVC at baseline were all linked with ILD progression and according to the multivariate logistic regression LDH is an independent risk factor for ILD progression in a single-center retrospective analysis (29). In another study, multiple logistic regression analysis revealed that substantial lung involvement is an independent risk factor for the progression of pSS-ILD (30). In our study, due to the inadequate PFT data in most pateints in medical records, we evaluated radiographic progression based on HRCT and/or TCT results. To our best knowledge, there is currently a valid method for pSS to quantify involved lung parenchyma. Therefore, we used the method described by Goh et al. (13) to semi quantitatively calculate percentage of lung volume affected in radiographic scans. According to the results of or study, in addition to aforementioned risk factors reported in the literature, being diagnosed with ILD after the age of 60 may be another risk factor for progression.

A precise algorithm for management of pSS-ILD is currently not established. The treatment approach for pSS-ILD should be adjusted to the extent and progression of lung involvement. As for medical treatment glucocorticoids and/or other immunosuppressive drugs and antifibrotics can be used(31), drawing on experience with other immune-mediated diseases (32). There are also retrospective studies on Sjögren's-ILD treatment, but prospective studies are needed (33). In our cohort, AZA, MMF, CTX, RTX were frequently used for ILD treatment, with only three patients receiving antifibrotic treatment. During the follow-up period of 25.92±17.54 months after treatment, 39% of the patients were stable, 29.3% had regression and 31.7% had radiographic progression. In our study all of the 7 cases with mortality had ILD and were in the progressing group. Although, we could not elucidate the cause of mortality in these cases, this cluster implies a mortality burden due to presence of ILD. Another issue that fore came was the fact that malignancies were more common in ILD patients in our cohort. We noted 7 patients with malignancies comprising 3 cases of breast cancer, 2 of lung cancer and 2 of lymphoma. Diffuse parenchymal lung disease is a known risk factor for lung cancer, yet in the study of Xu et al. (34), only 50% of pSS pateints with lung cancer had ILD and the frequency was not significantly different from pSS pateints without lung cancer. Higher load of immunosuppression may be speculated to be another risk factor for cancer in ILD patients.

The retrospective design of the study and the small number of patients were our main limitations. Because of the retrospective analysis, the cause-and-effect relationship could not be properly assessed. Another major limitation was the absence of PFT follow-up and only 41 patients could be evaluated

for radiographic progression with HRCT. Therefore, subgroup analysis could not be performed in this patient group. Moreover, since the design of the study was not suitable for determining the specific effect of any drug, statistical data on this subject could not be given in the manuscript. Finally, due to different characteristic features LIP and NSIP/UIP patients could be evaluated separately as subgroups, however, patient number was not ample for such evaluation.

All in all, our results provided a large spectrum view for pSS-ILD and pointed out several risk factors for ILD occurrence and radiographic progression. We believe our results further contribute to the limited knowledge in the literature. Large, prospective cohort studies and studies inspecting different aspects are needed to for better understanding of pSS-ILD.

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