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Prevalence, risk factors, and prognosis of interstitial lung disease in a large cohort of Chinese primary Sjögren syndrome patients

A case-control study

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Abstract

To determine the prevalence of pulmonary complications in primary Sjögren syndrome (pSS), and to identify the risk factors and the prognosis associated with pulmonary involvement in pSS patients.

A total of 1341 hospitalized patients (853 with pSS and 488 with secondary Sjögren syndrome [sSS]) were retrospectively reviewed. Of these, 165 hospitalized patients with pSS-associated interstitial lung disease (ILD) were analyzed and recruited as a study group. Eighty-four pSS patients without organ damage were included as a control group.

One hundred and sixty-five patients (19.34%) from the pSS group and 126 patients (25.82%) from the sSS group presented with lung involvement. Of the 165 pSS patients with lung complications, 151 (91.5%) were women. The mean age was 61.25 ± 9.79 years, and the median disease duration was 84 (24–156) months. Non-specific interstitial pneumonia (NSIP; 39.1%) was the predominant pattern on high-resolution computed tomography (HRCT). The total HRCT score was 9.71 ± 4.77. Impairment in diffusion capacity was the most common (74.3%) and severe complication (predicted value of T_{LCO} was 57.5 ± 21.2%). The 5-year survival rate for all patients with pSS-ILD was 88.5%. Age, disease duration, rheumatoid factor (RF), and C-reactive protein (CRP) were significantly higher than in controls, whereas anti-SSA was less common. Age, RF, and CRP were independent predictors of ILD after adjustment for confounders.

Lung involvement is a common and severe complication of Sjögren syndrome. Age and disease activity are correlated with pulmonary involvement in pSS patients.

Abbreviations: ACR = American College of Rheumatology, ANA = antinuclear antibodies, C3/C4 = complement 3/4, COP = cryptogenic organizing pneumonia, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FEF = forced expiratory flow, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HRCT = high-resolution computed tomography, IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, ILD = interstitial lung disease, LIP = lymphocytic interstitial pneumonia, NSIP = non-specific interstitial pneumonia, PEF = peak expiratory flow, PFT = pulmonary function test, pSS = primary Sjögren syndrome, RA = rheumatoid arthritis, RBILD = respiratory bronchiolitis interstitial lung disease, RF = rheumatoid factor, RV = residual volume, SD = standard deviation, sSS = secondary Sjögren syndrome, TLC = total lung capacity, T_{LCO} = transfer factor for carbon monoxide, UIP = usual interstitial pneumonia.

Keywords: high-resolution computed tomography, primary Sjögren syndrome, pulmonary involvement, risk factor, survival rate

1. Introduction

Primary Sjögren syndrome (pSS) is a chronic systemic autoimmune disease.[1] The lung is a common target for pSS because of abundant vasculature and connective tissue. The reported frequency of pulmonary involvement in pSS varies widely, ranging from 8.0% to 79.2%.[2–10]

While sicca features associated with pSS are primarily related to quality of life and local complications in the involved mucosa, systemic involvement defines disease prognosis.[1] Ito et al[11] and Enomoto et al[12] reported 5-year survival rates of 83.0% and 87.3%, respectively, in pSS complicated by interstitial lung disease (ILD). Other studies have shown mortality rates from 7.1% to 39% during the 2- to 8-year follow-up periods.[2,9,13–15] This indicates that early detection is crucial for improving pulmonary function and quality of life in pSS patients.

Information regarding risk factors is limited in the published literature regarding the pulmonary manifestations of pSS.[2,4] Moreover, the majority of studies are small case-control studies, often including control patients with non-pulmonary systemic

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involvement that may bias results. Therefore, the risk factors for pulmonary involvement in pSS require further exploration.

Despite growing evidence regarding the prevalence of ILD in pSS, many previous studies have been limited by small populations, with reported prevalence varying considerably. In addition, information regarding prognosis and risk factors is limited. To explore these questions, we evaluated the prevalence of pulmonary complications in a large cohort of Chinese pSS patients and identified the risk factors and prognosis associated with pulmonary involvement in pSS.

2. Methods

2.1. Patients

A total of 1341 hospitalized patients (853 with pSS and 488 with secondary Sjögren syndrome [sSS]) admitted to Peking University People's Hospital from January 2003 to March 2012 was retrospectively reviewed. All patients fulfilled the American-European Consensus Group (AECG) 2002 revised classification criteria for pSS and sSS. The study was approved by the Research Ethics Committee at the Peking University People's Hospital (ethics approval number: 2014PHB087-04).

