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ORIGINAL ARTICLE

Clinical profiles of SS-ILD compared with SS-NILD in a Chinese population: a retrospective analysis of 735 patients

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ABSTRACT

Background: Interstitial lung disease (ILD) is a serious complication in patients with Sjögren's syndrome (SS). Most studies on primary SS (pSS) with ILD are limited in sample size, and studies on secondary SS (sSS) with ILD are rare. This study aimed to elucidate both primary and secondary SS-associated ILD (SS-ILD) based on a large cohort.

Methods: The medical records of hospitalized patients diagnosed with SS at the Second Xiangya Hospital of Central South University from January 2010 to May 2020 were retrospectively reviewed. Clinical manifestations, medical history, biological results and imaging data were collected.

Results: Of the 735 SS patients enrolled in this study, 563 (76.6%) were diagnosed with pSS, 172 (23.4%) were diagnosed with sSS. Additionally, 316 (43.0%) were diagnosed with SS-ILD. No significant difference was found between the pSS and sSS groups concerning the incidence of ILD ($p = .718$). Factors associated with SS-ILD were older age ($p < .001$), male sex ($p = .032$), female sex at menopause ($p = .002$), Raynaud's phenomenon ($p < .001$), low levels of albumin ($p = .010$) and respiratory symptoms ($p < .001$). The SS-ILD group showed higher counts of platelets ($p < .001$). The three most frequent high-resolution CT (HRCT) findings of SS-ILD were irregular linear opacities (42.7%), grid shadows (30.7%) and pleural thickening (28.5%). NSIP (56.3%) was the most frequent HRCT pattern. Compared with pSS patients with ILD (pSS-ILD) patients, sSS patients with ILD (sSS-ILD) patients had a higher incidence of proteinuria ($p < .001$) and hypercreatinaemia ($p = .013$), a higher level of erythrocyte sedimentation rate (ESR) ($p = .003$), low levels of complement 3 (C3) ($p = .013$), lymphocytes ($p = .009$) and leukocytes ($p = .024$), and worse DLCO (%Pred) ($p = .035$).

Conclusions: ILD is a common pulmonary involvement in both pSS patients and sSS patients. Older age, male sex, female sex at menopause, Raynaud's phenomenon, low albumin levels and respiratory symptoms are risk factors associated with SS-ILD. NSIP is important HRCT feature of SS-ILD. sSS-ILD patients showed worse laboratory results and pulmonary function.

KEY MESSAGE

- Older age, male sex, female sex at menopause, Raynaud's phenomenon, low albumin levels and respiratory symptoms are risk factors associated with SS-ILD.
- SS-ILD patients show higher counts of platelets and less purpura.
- sSS-ILD patients have worse laboratory results and pulmonary function.

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Interstitial lung disease; pulmonary fibrosis; primary Sjögren's syndrome; secondary Sjögren's syndrome

Introduction

Sjögren's syndrome (SS) is a multisystem autoimmune disease characterized by hypofunction of exocrine glands and possible systemic multiorgan manifestations. The disease mainly occurs in adults and affects female individuals more often than male individuals [1]. SS can affect various extraglandular organs, including the lung, kidney, liver and vessels [2,3]. Primary Sjögren's syndrome (pSS) is a disorder excluding other connective tissue diseases. Patients with secondary Sjögren's syndrome (sSS) usually overlap with other well-defined connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, polymyositis and

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primary biliary cirrhosis [4]. Interstitial lung disease (ILD) secondary to SS contributes to a decreased quality of life and survival rate [5]. The mortality of pSS may increase over time with the pulmonary lesions involved, as prospective studies have shown that the 10-year survival rate in pSS patients without ILD (pSS-NILD) was 95.5%, whereas the rate decreased to 83% [6] in pSS patients with ILD (pSS-ILD). The main cause of death was respiratory failure with or without coexisting pneumonia [7,8]. Pulmonary involvement has been observed in 9–75% of patients with pSS depending on the diagnostic modality of ILD[9]. Although several studies associated with pSS-ILD have been reported, large systemic studies and literature describing the clinical features of SS patients with ILD involving both pSS patients and sSS patients are rare. Knowledge of sSS patients with ILD (sSS-ILD) is limited, as most studies have focussed on pSS-ILD. In this retrospective study, we aimed to compare the characteristics of SS patients with and without ILD in a large cohort and further summarized the features of sSS-ILD.

