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Characteristics and mortality in primary Sjögren syndrome–related interstitial lung disease

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Abstract

Aim of the study was to determine the characteristics and prognosis, and to identify the risk factors for mortality in patients with primary Sjögren syndrome (pSS) with interstitial lung disease (pSS-ILD).

A total of 1422 patients with SS were screened and 178 patients with pSS-ILD were recruited. The medical records and outcomes were retrospectively reviewed. Overall survival and case control study were performed to explore the predictors of death.

Among 178 pSS-ILD patients, 87.1% were women. Mean age was 61.59 ± 11.69-year-old. Median disease duration was 72.0 (24.0, 156.0) months. Nonspecific interstitial pneumonia was the predominant high-resolution computed tomography pattern (44.9%). Impairment in diffusion capacity was the most common abnormality of pulmonary function test (75.8%) and the most severe consequence. Type 1 respiratory failure and hypoxia were observed in 15.0% and 30.0% patients, respectively. Mean survival time after confirmation of pSS-ILD diagnosis was 9.0 (6.8, 13.0) years. The 10-year survival rate for all patients with pSS-ILD was 81.7%. Forty-four (24.7%) of 178 patients died during the follow-up period. The most predominant cause of death was respiratory failure (n = 27). Twenty-seven patients died of ILD and formed study group. The 78 patients who survived formed control group. Age and smoking were risk factors for mortality in patients with pSS-ILD. In addition, severity of ILD, as reflected by high-resolution computed tomography, pulmonary function test, and arterial blood gas, was an independent risk factor. However, inflammation status (erythrocyte sedimentation rate, C-reactive protein) and anti-Sjögren syndrome–related antigen A and anti-Sjögren syndrome–related antigen B were not.

ILD is a severe complication of pSS. Age, smoking, and severity of lung involvement are more critical for prognosis rather than inflammation status and autoantibodies.

Abbreviations: ABG = arterial blood gas, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FEV_1 = forced expiratory volume in 1 s, FVC, forced vital capacity, HRCT = high-resolution computed tomography, ILD = interstitial lung disease, NSIP = nonspecific interstitial pneumonia, PFT = pulmonary function test, pSS = primary Sjögren syndrome, RF = rheumatoid factor, RV = residual volume, SSA = Sjögren syndrome–related antigen A, SSB = Sjögren syndrome–related antigen B, TLCO/VA = transfer factor of carbon monoxide/alveolar volume, UIP = usual interstitial pneumonia.

Keywords: characteristic, interstitial lung disease, mortality, primary Sjögren syndrome

1. Introduction

Primary Sjögren syndrome (pSS), a chronic inflammatory autoimmune disorder, is known to present with a wide spectrum of bronchopulmonary manifestations.[1–4] The reported frequency of pulmonary involvement in pSS varies widely, ranging from 8.0% to 79.2%.[5–14]

While sicca features associated with pSS are primarily related to the quality of life and local complications in the involved mucosa, systemic involvement defines the disease prognosis.[15] Although pSS with interstitial lung disease (pSS-ILD) is generally considered mild and not aggressive, the reported mortality rates were between 7.1% and 39% for follow-up durations of 2 to 8 years.[5,12,16–18] Thus it is required to identify predictors of poor outcomes. However, only a few investigators have evaluated the outcome of ILD in patients with pSS, and these studies were based on small series (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G318).[5,17,18] Despite growing evidence regarding the prevalence and risk factors of ILD in pSS,[1–12,16–23] the exact risk factors for mortality in this subgroup have not been fully elucidated.

Based on our previous studies on pSS-ILD,[14,21] we identified the risk factors for mortality in patients with pSS-ILD in a large cohort of Chinese patients with pSS. To our knowledge, this

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HG, YS, and XYZ contributed equally.