Diagnosis of pSS-ILD was made according to high-resolution computed tomography (HRCT) abnormalities and/or impaired pulmonary function tests (PFT), with or without pulmonary signs and/or symptoms. Patients with lung damage unrelated to pSS were excluded, including those with asthma, chronic obstructive pulmonary disease, and other chronic diseases of the lung. All pSS patients with lung complications were enrolled as a study group, and 84 selected pSS patients without any organ damage were recruited as a control group.

2.2. Study design

Medical records of pSS patients were retrospectively reviewed. General data, laboratory, and clinical information at onset were collected, including first presentation, time and sign/symptom suggesting SS and ILD. The levels of immunoglobulins (immunoglobulin G [IgG], immunoglobulin M [IgM], and immunoglobulin A [IgA]), complement (C3 and C4), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-SSA, and anti-SSB were retrieved from the case files. Anti-SSA was detected by dot immunoblot for qualitative results (165 patients) and enzyme-linked immunosorbent assay (ELISA) for quantitative results (36 patients).

HRCT scans were re-evaluated by 2 experienced chest radiologists (LC and SZ). HRCT abnormalities and patterns were categorized according to the 2013 international multidisciplinary classification of idiopathic interstitial pneumonias.[16] Grades were defined as: grade 0 = normal; grade 1 $\leq$25% of the lobe involved; grade 2 = 26% to 50% of the lobe involved; and grade 3 >50% of the lobe involved. The lingula was counted as a separate lobe, and each of the 6 lobes was assessed based on the percentage of affected lung parenchyma. The total HRCT score was obtained by adding grades for each lobe, with a possible range of 0 to 18.

The following PFT data were obtained from patient charts: total lung capacity (TLC); forced expiratory volume in 1 second (FEV_1); forced vital capacity (FVC); residual volume (RV), peak expiratory flow (PEF); forced expiratory flow ($FEF_{25/50/75}$); and transfer factor for carbon monoxide (T_{LCO}).

Overall survival was estimated using the Kaplan–Meier method. Survival time was calculated as the number of years from diagnosis of pSS-ILD to death or censoring. Patients were censored if they were alive on December 1st, 2017, or had died prior to this date due to a cause unrelated to the disease.

A case-control study was performed to explore potential risk factors for lung involvement in pSS patients. Patients with lung complications (n = 165) were recruited as a study group, and pSS patients without organ damage (n = 84) were enrolled as a control group. General data, lab, and clinical information were compared between groups. Multiple logistic regression analysis was performed to identify independent risk factors for lung complications in pSS patients.

2.3. Statistical analysis

Data are presented as mean ± SD, median and interquartile range, or percentage frequencies, as appropriate. Overall survival was estimated using the Kaplan–Meier method. Intergroup comparisons were made using the *t* test/Mann–Whitney *U* test for continuous variables and chi-square analysis for categorical variables. Multiple logistic regression analysis was performed with lung involvement as the dependent variable, with all other significant variables from the case-control study included as independent variables. All calculations were made using a standard statistical package (SPSS for Windows, version 16.0, SPSS Inc., Chicago, IL). *P*-values <.05 (2-tailed) were considered significant.

3. Results

3.1. Prevalence of ILD in pSS

Of the 1341 Sjögren syndrome patients, 853 were diagnosed with pSS and 488 with sSS. Pulmonary involvement rates were 19.34% (165/853) and 25.82% (126/488) for pSS and sSS patients, respectively. Among the 165 pSS patients with lung involvement, 151 (91.5%) were women and 14 (8.5%) were men. The mean age was 61.25 ± 9.79 years. The median disease duration was 84 (24–156) months.

3.2. HRCT findings and pulmonary function

Of the 165 pSS patients with lung involvement, 69 patients underwent HRCT. Non-specific interstitial pneumonia (NSIP) was the predominant HRCT pattern (n = 27, 39.1%, Table 1). Chest HRCT findings revealed a lymphocytic interstitial pneumonia (LIP) pattern in 12 patients (17.4%), a NSIP + LIP pattern in 4 (5.8%), and a usual interstitial pneumonia (UIP) pattern in 11 (15.9%). The rest of the findings were as follows: 1 (1.4%) cryptogenic organizing pneumonia (COP), 1 (1.4%)

Table 1

High-resolution computed tomography patterns of primary Sjögren syndrome (pSS)-associated lung involvement.