Materials and methods

Patients

Hospitalized patients who had received a diagnosis of SS at the Second Xiangya Hospital of Central South University from January 2010 to May 2020 were included. Patients who had a neoplasm, malignancy, were pregnant or who had received hormonotherapy at the time of diagnosis were excluded. The medical records of the first hospitalization were retrospectively reviewed if the patients were hospitalized several times. All SS patients fulfilled the 2002 International Classification Criteria [4] or the 2016 ACR/EULAR classification [9] for pSS and sSS. Concisely, in 2002 criteria, the patients diagnosed with pSS should meet four items among the six criteria: ocular symptoms, oral symptoms, ocular signs, histopathology of salivary gland focal lymphocytic sialoadenitis, positive results of salivary gland involvement test, and antibodies to Ro(SSA) or La(SSB) antigens. Additionally, histopathology or serology is required. If no obvious symptoms are observed, the presence of any three of the four objective criteria items is necessary. In 2016 criteria, ocular or oral symptoms are necessary, and a score $\geq$4 must be reached: focal lymphocytic sialoadenitis or positive anti-SSA is scored as 3, and an ocular sign or a positive salivary gland involvement test is counted as 1. Specifically, if patients are diagnosed with a well-defined connective tissue disease, the presence of ocular symptoms or oral symptoms plus any two pieces of evidence from among ocular signs, histopathology-indicated focal lymphocytic sialoadenitis, and a positive result of salivary gland involvement can be considered secondary SS (sSS). ILDs were diagnosed according to the guidelines described in Goldman's Cecil Medicine (24th edition) chapter 92 [10], based on related clinical symptoms, physical signs, the results of lung function examinations, and high-resolution CT (HRCT).

Study design

All patients were retrospectively divided into an SS with ILD (SS-ILD) group and an SS without ILD (SS-NILD) group. Demographics and general information, such as sex, age and menopause, were collected. Laboratory examinations, such as erythrocyte sedimentation rate (ESR), complement 3 (C3), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), globulin, blood cell counts and C-reactive protein (CRP) levels, were reviewed. The results of serologic autoantibodies, including anti-SSA, anti-SSB, anti-Ro52, rheumatoid factor (RF), antimitochondrial M2 (AMA-M2), anti-glycoprotein 210 (gp210), anti-Smith (Sm) and anti-double-stranded DNA (dsDNA) antibodies, as well as antinuclear (ANAs) antibodies, were assessed. General information, clinical manifestations and laboratory data were compared between the SS-ILD and SS-NILD groups. We further compared pSS-ILD and pSS-NILD. Primary autoimmune diseases were compared between sSS-ILD and those without ILD (sSS-NILD). Notably, characteristics including pulmonary function of pSS-ILD and sSS-ILD were compared.

We analysed the HRCT characteristics of the SS-ILD group. HRCT scans were re-evaluated independently by two experienced chest radiologists to determine HRCT patterns. The following HRCT characteristics were particularly focussed: irregular linear opacities, honeycombing, ground-glass opacities, septal thickening, grid shadow and pleural thickening. Additionally, the HRCT patterns were divided into non-specific interstitial pneumonitis (NSIP), usual interstitial pneumonia (UIP), cryptogenic organizing pneumonia (COP), lymphocytic interstitial pneumonia (LIP) and mixed multiple patterns based on idiopathic pulmonary fibrosis (IPF) guidelines implemented in 2013 [11].

Statistical analysis

Statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, IL). For group comparisons

involving categorical data, we used either the chi-squared test, Yates's continuity correction or Fisher's exact test depending on the sample size. Comparisons involving continuous data were made using the Mann–Whitney's *U* test. The data were expressed as medians (*M*) and range. The results were regarded as statistically significant when the *p* value was less than .05.

Results

Baseline characteristics and laboratory features of all SS patients

In total, this retrospective analysis enrolled 735 SS patients, and 316 (43.0%) patients were SS-ILD cases. Additionally, 563 (76.6%) patients were identified with primary SS (pSS), and 172 (23.4%) were identified with sSS. In the pSS group, 240 patients (42.6%) were diagnosed with ILD. In the sSS group, 76 individuals (44.2%) had ILD. No significant difference was found between the pSS and sSS groups concerning the incidence of ILD ($p = .718$). The mean age of SS-ILD patients was older than that of SS-NILD patients (median: 58 years vs. 51 years; $p < .001$). The SS-ILD group had a significantly higher percentage of male patients than the SS-NILD group (12.7% vs. 7.9%; $p = .032$). Seventy-three male patients were divided into non-smokers (16), current smokers (42) and ex-smokers (15), and the ILD patients in each group numbered nine (56.3%), 19 (45.2%) and eight (53.3%), respectively. Additionally, no statistical difference was found regarding the smoking status or ILD incidence rate ($p = .710$). Concerning clinical symptoms, SS-ILD patients showed more Raynaud's phenomenon (18.7% vs. 8.4%; $p < .001$) and respiratory symptoms (67.1% vs. 16.7%; $p < .001$). The SS-NILD group showed a higher percentage of purpura (12.9% vs. 3.2%; $p < .001$) (Table 1). We further compared menopause among female patients between the groups, and the SS-ILD group had a higher rate of female patients with menopause ($n = 182$; 65.9% vs. $n = 208$; 53.9%; $p = .002$).