The authors report no conflicts of interest.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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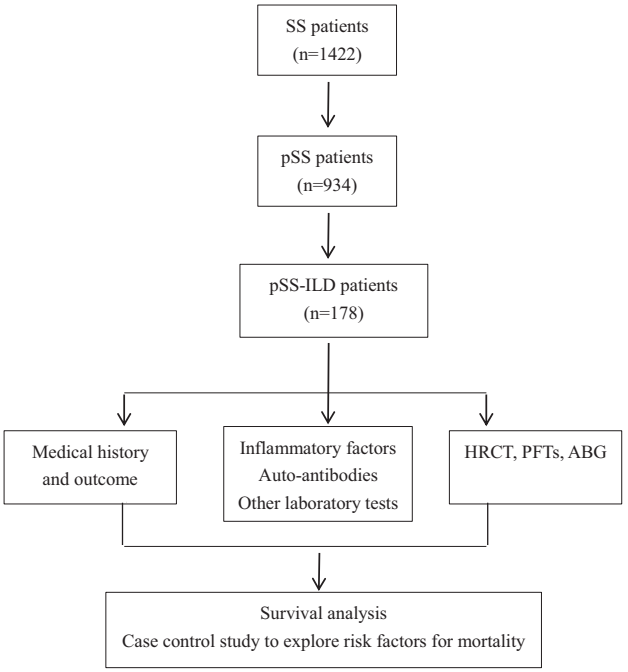

Figure 1. Design of this study. ABG = arterial blood gas analysis, HRCT = high-resolution computed tomography, ILD = interstitial lung disease, PFT = pulmonary function test, pSS = primary Sjögren syndrome, SS = Sjögren syndrome.

study is the first to evaluate mortality associated with pSS-ILD in a large Chinese cohort. A total of 1422 patients with SS were screened and 178 pSS patients with ILD were recruited. The medical history, inflammation factors, autoantibodies, high-resolution computed tomography (HRCT), pulmonary function tests (PFTs), arterial blood gas (ABG) analysis, and the outcomes were reviewed. Overall survival and case control study were performed to explore the predictors of death.

2. Methods

2.1. Patients

As shown in Figure 1, a total of 1422 patients with SS admitted to Peking University People's Hospital from January 2000 to March 2012 were screened. Among them, 934 patients with pSS fulfilled the American-European Consensus Group 2002 revised classification criteria for pSS. A diagnosis of pSS-ILD was made according to HRCT abnormalities, with or without pulmonary signs and/or symptoms. Patients with lung damage unrelated to pSS-ILD were excluded, including those with asthma, chronic obstructive pulmonary disease, and other chronic diseases of the lung. A total of 178 patients with pSS-ILD were enrolled in this study.

The study was approved by the Research Ethics Committee at the Peking University People's Hospital (ethics approval number: 2014PHB087-04). The requirement for informed consent was waived because of the retrospective nature of the research.

2.2. Study design

The medical records of patients with pSS were retrospectively reviewed. General data and data from laboratory and ABG analyses were collected. The levels of immunoglobulins (IgG, IgM, and IgA), complement (C3 and C4), C-reactive protein (CRP), and rheumatoid factor (RF), the erythrocyte sedimentation rate (ESR), as well as data on the presence of antinuclear (ANA), anti-Sjögren syndrome–related antigen A (anti-SSA), and anti-Sjögren syndrome–related antigen B (anti-SSB) antibodies were retrieved from case files.

HRCT scans were re-evaluated by an experienced chest radiologist (Dr. Ye Sun). HRCT abnormalities and patterns were categorized according to the 2013 international multidisciplinary classification of idiopathic interstitial pneumonias.[24] Grades were defined as grade 0 = normal, grade 1 = ≤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 were assessed on the basis of 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.[7,16]

The following PFT data were obtained from patient charts: total lung capacity, forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), residual volume (RV), peak expiratory flow, forced expiratory flow ($FEF_{25/50/75}$), and transfer factor of carbon monoxide/alveolar volume (TLCO/VA).

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 1, 2017 or had died before this date from a cause unrelated to the disease.