HRCT pattern (n = 69)	No. of cases (%)
Nonspecific interstitial pneumonia (NSIP)	27 (39.1%)
Lymphocytic interstitial pneumonia (LIP)	12 (17.4%)
NSIP+LIP	4 (5.8%)
Usual interstitial pneumonia (UIP)	11 (15.9%)
Cryptogenic organizing pneumonia (COP)	1 (1.4%)
Respiratory bronchiolitis-interstitial lung disease (RBILD)	1 (1.4%)
Indeterminate	13 (18.8%)

Of the 165 pSS patients with lung involvement, 69 patients underwent HRCT. HRCT = high-resolution computed tomography.

Table 2

Pulmonary function characteristics of primary Sjögren syndrome-associated lung involvement.

Variables	Result (%)
TLC of predicted value	92.1 ± 21.0
TLCO of predicted value	**57.5 ± 21.2**
FEV_1 of predicted value	95.2 ± 27.6
FVC of predicted value	95.1 ± 27.8
FEV_1/FVC	81.4 ± 5.8
RV of predicted value	97.4 ± 25.1
PEF of predicted value	100.7 ± 27.9
FEF_{25} of predicted value	100.7 ± 31.2
FEF_{50} of predicted value	83.0 (52.2–112.8)
FEF_{75} of predicted value	66.4 (45.1–102.8)

FEF = forced expiratory flow, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, PEF = peak expiratory flow, RV = residual volume, TLC = total lung capacity, TLCO = transfer factor of carbon monoxide.

respiratory bronchiolitis-interstitial lung disease (RBILD), and 13 indeterminates. The total HRCT score was 9.71 ± 4.77. Details regarding HRCT analysis are provided in the online supplement (see Table 1 and 2, Supplemental Content, http://links.lww.com/MD/C275, which illustrates the analysis of each lung lobe). The most frequent HRCT findings were linear opacities (94.2%), ground-glass attenuation (87.0%), reticular pattern (65.2%), and pleural involvement (65.2%), which is consistent with previous studies (see Table 3, Supplemental Content, http://links.lww.com/MD/C275, which illustrates the HRCT abnormality types of pSS-associated lung involvement patients).

Among the 165 patients with lung complications, 72 had PFTs recorded (Table 2). Impairment in diffusion capacity was the most common manifestation of pulmonary involvement (74.3%) and the most severe complication. The predicted value of T_{LCO} was 57.52 ± 21.23%. Moreover, it was shown that 48.6% of the patients had impaired ventilatory function, 21.57% had a restrictive disease pattern, and 19.61% demonstrated small airway dysfunction. Impaired RV (25%) and airway resistance (8.2%) were uncommon in this population. Negative correlations were found between the total HRCT score and the predicted values of TLC, FVC, FEV_1, and T_{LCO} ($P < .05$).

3.3. Prognosis analysis

The Kaplan–Meier survival curve for all patients is shown in Fig. 1. The 5-year survival rate for all patients with pSS-ILD was 88.5%. Thirty-five (21.2%) of 165 patients died during the follow-up period. Causes of death were as follows: respiratory failure (n = 27), progression of malignant disease (n = 5), gastrointestinal bleeding (n = 1), viral meningoencephalitis (n = 1), and cerebral hemorrhage (n = 1).

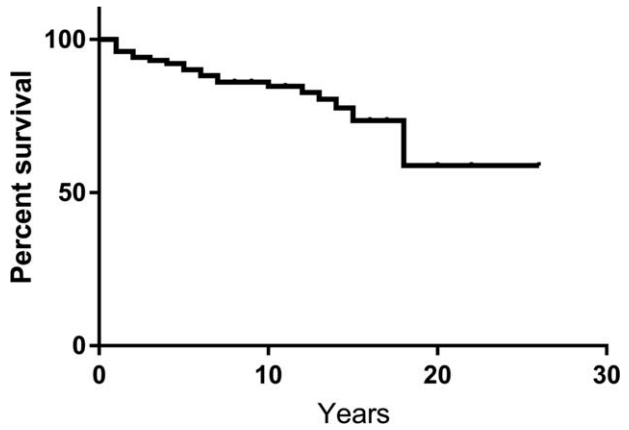

Figure 1.

Table 3

Clinical and immunologic parameters.