Compared with the SS-NILD group, SS-ILD patients had lower albumin levels (34.8 g/L vs. 36 g/L; $p = .010$). Additionally, the SS-ILD group showed higher platelet

Table 1. Comparison of clinical characteristics between SS-NILD group and SS-ILD group.

	Total ($n = 735$)	SS-NILD ($n = 419$, 57.0%)	SS-ILD ($n = 316$, 43.0%)	*p*
Age at diagnosis (years)	54 (16–84)	51 (16–83)	58 (23–84)	<.001
Duration of disease (years)	2.0 (0.8–4.8)	1.95 (0.8–4.5)	2.0 (0.9–4.8)	.841
Male	73 (9.9%)	33 (7.9%)	40 (12.7%)	.032
Sicca symptoms	461 (62.7%)	253 (60.4%)	208 (65.8%)	.131
Rampant caries	130 (17.7%)	66 (15.8%)	64 (20.3%)	.113
Arthralgia	249 (33.9%)	143 (34.1%)	106 (33.5%)	.868
Purpura	64 (8.7%)	54 (12.9%)	10 (3.2%)	<.001
Raynaud's phenomenon	94 (12.8%)	35 (8.4%)	59 (18.7%)	<.001
Respiratory symptoms	282 (38.4%)	70 (16.7%)	212 (67.1%)	<.001
Digestive symptoms	97 (13.2%)	57 (13.6%)	40 (12.7%)	.708
Laboratory results				
Anti-SSA body	562 (76.5%)	317 (75.7%)	245 (77.5%)	.553
Anti-SSB body	237 (32.2%)	138 (32.9%)	99 (31.3%)	.645
Anti-Ro-52 body	533 (72.5%)	298 (71.1%)	235 (74.4%)	.329
Antinuclear antibodies	499 (67.9%)	278 (66.3%)	221 (69.9%)	.302
Anti-AMA-M2 body	58 (7.9%)	30 (7.2%)	28 (8.9%)	.397
Anti-gp210 body	24 (3.3%)	10 (2.4%)	14 (4.4%)	.123
Anti-dsDNA body	35 (4.8%)	20 (4.8%)	15 (4.7%)	.987
Anti-Sm body	29 (3.9%)	15 (3.6%)	14 (4.4%)	.558
Rheumatoid factor	189 (25.7%)	97 (23.2%)	92 (29.1%)	.907
Proteinuria[a]	169 (23.0%)	89 (21.2%)	80 (25.3%)	.194
Hypercreatinaemia, >133.0 μmol/L	27 (3.7%)	15 (3.6%)	12 (3.8%)	.877
Hyperglobulinaemia, >40.0 g/L	159 (21.6%)	85 (20.3%)	74 (23.4%)	.307
C3 (g/L)	0.85 (0.08–3.15)	0.85 (0.17–3.15)	0.86 (0.08–1.70)	.892
Albumin (g/L)	35.5 (11.7–50.8)	36 (11.7–50.1)	34.8 (15.7–50.8)	.010
Elevated ALT, >42 U/L	29 (3.9%)	13 (3.1%)	16 (5.1%)	.176
Elevated AST, >37 U/L	25 (3.4%)	10 (2.4%)	15 (4.7%)	.081
ESR (mm/h)	39 (1–140)	37 (2–140)	41.4 (1–140)	.053
CRP (mg/L)	4.71 (0.08–251)	4.78 (0.1–251)	5.99 (0.08–165)	.245
Haemoglobin (g/L)	116 (18–200)	114 (18–173)	117 (57–200)	.091
Leukocytes ($\times 10^9$/L)	5.88 (0.41–20.59)	5.8 (0.41–20.59)	6.07 (1.56–20.01)	.200
Lymphocytes ($\times 10^9$/L)	1.32 (0.15–5.76)	1.29 (0.15–5.76)	1.37 (0.22–4.32)	.126
Platelets ($\times 10^9$/L)	184 (1–736)	179 (1–631)	191 (2–736)	<.001

SS-NILD: Sjögren's syndrome patients without interstitial lung disease; SS-ILD: Sjögren's syndrome patients with interstitial lung disease; C3: complements 3; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
Values are presented as number (%) or median (range).
[a]The proteinuria is defined as the amount of protein in the urine beyond 150 mg/24 h.

counts (191×10^9/L vs. 179×10^9/L; $p < .001$). However, the two groups did not differ in the presence of anti-SSA, anti-SSB, anti-Ro52, RF, anti-AMA-M2, anti-gp210, anti-dsDNA and anti-Sm antibodies, ANA, C3, haemoglobin, leukocytes, lymphocytes, ESR, ALT, AST and CRP. We also found no correlation between ILD and the presence of proteinuria and hypercreatinaemia (Table 1).