A case-control study was performed to explore the potential risk factors for mortality in patients with pSS-ILD. Twenty-seven patients who died of ILD and 78 survivors were recruited as the study group (expired group) and control group (survived group), respectively. General data, laboratory findings, and HRCT, PFT, and ABG results were compared between groups. Multiple logistic regression analysis was performed to identify independent risk factors for mortality in patients with pSS-ILD.

2.3. Statistical analysis

Data are presented as mean ± SD, median and interquartile range, or number and percentage, as appropriate. Overall survival was estimated using the Kaplan-Meier method. Intergroup comparisons were made using the Student *t* test/Mann-Whitney test for continuous variables and chi-square analysis for categorical variables. Multiple logistic regression analysis was performed with ILD-related death as a dependent variable and all other significant variables from the case-control study as independent variables. All calculations were performed 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

Among the 178 patients with pSS with lung involvement, 155 (87.1%) were women. The mean age was 61.59 ± 11.69 years. The median disease duration was 72.0 (24.0, 156.0) months. Mean survival time after confirmation of pSS-ILD diagnosis was 9.0 (range: 6.8–13.0) years.

3.1. Pulmonary impairment in primary Sjögren syndrome-interstitial lung disease

Of the 178 patients with pSS-ILD, 127 patients underwent HRCT at our hospital. Nonspecific interstitial pneumonia (NSIP)

was the predominant HRCT pattern (n=57, 44.9%). Chest HRCT findings revealed a lymphocytic interstitial pneumonia pattern in 26 patients (20.5%) and a usual interstitial pneumonia (UIP) pattern in 19 patients (15.0%). The rest of the findings were as follows: 5 (3.9%) cases of organizing pneumonia, 2 (1.6%) cases of respiratory bronchiolitis-interstitial lung disease, 1 (0.8%) case of desquamative interstitial pneumonitis, 4 (3.1%) cases of NSIP + lymphocytic interstitial pneumonia pattern, and 13 indeterminates (Fig. 2). The mean total HRCT score was 8.0 (5.0, 13.0).

A total of 91 patients with pSS-ILD underwent PFT. Impairment in diffusion capacity was the most common manifestation of pulmonary involvement (69/91, 75.8%) and the most severe consequence (Table S2, Supplemental Digital Content, http://links.lww.com/MD/G319). A total of 80 pSS-ILD patients underwent ABG. Among them, 41 (51.2%) patients had normal ABG results. ABG indicated type 1 respiratory failure in 12 (15.0%) patients, type 2 respiratory failure in 3 (3.8%) patients, and hypoxia in 24 (30.0%) patients.

3.2. Prognosis analysis

The 10-year survival rate for all patients with pSS-ILD was 81.7%. Forty-four (24.7%) of 178 patients died during the follow-up period. Causes of death were as follows: respiratory failure (n=27), progression of malignant disease (n=7), gastrointestinal bleeding (n=2), pulmonary embolism (n=1), viral meningoencephalitis (n=1), cerebral hemorrhage (n=1), and nondetermined cause (n=5). The Kaplan-Meier survival curve for all patients is shown in Figure 3.

Apart from 44 of 178 patients who died during the follow-up period, 56 were lost to follow-up and 78 survived. Twenty-seven patients died of ILD and formed a study group (expired group). The 78 patients who survived formed a control group (survived group). This enabled us to explore potential risk factors for mortality in patients with pSS-ILD (Table S3, Supplemental Digital Content, http://links.lww.com/MD/G320).