Variables	Case (n = 165)	Control (n = 84)	*P*-value
Sex (female, %)	151 (91.50)	81 (96.40)	.15
Age, yr	61.25 ± 9.93	49.25 ± 10.60	**<.001**
Disease duration, m	84.00 (24.00–156.00)	54.00 (24.00–120.00)	**.036**
IgG, g/L	17.90 (14.00–25.30)	19.90 (13.92–25.05)	.70
IgA, g/L	3.21 (2.26–4.70)	3.28 (2.50–4.84)	.70
IgM, g/L	1.19 (0.75–2.12)	1.22 (0.79–1.66)	.91
C3, g/L	0.86 ± 0.21	0.91 ± 0.29	.23
C4, g/L	0.18 (0.12–0.24)	0.19 (0.15–0.25)	.12
RF, IU/mL	39.85 (20.00–197.75)	20.00 (0.00–85.00)	**<.001**
CRP, mg/L	2.82 (1.00–9.58)	1.12 (0.00–15.70)	**.036**
ESR, mm	46.00 (17.00–76.00)	34.00 (14.00–58.00)	.19
ANA (%)	86 (52.1)	50 (59.5)	.27
Anti-SSA (%)	82 (49.7)	57 (67.8)	**.006**
Anti-SSA, RU/mL	130.69 (2.00–173.54)	141.86 (7.43–184.28)	.62
Anti-SSB (%)	58 (35.2)	30 (35.7)	.93

Data are expressed as mean ± SD, median (interquartile range), or as percentage frequencies, as appropriate. Significant differences between the groups are indicated in bold. ANA = antinuclear antibody, C3 = complement 3, C4 = complement 4, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, RF = rheumatoid factor.

3.4. Risk factors for ILD in pSS patients

A case-control study was performed to explore potential risk factors for lung involvement in pSS patients. The main demographic, clinical, and biochemical data from the case-control study are listed in Table 3.

The study and control groups were similar with respect to the distribution of sex; however, the mean age and disease duration were found to be higher in patients with lung involvement ($P < .001$ and .036, respectively). In addition, RF and CRP were significantly higher in the study group ($P < .001$ and .036, respectively), whereas the anti-SSA positive rate was less common ($P = .011$). Among them, the quantitative results for anti-SSA in only 19 patients in the study group and 17 in the control group were evaluated. Patients in the study group were noted to have lower levels of anti-SSA than those in the control group; however, this trend did not reach statistical significance. ESR was higher, and levels of C3 and C4 were lower in the study group. No differences were noted with respect to IgG, IgM, IgA, ANA, and anti-SSB. Multiple logistic regression analysis was used to examine predictors of pulmonary involvement, with age, RF, and CRP identified as independent correlates after adjusting for all other significant associations (Table 4).

4. Discussion

Sjögren syndrome, a chronic inflammatory autoimmune disorder, is known to present with a wide spectrum of bronchopulmonary manifestations.[17–20] The reported frequency of lung involvement in pSS varies widely, ranging from 8.0% to 79.2%.[2–9] Screening for pulmonary involvement in Sjögren syndrome remains a topic of debate. Conventional chest radiography may delay early treatment due to low sensitivity.[21] Although pathology has a higher sensitivity, it remains

Table 4

Independent risk factors for lung involvement in primary Sjögren syndrome patients.

Variables	β	SE	*P*-value	OR	95% CI
Age	−0.150	0.026	<.001	0.860	0.817–0.906
RF	−0.002	0.001	.076	0.998	0.997–1.000
CRP	0.020	0.007	.005	1.020	1.006–1.034

CI = confidence interval, CRP = C-reactive protein, OR = odds ratio, RF = rheumatoid factor.

impractical to perform a screening test, given the invasive sampling required.[6] HRCT has been shown to be well-associated with pathology, and reflects pathological findings in patients with rheumatoid arthritis (RA) and pSS.[11,22] In this study, PFT results were consistent with the HRCT-based diagnosis. Additionally, the predicted values of TLC, FVC, FEV_1, and T_{LCO} were negatively correlated with the total HRCT score. Thus, we used HRCT and PFTs to detect pulmonary involvement in pSS. The results showed that the prevalence of lung involvement was 19.34%, which is comparable with a meta-analysis based on 4897 pSS patients (16%).[1]

Previous findings have indicated that pulmonary involvement is both common and severe in patients with pSS. The predicted value of T_{LCO} in this study was $57.5 \pm 21.2\%$. In addition, 55.56% (20/36) of patients were hypoxic, and 19.44% (7/36) presented with type 1 respiratory failure (data not shown). A previous multivariate analysis on 33 pSS patients with lung complications found that low PaO_2 was independently associated with survival, with a 5-year survival rate of 84%.[11] Another study identified $PaCO_2$, reticular abnormalities on HRCT, and fibroblastic foci on pathology as prognostic factors in pSS-ILD, with a 5-year survival rate of 87.3%.[12] Other studies have shown mortality rates from 7.1% to 39% for follow-up durations of 2 to 8 years.[2,9,13–15] The 5-year survival rate in this study was 88.5%. To our knowledge, this study is the first to evaluate mortality associated with pSS-ILD in a large Chinese cohort.