Characteristics of primary autoimmune disease in sSS patients

Among the 172 sSS patients, primary biliary cirrhosis is the most frequent primary autoimmune disease ($n = 60$; 34.9%), followed by rheumatoid arthritis ($n = 47$; 27.3%), systemic lupus erythematosus ($n = 38$; 22.1%), vasculitis ($n = 12$; 7.0%), systemic sclerosis ($n = 9$; 5.2%), myositis ($n = 2$; 1.2%), ankylosing spondylitis ($n = 2$; 1.2%) and mixed connective tissue disease ($n = 2$; 1.2%). In the sSS-ILD group, the most common primary autoimmune diseases were primary biliary cirrhosis ($n = 22$; 28.9%), systemic lupus erythematosus ($n = 22$; 28.9%) and rheumatoid arthritis ($n = 18$; 23.7%) (Table 2). Furthermore, we compared antibodies between sSS-ILD patients and sSS-NILD patients, and no differences were found regarding anti-AMA-M2, anti-gp210 bodies, anti-dsDNA bodies and anti-Sm bodies. The sSS-ILD group showed a higher positive rate of RF (75%), and the sSS-NILD group was 46.9% ($p < .001$).

Characteristics of pSS patients

We compared clinical features and laboratory results between pSS-ILD patients and pSS-NILD patients. In contrast with the pSS-NILD group, the pSS-ILD group was much older (59 years vs. 50 years; $p < .001$) and showed a male preference (13.3% vs. 7.1%; $p = .014$). Additionally, pSS-ILD patients were more likely to present with Raynaud's phenomenon (17.1% vs. 6.2%; $p < .001$) and respiratory symptoms (63.8% vs. 17.0%; $p < .001$), but they showed less purpura (2.9% vs. 14.2%; $p < .001$) (Table 3). Regarding the laboratory findings, a significant difference was observed in the levels of albumin (36.4 g/L vs. 34.8 g/L; $p = .001$) and platelets (196×10^9/L vs. 179×10^9/L, $p < .001$) between the pSS-ILD and pSS-NILD group.

Comparison between the pSS-ILD and sSS-ILD groups

We further compared the clinical features and laboratory findings between pSS-ILD patients and sSS-ILD patients. No differences were found regarding the age at diagnosis or sex between the groups. sSS-ILD patients were more likely to present with arthralgia (43.4% vs. 30.4%; $p = .036$) and show more respiratory symptoms (77.6% vs. 63.8%; $p = .025$) (Table 4). Regarding the laboratory findings, sSS-ILD patients showed more proteinuria (44.7% vs. 19.2%; $p < .001$) and hypercreatinaemia (9.2% vs. 2.1%; $p = .013$). Additionally, the sSS-ILD group presented lower levels of C3 (0.80 g/L vs. 0.88 g/L; $p = .013$), higher ESR (53 mm/h vs. 39.5 mm/h; $p = .003$), fewer leukocytes (5.5×10^9/L vs. 6.43×10^9/L; $p = .024$) and fewer lymphocytes (1.19×10^9/L vs. 1.47×10^9/L; $p = .009$). Compared with pSS-ILD patients, sSS-ILD show a higher proportion of positive RFs (14.6% vs. 75%; $p < .001$).

The lung HRCT data were available in all 316 SS patients with ILD. The most common abnormality was irregular linear opacities ($n = 135$, 42.7%); the second most common abnormality was a grid shadow ($n = 97$, 30.7%). The proportions of patients showing pleural thickening, septal thickening and ground-glass opacities were 28.5% ($n = 90$), 26.6% ($n = 84$) and 24.4% ($n = 77$), respectively. Honeycombing was the least common HRCT presentation ($n = 48$, 15.2%). Regarding HRCT patterns, the most frequent was NSIP, which accounted for 56.3% ($n = 178$) of all SS-ILD patients. The SS-ILD patients with UIP accounted for 10.1% ($n = 32$). LIP and OP accounted for 4.4% ($n = 14$) and

Table 2. Comparison of primary autoimmune disease between sSS-NILD group and sSS-ILD group.

Primary autoimmune disease	Total ($n = 172$)	sSS-NILD ($n = 96$)	sSS-ILD ($n = 76$)	p
Primary biliary cirrhosis	60 (34.9%)	38 (39.6%)	22 (28.9%)	.146
Systemic lupus erythematosus	38 (22.1%)	16 (16.7%)	22 (28.9%)	.054
Rheumatoid arthritis	47 (27.3%)	29 (30.2%)	18 (23.7%)	.340
Vasculitis	12 (7.0%)	7 (7.3%)	5 (6.6%)	.855
Systemic sclerosis	9 (5.2%)	2 (2.1%)	7 (9.2%)	.082
Myositis	2 (1.2%)	1 (1.0%)	1 (1.3%)	1.000
Ankylosing spondylitis	2 (1.2%)	2 (2.1%)	0 (0)	.504
Mixed connective tissue disease	2 (1.2%)	1 (1.0%)	1 (1.3%)	1.000

sSS-NILD: secondary Sjögren's syndrome patients without interstitial lung disease; sSS-ILD: secondary Sjögren's syndrome patients with interstitial lung disease.
Values are presented as number (%).