The study and control groups were similar with respect to immunoglobulins (IgG, IgM, and IgA), complement (C3 and C4), autoantibodies (RF, ANA, anti-SSA, and anti-SSB), as well as ESR and CRP. Mean age was higher in the study group (69.0±9.5 vs 57.3±11.3 years, $P=.000$), whereas disease duration was shorter (60.0 [12.0, 120.0] vs 114.0 [36.0, 171.0] months, $P=.040$) in the study group. There was a higher rate of men and a higher rate of smokers in the study group (29.6% vs 11.5%, $P=.028$ and 28% vs 8%, $P=.010$, respectively). Interestingly, incidences on family history of cancer was higher (14.8% vs 9.0%, $P=.393$), whereas, family history of autoimmune disease was lower in the study group (0.0% vs 6.4%, $P=.178$). More importantly, total HRCT scores were higher (11.43±4.94 vs 7.36±4.62, $P=.001$) in the study group, whereas TLCO/VA, FEV_1, FVC, and MEF_{25} were lower (Table S3, Supplemental Digital Content, http://links.lww.com/MD/G320). In addition, PaO_2 was significantly lower in the study group (72.6±17.9 vs 90.8±29.1, $P=.034$). These results demonstrated that lung involvement was more severe in the study group. Multivariate analysis showed that smoking, TLCO/VA, MEF_{25}, and PaO_2 were independent risk factors for mortality in patients with pSS-ILD (Table 1).

4. Discussion

A total of 1422 patients with SS were screened in this study and 178 patients with pSS-ILD were recruited to explore the prognosis. The 10-year survival rate for all patients with pSS-ILD was 81.7%. Forty-four (24.7%) of the 178 patients died during the follow-up period. Main cause of death was respiratory failure (n=27). Smoking and severity of lung involvement (as reflected by HRCT, PFT, and ABG) were independent risk factors, whereas inflammation status (such as ESR, CRP) and autoantibodies (including anti-SSA and anti-SSB) were not. ILD is a severe complication of pSS. Age, smoking, and severity of lung involvement are more critical for prognosis rather than inflammation status and autoantibodies.

Among studies of idiopathic interstitial pneumonias, several report associations between mortality and baseline physiologic tests[30–32] pathologic findings,[30,33–36] and, more recently, serial PFTs.[37,38] One 10-year follow-up study of 30 British patients with pSS published by Davidson et al[29] found that most patients had stable pulmonary function. Recent studies from different countries have, however, all suggested that prognosis of pulmonary involvement is not favorable in patients with pSS. Roca et al[5] highlighted that ILD is correlated with a decrease in functional status in pSS patients. They found that no pSS patient with ILD had resolution of their pulmonary status. On the contrary, 36.8% of pSS patients with ILD experienced a marked reduction in activities because of ILD deterioration, leading to respiratory failure and O_2 dependency in 11% of cases. Parambil et al[18] and Shi et al[17] reported resolution in 0% to 14%, improvement in 56% to 57%, stabilization in 16% to 21%, and worsening in 7% to 28% of cases in which ILD was followed-up. Palm et al[12] found pSS patients with lung involvement had reduced quality of life, represented by the Physical Functioning subscale, and a 4-fold increased mortality risk after 10 years of disease. So far, previous studies have reported mortality rates in pSS-ILD subgroups of between 7.1% and 39% for follow-up durations of 2 to 8 years.[5,12,16–18] The 10-year survival rate for all patients with pSS-ILD in this study was 81.7%, which is consistent with the findings of previous studies. Thus, it is required to identify predictors of poor outcomes, which could help physicians to improve outcome of this subgroup.

Need for clinicians to evaluate and monitor lung involvement has been emphasized, especially for those patients lacking pulmonary manifestations.[39] However, information regarding risk factors for mortality is limited in the published literature. In this study, age remained a risk factor for mortality, although this association disappeared on multivariate analysis. Interestingly, previous studies revealed a similar finding. Roca et al[5] found that ILD deterioration was more commonly encountered in a group of patients with pSS who were older at ILD diagnosis. Ito et al[19] also found that age was a risk for death (HR 1.095, 5% confidence interval 0.001–0.779, $P=.036$). In addition, age was found to be risk factors for pSS-ILD in our previous study.[14] Thus, we emphasized that elder pSS-ILD patients should be closely monitored during the follow up.