Early detection and treatment of lung involvement may improve pulmonary function and overall quality of life in pSS patients. A recent study noted a significant improvement in FVC in patients treated with an azathioprine-based regimen, when compared with untreated patients.[23] Moreover, Shi et al[14] reported that corticosteroid therapy combined with oral cyclophosphamide produces a favorable response in the majority of pSS patients with lung involvement.

However, information regarding the risk factors for lung involvement in pSS is limited in the published literature.[2,4] Furthermore, previous studies have been largely small pilot studies, and have included patients in the control group with non-pulmonary systemic damage, which may bias results. In this study, we recruited pSS patients without any organ damage as a control group, and found that age, disease duration, CRP, RF, and an anti-SSA negative status were risk factors for lung involvement.

O'Neill and Scully[24] have reported that age at pSS diagnosis plays a significant role in the clinical expression of disease, with an age at diagnosis >70 years noted to be an independent risk factor for lung involvement. Furthermore, they found that patients with a disease duration >10 years had a higher prevalence of lung complications.[24] In this study, we found that lung involvement was frequently observed in older patients and those with a longer duration of disease. Multiple logistic regression analysis confirmed age as an independent correlate after adjusting for other demographic and laboratory factors. This suggests that, in particular, elderly patients with pSS should be evaluated for lung involvement.

Risk factors for lung involvement in RA are well defined. It has been reported that the presence of a high RF titer is associated with lung complications in RA.[25–27] In this study, we also found that the RF titer was higher in the pSS group with lung involvement, and observed similar trends with respect to CRP and ESR. High titers of inflammatory and disease-specific markers in the study group may reflect activation of the immune response, and play an important role in systemic damage, including lung complications.

The role of anti-SSA in pulmonary complications of pSS remains controversial.[4,28–30] Davidson et al[28] and Yazisiz et al[4] have previously shown that pulmonary disease occurs predominantly in anti-SSA antibody positive pSS patients. However, both of these reports were based on small pilot studies. Another 2 studies in Chinese populations suggested that anti-SSA and SSB were not related with lung complications. Yan et al[30] found that anti-SSA and SSB positivity rates in pSS patients with lung involvement were 82.8% and 39.8%, respectively, whereas those in pSS patients without lung involvement were 83.4% and 39.9% ($P = .85$ and .99, $n = 522$). Similarly, An et al[29] demonstrated anti-SSA and SSB positivity rates of 68.2% and 31.8%, respectively, in pSS patients with lung involvement, and 67.6% and 36.1% in pSS patients without lung involvement ($P = .96$ and .70, $n = 130$). Nonetheless, patients from the control group in both such reports may have had other non-pulmonary systemic damage that could be a source of bias for these studies.

Studies using the general population as their control group would be able to obtain the risk factors for pSS. However, we would like to analyze why some pSS patients were prone to ILD compared with those with sicca symptoms only. Previous similar studies included pSS patients without ILD as a control group, not excluding those with other organ damages, such as abnormal hematologic findings and liver damage. We suspected that the control group with other systemic abnormalities would bring bias. In the current study, we performed a case-control study in a relatively large cohort of 249 patients, including 165 pSS patients with lung disease and 84 control patients without any systemic damage. This design should limit the bias introduced by systemic damage in other organ systems. Indeed, we recruited 40 patients with abnormal hematologic findings and liver damage (data not shown). A total of 20 patients (50%) was anti-SSA positive. Among them, 4 patients were tested to obtain a quantitative result for anti-SSA levels, which was 73.36 (3.14–173.02) RU/mL. This was comparable to pSS patients with lung complications ($P = .96$), which may indicate that previous studies including patients with systemic damage in the control group are less reliable. The exact role of anti-SSA in lung involvement in pSS should be further confirmed in future studies.

Our study as an observational study based on the Chinese population has several limitations. Firstly, although most of the patients suspected as pSS would be admitted in our department to

confirm their diagnosis, evaluate systemic involvement and disease activity, and make treatment strategy, we cannot assure that all pSS patients have been enrolled since clinic patients were not included in this study. Secondly, patients without HRCT stored in our hospital (including both HRCT of other hospitals and only chest x-ray of our hospital) cannot be analyzed to evaluate their HRCT score and patterns. Thirdly, this is a single center study. Fourthly, our study has a retrospective design, thereby, the causative relationship cannot be determined. In conclusion, lung involvement is a common and severe complication for pSS patients. Age and disease activity (RF and CRP) are risk factors for pulmonary complications in pSS patients. However, the pathogenesis of lung involvement in pSS is complex. It is necessary to clarify the causative relationship between those risk factors and pSS associated lung complication in a large multicenter prospective study.

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