Table 3. Comparison of clinical characteristics between pSS-NILD group and pSS-ILD group.

	Total ($n = 563$)	pSS-NILD ($n = 323$, 57.4%)	pSS-ILD ($n = 240$, 42.6%)	p
Age at diagnosis (years)	53 (16–83)	50 (16–83)	59 (23–83)	<.001
Duration of disease (years)	1.95 (0.8–3.2)	1.95 (0.8–3.2)	1.9 (0.9–2.8)	.912
Male	55 (9.8%)	23 (7.1%)	32 (13.3%)	.014
Sicca symptoms	357 (63.4%)	202 (62.5%)	155 (64.6%)	.618
Rampant caries	95 (16.9%)	49 (15.2%)	46 (19.2%)	.211
Arthralgia	168 (29.8%)	95 (29.4%)	73 (30.4%)	.797
Purpura	53 (9.4%)	46 (14.2%)	7 (2.9%)	<.001
Raynaud's phenomenon	61 (10.8%)	20 (6.2%)	41 (17.1%)	<.001
Respiratory symptoms	208 (36.9%)	55 (17.0%)	153 (63.8%)	<.001
Digestive symptoms	73 (13.0%)	45 (13.9%)	28 (11.7%)	.429
Laboratory results				
Anti-SSA body	429 (76.2%)	249 (77.1%)	180 (75.0%)	.565
Anti-SSB body	160 (28.4%)	86 (26.6%)	74 (30.8%)	.274
Anti-Ro-52 body	404 (71.8%)	232 (71.8%)	172 (71.7%)	.967
Antinuclear antibodies	387 (68.7%)	217 (67.2%)	170 (70.8%)	.355
Rheumatoid factor	87 (15.5%)	52 (16.1%)	35 (14.6%)	.623
Proteinuria[a]	118 (21.0%)	72 (22.3%)	46 (19.2%)	.368
Hypercreatinaemia, >133.0 μmol/L	18 (3.2%)	13 (4.0%)	5 (2.1%)	.195
Hyperglobulinaemia, >40.0 g/L	104 (18.5%)	53 (16.4%)	51 (21.3%)	.143
C3 (g/L)	0.85 (0.17–3.15)	0.85 (0.17–3.15)	0.88 (0.22–1.7)	.085
Albumin (g/L)	35.7 (11.7–50.8)	36.4 (11.7–50.1)	34.8 (15.7–50.8)	.001
Elevated ALT, >42 U/L	18 (3.2%)	8 (2.5%)	10 (4.2%)	.260
Elevated AST, >37 U/L	14 (2.5%)	6 (1.9%)	8 (3.3%)	.266
ESR (mm/h)	37 (1–140)	36 (2–140)	39.5 (1–140)	.268
CRP (mg/L)	5.17 (0.08–251)	4.73 (0.11–251)	5.87 (0.08–165)	.153
Haemoglobin (g/L)	118 (18–200)	118 (18–173)	118 (60–200)	.767
Leukocytes ($\times 10^9$/L)	6.13 (0.41–20.59)	6.06 (0.41–20.59)	6.43 (1.93–20.01)	.384
Lymphocytes ($\times 10^9$/L)	1.41 (0.15–5.76)	1.37 (0.15–5.76)	1.47 (0.33–4.32)	.272
Platelets ($\times 10^9$/L)	186 (1–631)	179 (1–631)	196 (3–526)	<.001

pSS-NILD: primary Sjögren's syndrome patients without interstitial lung disease; pSS-ILD: primary Sjögren's syndrome patients with interstitial lung disease; C3: complements 3; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. Values are presented as number (%) or median (range).

[a]The proteinuria is defined as the amount of protein in the urine beyond 150 mg/24 h.

3.2% ($n = 10$), respectively. The proportion of mixed multiple patterns was 25.9% ($n = 82$). No difference was found regarding imaging patterns between the pSS-ILD and sSS-ILD groups (Table 4). Regarding pulmonary function, the sSS-ILD group showed worse DLCO (%Pred) than the pSS-ILD group (65 vs. 73, $p = .035$). Additionally, no difference was found concerning FVC (%Pred) and FEV1/FVC between the groups.