Environmental exposure and geographical factors might play important role in many diseases.[40,41] Interestingly, incidences on family history of cancer was higher, whereas, family history of autoimmune disease was lower in the study group, although both without significant difference. However, both groups were similar with respect to immunoglobulins (IgG, IgM, and IgA), complement (C3 and C4), autoantibodies (RF, ANA, anti-SSA, and anti-SSB), as well as ESR and CRP. Ito et al's[19] study showed similar results, supporting sex and smoking history were also risk factors for death, but not inflammatory factors, such as ESR and CRP. Although Roca et al[5] found no correlation

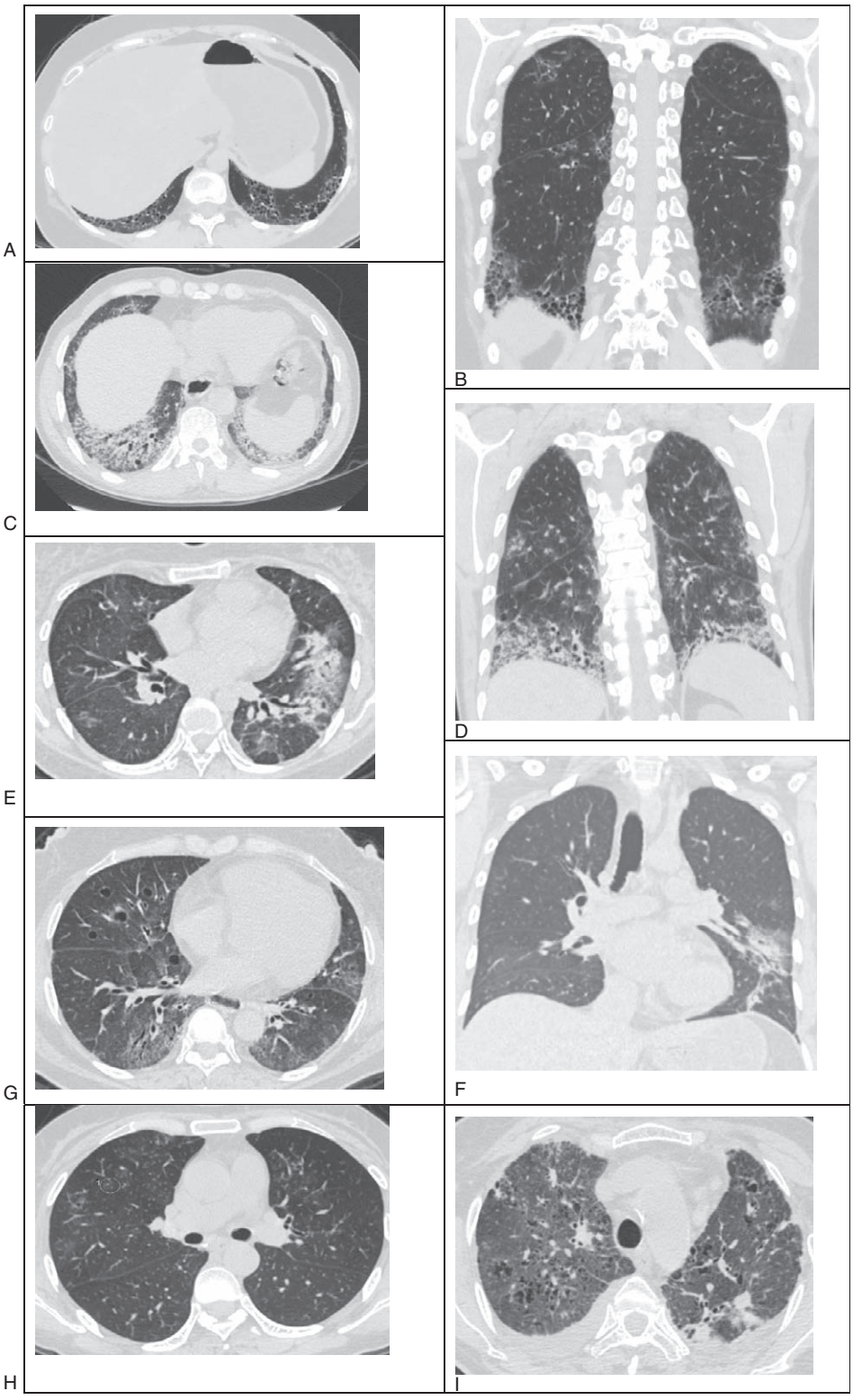

Figure 2. Sjögren syndrome–associated interstitial lung disease (SS-ILD) high-resolution computed tomography (HRCT) patterns. Usual interstitial pneumonia (UIP): (A) axial and (B) coronal CT reconstructions of the chest show fine reticular opacities with honeycombing in the lower lobes, predominantly peripheral and basal patterns of distribution. Nonspecific interstitial pneumonia (NSIP): Axial CT scan of the chest (C) and coronal reformatting (D). Ground-glass opacities with traction bronchiectasis and lower lobe volume loss. Discrete subpleural preservation. Predominantly basal and symmetric patterns of distribution. Cryptogenic organizing pneumonia (COP): axial CT image (E) and coronal formatting (F). Consolidation and ground-glass opacities in left lung. Predominantly subpleural and peribronchial patterns of distribution. Lymphocytic interstitial pneumonia (LIP): CT axial image (G) shows some ground-glass opacities and thin-walled cysts of varying sizes with a diffuse, bilateral distribution. Respiratory bronchiolitis interstitial lung disease (RB-ILD): CT axial image (H) shows mildly extensive ground-glass opacities and centrilobular nodules (in the circle). Desquamative interstitial pneumonia (DIP): CT axial image (I) shows linear reticular opacities with sparse bilateral ground-glass opacity, predominantly distributed peripherally%.