Discussion

In the current study, 316 patients (43.0%) were diagnosed with SS-ILD. Previous studies have reported that ILD occurs in 9–75% of pSS patients [12]. The proportion of SS-ILD was relatively high in our cohort, likely because of the inclusion criteria, which included conducting the study among hospitalized patients. Compared with outpatients, more details are available in the medical records of inpatients, including clinical manifestations, laboratory results and radiological data. However, patients with multisystem manifestations, including pulmonary complications, are more likely to be hospitalized, resulting in a higher percentage of SS-ILD patents in this study. Furthermore, in a previous study based on the Chinese population, the pSS-ILD prevalence was 39.1% [5], suggesting that Chinese patients may be vulnerable to ILD. Taken together, we believe ILD is common in patients with SS. These patients require close follow-up of lung parameters.

sSS patients were enrolled in this study, a population that has seldom been reported in previous studies concerning SS-ILD patients. From our cohort, patients with primary biliary cirrhosis, rheumatoid arthritis and systemic lupus erythematosus were more susceptible to SS than those with other autoimmune diseases, a finding that agrees with previous studies indicating that sSS coexists, particularly with systemic lupus erythematosus (15–36%), rheumatoid arthritis (20–32%) and primary biliary cirrhosis (21–81%) [13–15]. Additionally, in the current study, these patients accounted for most patients in the sSS-ILD group. Thus, special attention should be given to sSS patients with primary biliary cirrhosis, rheumatoid arthritis or systemic lupus erythematosus to detect ILD early.

Patients with ILD had older age at diagnosis in our series. Current studies support that age plays a significant role in the pSS-ILD prevalence. For example, Dong et al. [5] showed a mean age of 61.00 ± 11.23 years in the pSS-ILD group and 57.44 ± 14.08 years in the

Table 4. Comparison of clinical characteristics between pSS-ILD group and sSS-ILD group.

	Total ($n = 316$)	pSS-ILD ($n = 240$)	sSS-ILD ($n = 76$)	p
Age at diagnosis (years)	58 (23–84)	59 (23–83)	56.5 (35–84)	.281
Duration of disease (years)	2.0 (0.9–4.8)	1.90 (0.9–2.8)	2.05 (1.5–4.8)	.481
Male	40 (12.7%)	32 (13.3%)	8 (10.5%)	.521
Sicca symptoms	208 (65.8%)	155 (64.6%)	53 (69.7%)	.409
Rampant caries	64 (20.3%)	46 (19.2%)	18 (23.7%)	.393
Arthralgia	106 (33.5%)	73 (30.4%)	33 (43.4%)	.036
Purpura	10 (3.2%)	7 (2.9%)	3 (3.9%)	.942
Raynaud's phenomenon	59 (18.7%)	41 (17.1%)	18 (23.7%)	.198
Respiratory symptoms	212 (67.1%)	153 (63.8%)	59 (77.6%)	.025
Digestive symptoms	40 (12.7%)	28 (11.7%)	12 (15.8%)	.346
Laboratory results				
Anti-SSA body	245 (77.5%)	180 (75.0%)	65 (85.5%)	.055
Anti-SSB body	99 (31.3%)	74 (30.8%)	25 (32.9%)	.736
Anti-Ro-52 body	235 (74.4%)	172 (71.7%)	63 (82.9%)	.051
Antinuclear antibodies	221 (69.9%)	170 (70.8%)	51 (76.1%)	.394
Rheumatoid factor	92 (29.1%)	35 (14.6%)	57 (75.0%)	<.001
Proteinuria[a]	80 (25.3%)	46 (19.2%)	34 (44.7%)	<.001
Hypercreatinaemia, >133.0 μmol/L	12 (3.8%)	5 (2.1%)	7 (9.2%)	.013
Hyperglobulinaemia, >40.0 g/L	74 (23.4%)	51 (21.3%)	23 (30.3%)	.106
C3 (g/L)	0.86 (0.08–1.7)	0.88 (0.22–1.7)	0.80 (0.08–1.42)	.013
Albumin (g/L)	34.8 (15.7–50.8)	34.8 (15.7–50.8)	34.6 (20.8–46.5)	.575
Elevated ALT, >42 U/L	16 (5.1%)	10 (4.2%)	6 (7.9%)	.229
Elevated AST, >37 U/L	15 (4.7%)	8 (3.3%)	7 (9.2%)	.057
ESR (mm/h)	41.4 (1–140)	39.5 (1–140)	53 (7–140)	.003
CRP (mg/L)	5.99 (0.08–165)	5.87 (0.08–165)	6.09 (0.08–99.7)	.459
Haemoglobin (g/L)	117 (57–200)	118 (60–200)	114 (57–171)	.072
Leukocytes ($\times 10^9$/L)	6.03 (1.56–20.01)	6.43 (1.93–20.01)	5.5 (1.56–17.71)	.024
Lymphocytes ($\times 10^9$/L)	1.37 (0.22–4.32)	1.47 (0.33–4.32)	1.19 (0.22–4.04)	.009
Platelets ($\times 10^9$/L)	191 (2–736)	196 (3–526)	179 (2–736)	.341
Image abnormalities				
Irregular linear opacities	135 (42.7%)	105 (43.8%)	30 (39.5%)	.511
Grid shadow	97 (30.7%)	69 (28.8%)	28 (36.8%)	.183
Pleural thickening	90 (28.5%)	70 (29.2%)	20 (26.3%)	.631
Septal thickening	84 (26.6%)	64 (26.7%)	20 (26.3%)	.952
Ground-glass opacities	77 (24.4%)	58 (24.2%)	19 (25.0%)	.883
Honeycombing	48 (15.2%)	34 (14.2%)	14 (18.4%)	.368
HRCT patterns				
NSIP	178 (56.3%)	138 (57.5%)	40 (52.6%)	.456
UIP	32 (10.1%)	25 (10.4%)	7 (9.2%)	.761
COP	14 (4.4%)	9 (3.8%)	5 (6.6%)	.337
LIP	10 (3.2%)	7 (2.9%)	3 (3.9%)	.708
Mixed multiple patterns	82 (25.9%)	61 (25.4%)	21 (27.6%)	.701
Lung functions				
FVC (%Pred)	78.5 (43–120)	79.1 (43–113)	78.5 (48–120)	.764
FEV1/FVC	83 (70–102)	84 (70–102)	82.5 (78–99)	.892
DLCO (%Pred)	69 (42–88)	73 (43–88)	65 (42–87)	.035

pSS-ILD: primary Sjögren's syndrome patients with interstitial lung disease; sSS-ILD: secondary Sjögren's syndrome patients with interstitial lung disease; C3: complements 3; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HRCT: high-resolution CT; NSIP: non-specific interstitial pneumonitis; UIP: usual interstitial pneumonia; COP: cryptogenic organizing pneumonia; LIP: lymphocytic interstitial pneumonia.

Values are presented as number (%) or median (range).

[a]The proteinuria is defined as the amount of protein in the urine beyond 150 mg/24 h.

pSS-NILD group, and Roca et al. [12] revealed a median age of 63 years in pSS-ILD and 55 years in pSS-NILD. This finding suggests that elderly patients with SS should be monitored closely for lung involvement during follow-up. Age is regarded as a potential risk factor for several connective tissue disease-related ILDs, including rheumatoid arthritis [16], mixed connective tissue disease [17] and systemic sclerosis [18]. To date, the relationship between old age and ILD has not yet been clearly clarified, and aging-related persistently activated reactive oxygen species, abnormal shortening of telomeres, and epigenetic changes may contribute to fibrogenesis [19,20].

Our study confirms that male patients with SS are more vulnerable to ILD. From previous studies, Roca et al. [12] showed no sex difference between the pSS-ILD and pSS-NILD groups, but the ratio of male patients was higher in the pSS-ILD group than in the pSS-NILD group (14.3% vs. 1.7%). In a retrospective study [5], fewer female patients were in the pSS-ILD group than in the pSS-ILD group. Yazisiz et al. [21] also revealed a higher male/female ratio in pSS patients with lung involvement. The above findings indicate that male patients with SS are more likely to develop ILD. Importantly, we identified more female patients with menopause in the SS-ILD group; this

study is the first to report the relationship between menopause and SS-ILD. This finding also suggests that hormonal factors participate in the pathogenesis of SS-ILD. Oestrogen may play a protective role, but the specific underlying mechanism requires further confirmation and exploration.

The present study emphasizes that Raynaud's phenomenon is strongly correlated with ILD in SS. We found an obviously higher frequency of Raynaud's phenomenon in patients with ILD (18.7% vs. 8.4%; $p<.001$), a finding that was also confirmed in a previous study [12]. Raynaud's phenomenon is a common manifestation in pSS patients. Based on a cross-sectional study enrolling 320 pSS patients, 13% of them had Raynaud's phenomenon [22]. These findings help elucidate pathological mechanisms in ILD related to SS, indicating that an ischaemic process may play a role in the onset of lung damage.

Interestingly, in the present study, the SS-NILD group showed lower levels of platelets and more patients with purpura than those in the SS-ILD group. Previously, Roca et al. [12] also found more cases with purpura in pSS-NILD than in those with ILD, although the difference was not statistically significant. These phenomena are noteworthy. Platelet destruction is often implicated in autoimmune disease, and elevated P-selectin autoantibodies and FcγRIIb suppression on B cells may promote thrombocytopenia in pSS patients [23,24]. Our study suggests that ILD reduces the possibility of thrombocytopenia in SS patients. However, the causality between ILD and platelet changes remains clear because the sequence of ILD and purpura has not been investigated. A recent study showed that pSS patients with immune thrombocytopenia exhibited a lower frequency of ILD [25], and a large cohort study showed that patients with venous thromboembolism had a higher incidence of idiopathic interstitial pneumonia [26], indicating that platelets may act as a profibrotic factor in the pathogenesis of pulmonary fibrosis. Additionally, platelets from IPF patients showed higher reactivity than those from non-IPF patients [27]. Overall, the relationship between platelets and SS-ILD is uncertain, and the underlying mechanism warrants further investigation.