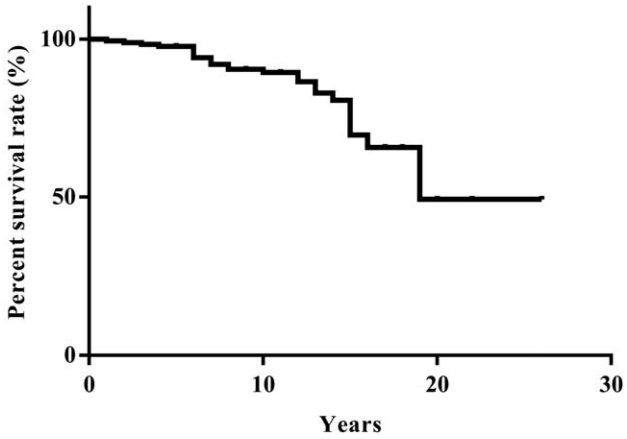

Figure 3. Survival of all patients (n = 178) with primary Sjögren syndrome–associated interstitial lung disease (pSS-ILD). The 10-year survival rate was 81.7%.

between ILD deterioration and sex, interestingly, they also found no correlation between ILD deterioration and other extrapulmonary manifestations, the presence of anti-SSA antibodies or anti-SSB antibodies, or cryoglobulin. According to these studies, inflammation (CRP and ESR) and autoantibodies (anti-SSA and SSB) were not predictors for death, but history of smoking. The role of family history remains to be explored further in a large multicenter study.

Although there were controversial at some points among those studies (such as sex mentioned above), the severity of ILD had been agreed to be the main cause of death. In this study, total HRCT scores were higher in the study group, while TLCO/VA, FEV_1, FVC, and MEF_{25} were lower (Table S3, Supplemental Digital Content, http://links.lww.com/MD/G320). In addition, PaO_2 was significantly lower in the study group. These results demonstrated that lung involvement was more severe in the study group, which was supported by other research as well. Ito et al[19] found that predicted FVC%, TLCO/RV, PaO_2, and the presence of microscopic honeycombing were found to be risk factors in their univariate analysis. Enomoto et al[20] identified 3 clinical radiologic-pathologic prognostic factors in pSS-ILD-$PaCO_2$, extent of reticular abnormality on HRCT, and the severity of fibroblastic foci. Roca et al[5] showed that ILD deterioration was more commonly encountered in patients with pSS with lower median D_{LCO} values (47% vs 64%; $P = .048$). Chen et al[16] showed that an HRCT ≥13 was an independent risk factor for mortality.