To date, although some studies have suggested that a few antibodies may predict pSS-ILD, no consensus exists. AntiRo52 antibody is a promising predictor of ILD for patients with autoimmune disease, particularly myositis, systemic sclerosis and autoimmune liver disease [28–30]; in some studies, the reported positive rates were higher in pSS-ILD patients than in pSS-NILD patients [6,21]. ANA is a potential associated factor with pSS-ILD [12]. Patients with ILD are mostly associated with positive anti-SSB [31]. Davidson et al. [8] reported that pulmonary interstitial disease occurs mainly in anti-SSA-positive pSS patients. However, two other studies based on Chinese populations support that anti-SSA and anti-SSB are not related to lung complications [32,33]. Conversely, Gao et al. [34] showed that the proportion of anti-SSA-positive patients is significantly higher in the pSS-NILD group. The differences between these studies may result from sample composition and size; in our study, no significant difference was found regarding antibodies between the SS-ILD and SS-NILD groups. Currently, it is challenging to reach a unified conclusion. Our data showed that albumin is much lower in both the SS-ILD and pSS-ILD groups, suggesting that the levels of albumin are associated with SS-ILD. This finding is consistent with some studies [35] and may indicate ILD. However, the causality between low albumin and pulmonary complications must be clarified.

HRCT is a practical and excellent method to detect lung abnormalities in ILD. Our series revealed that irregular linear opacities, grid shadows and pleural thickening are the most frequent HRCT manifestations in the SS-ILD group, while honeycombing is the least common pattern. Another study also reported that pSS patients seldom exhibited honeycombing on CT scans [7]. The lesion features of SS-ILD are different from IPF, in which honeycombing is one of the most important CT features [36]. Regarding HRCT patterns, a previous study indicated that NSIP and mixed multiple patterns are the most common patterns in pSS-ILD patients. We further verified that NSIP and mixed multiple patterns are not only the most frequent in pSS-ILD patients but also in sSS-ILD patients [5].

Currently, studies concerning comparisons between ILD in pSS and sSS patients are rare and limited to small sample sizes. A previous study indicated that bronchial hyperresponsiveness is common in both primary and sSS patients, and no difference was found in chest radiographs and lung functions; however, that study involved only 64 patients [37]. Another study enrolling 40 patients revealed that sSS-ILD show more lung abnormalities and worse DLCO than pSS-ILD patients [38]. Our study was conducted using a larger sample size comprising 240 pSS-ILD patients and 76 sSS-ILD patients, and we found that sSS-ILD patients showed worse laboratory findings than pSS-ILD patients, such as more patients with proteinuria, hypercreatinaemia, higher ESR, lower leukocytes and lymphocytes. Additionally, sSS-ILD patients exhibited

more respiratory symptoms and worse DLCO, suggesting that primary autoimmune disease may facilitate the severity of the disease systemically and promote lung impairment.

This study has several limitations. First, this is a retrospective study conducted at a single centre. Second, we focussed on the clinical characteristics and laboratory results of SS patients, and the analysis of treatment and prognosis requires further research. Third, other autoimmune diseases, such as primary biliary cirrhosis, rheumatoid arthritis, systemic lupus erythematosus and mixed connective tissue disease, are also accompanied by ILD, and confirming whether the ILD manifestation of sSS patients is secondary to SS is challenging. Fourth, as SS could be combined with PBC, it is hard to confirm some sSS patients were secondary to this disease. Finally, we enrolled inpatients with SS, and a prospective study including both inpatients and outpatients will be reported in a subsequent study.

In conclusion, ILD is a common pulmonary involvement of SS. Our study suggests that the following parameters can be considered risk factors for ILD: older age, male sex, female sex at menopause, low level of albumin, Raynaud's phenomenon and respiratory symptoms. The most frequent HRCT findings of SS-ILD are irregular linear opacities, grid shadows and pleural thickening. Honeycombing is uncommon, and multiple HRCT findings of ILD can coexist. NSIP and mixed multiple patterns are most common in SS-ILD patients. Importantly, the presence of such factors may suggest a closer follow-up of SS patients.

Ethics statement

The study was approved by the Human Investigations Committee of the Second Xiangya Hospital of Central-South University. Participants have provided with written informed consent.

Disclosure statement

The authors report no declarations of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Hong Peng, upon reasonable request.

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