Whether UIP predicts a poorer prognosis remains controversial. UIP in idiopathic interstitial pneumonia is a well-known determinant of a poor prognosis, in contrast to a better prognosis with idiopathic NSIP.[42] A similar tendency was reported in a study of ILD associated with rheumatoid arthritis.[43] With regard to HRCT findings in pSS, a UIP pattern was more common in a group of patients with ILD deterioration (42.9% vs 16.7%) in Roca et al's study.[5] However, UIP was not related to a poorer prognosis than NSIP in Enomoto et al's[20] findings, even when the ILD with a pathological UIP pattern in part or in whole was categorized as UIP. This result is different from results of a previous study on idiopathic interstitial pneumonia.[33] Interestingly, previous studies on ILD associated with collagen vascular diseases showed no significant difference on prognosis for UIP and NSIP patterns.[44,45] In the present study, there was also no association between poorer prognosis and HRCT patterns in patients with pSS-ILD.

Causes of death in pSS-ILD subgroups have been explored in several small series and results have differed.[5,16,19,20] In a study of 21 French patients with pSS-ILD, only 1 of 3 patients died due to lung complications.[5] However, the most common cause of death was respiratory failure (11 of 12 patients, 91.7%) in a Chinese study.[16] Results of the study by Enomoto et al,[20] based on a cohort of 33 Japanese patients with pSS-ILD, were similar. Causes of death were chronic respiratory failure (n = 5), acute exacerbation of ILD (n = 3), bacterial pneumonia (n = 1), and sepsis with unknown etiology (n = 1). In another Korean study, Ito et al[19] found that 9 of 10 patients died due to causes related to the disease, including progressive respiratory failure (n = 6), progression of malignant lymphoma (n = 1), *Aspergillus* infection during corticosteroid therapy for systemic malignant lymphoma (n = 1), and gastrointestinal bleeding during corticosteroid therapy for progressive interstitial pneumonia (n = 1). In the current study, 27 of the 44 patients died of respiratory failure, which was consistent with other studies on Asian populations. This also indicated that ILD in patients with pSS was quite severe and contributed to death. Malignance was the second cause of death, as expected (n = 7).

Our study has several limitations. First, although most of the patients suspected of having pSS would have been admitted to our department to confirm their diagnosis, evaluate systemic involvement and disease activity, and undergo treatment, some clinic patients were not included in this study. Second, patients who did not have records of HRCT stored in our hospital records (including patients who underwent HRCT at other hospitals and those who only underwent chest x-ray at our hospital) could not have their HRCT score and patterns analyzed. Third, 56 of 178 patients lost in follow-up, this might affect the results. Fourthly, this was a single-center study of a Chinese population, so the generalizability of the results is limited. In the future, multicenter studies will be required to further evaluate our findings.

Table 1

Smoking and severity of lung involvement were independent risk factors for mortality in primary Sjögren syndrome–associated interstitial lung disease.

Variables	OR	SE	β	*P*	95% CI
Smoking	1.192	0.289	0.657	.001	0.562–1.822
TLCO/VA	–0.006	0.003	–0.309	.062	–0.012–0.000
MEF_{25}	–0.009	0.002	–0.678	.002	–0.013—0.004
PaO_2	–0.013	0.006	–0.311	.049	–0.025–0.000

CI = confidence interval, MEF = maximum expiratory flow, OR = odds ratio, SE = standard error, TLCO = transfer factor of carbon monoxide, VA = alveolar volume.

In conclusion, ILD is a severe complication of pSS. Age, smoking, and severity of lung involvement are more critical for prognosis rather than inflammation status and autoantibodies. Thus, dosage of corticosteroids and immunosuppressant should be appropriate, at least not too aggressive as in other autoimmune disease related lung involvement. Now that we know the risk factors for mortality in this subgroup, physicians are able to monitor patients with these risk factors more closely and, ultimately, improve patients' outcome.

Author contributions

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