Original Article

Clinical characteristics and outcomes in patients with primary Sjogren's syndrome-associated interstitial lung disease

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Abstract:

BACKGROUND: Diagnosing primary Sjogren's syndrome (pSS)-associated interstitial lung disease (ILD) is complex and can be very challenging. In addition, information about the prognostic factors is limited.

AIMS: We aimed to determine the clinical characteristics and prognostic factors that impact pSS-ILD survival.

METHODS: This retrospective review included 84 consecutive patients diagnosed with pSS-ILD. The information analyzed included the clinical characteristics, laboratory findings, and physiological and hemodynamic data. Prognostic factors were identified using a Cox proportional hazards regression model.

RESULTS: The mean age was 60.5 years, and 61.9% were females. The mean time between the onset of symptoms and diagnosis was 21 months (range, 1–98 months). Minor salivary gland biopsy (MSGB) was positive for pSS in 92.3% of the cohort. Fifty percent of the patients had negative autoimmune serology related to pSS. Based on the available hemodynamic data, 40% had pulmonary hypertension (PH), and 20% had severe PH. During follow-up, acute exacerbation was noted in 38% of the cohort. The 5-year survival rate for all patients was 56%. Male sex, usual interstitial pneumonia pattern, and a reduced forced vital capacity were independent predictors of mortality in the pSS-ILD patients.

CONCLUSIONS: A significant delay between the onset of symptoms and diagnosis was noted in our cohort. Importantly, our study highlights the importance of MSGB and emphasizes that clinicians should not rely solely on serological tests to diagnose pSS in ILD patients. The overall survival was poor, and more efforts are needed to diagnose pSS-ILD at an early stage and refer patients to experienced centers.

Keywords:

Acute exacerbation, interstitial lung disease, minor salivary gland biopsy, primary Sjogren's syndrome, pulmonary hypertension, survival

Primary Sjogren's syndrome (pSS) is a systemic chronic inflammatory autoimmune disease characterized by lymphocytic infiltration of glandular and extraglandular organs.

The development of interstitial lung disease (ILD) in patients with connective tissue disease (CTD) is well established. It is estimated that approximately 20% of the pSS patients have an underlying ILD.[1] The commonly reported radiological patterns in pSS-ILD are nonspecific interstitial pneumonia (NSIP),

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usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia, and organizing pneumonia.[2-8] While data on the survival rate in patients with pSS-ILD are limited, previous studies have shown that the 5-year survival rate ranges between 84% and 89.9%, depending on the studied population.[3,9-11] Among the reported risk factors independently associated with survival in patients with pSS-ILD are the partial pressure of oxygen, microscopic honeycombing, the partial pressure of carbon dioxide, the extent of reticular abnormality based on high-resolution computed tomography (HRCT), the severity of fibroblastic foci, the percent predicted forced vital capacity (FVC), and the serum Krebs von den Lungen-6 level.[3,9,10]

In this context, we reviewed a series of consecutive pSS-ILD patients who were evaluated in one center to determine the clinical characteristics and prognostic factors associated with an increased risk of mortality.

Methods

The present study is a retrospective review of the ongoing ILD and pulmonary hypertension (PH) registry at the ILD and PH Centre at King Saud University Medical City. Consecutive ILD patients who were diagnosed with pSS between March 2008 and December 2019 were included. Any patients with Sjogren's syndrome associated with other well-defined CTDs were excluded. This study was approved by the Institutional Research Board at the College of Medicine, King Saud University, Riyadh, Saudi Arabia (approval number E-20-4608). The need to obtain written informed consent was waived because of the retrospective nature of the current study.

Clinical data from the first ILD clinic visit, including demographic and physiological data, were retrieved from our database. Pulmonary function testing (PFT) variables included FVC and the diffusion capacity of the lung for carbon monoxide (DLco).[12-14] In addition, the 6-min walk test (6MWT) parameters, including the initial and final oxygen saturation measured by pulse oximetry and the 6-min walk distance (6MWD), were collected.[15]

In 2013, minor salivary gland biopsy (MSGB) became a standard procedure in our center in any patient diagnosed with idiopathic interstitial pneumonia or undifferentiated CTD-associated ILD. However, a small number of ILD patients (n = 6) did not undergo MSGB based on the rheumatologist recommendation because their clinical findings were consistent with the diagnosis of pSS. MSGB was performed by an experienced head-and-neck surgeon. All specimens were reviewed by an experienced pathologist. The presence of focal lymphocytic sialadenitis in an MSGB with a focus score ≥1 (cluster of 50 or more lymphocytes) per 4 mm^2 of glandular tissue (i.e., positive MSGB) indicated the presence of the salivary component of pSS, as previously described [Figure 1a and b].[16,17] Specimens from patients who underwent surgical lung biopsy (n = 15) were reviewed by the same pathologist. Histopathological evidence of the UIP pattern was noted in 11 patients, 3 patients had the NSIP pattern, and 1 patient had organizing pneumonia.

Serological test results associated with pSS (antinuclear antibody [ANA], rheumatoid factor [RF], anti-Ro/anti-Sjogren's syndrome-related antigen A [SSA], and anti-La/SSB antibodies) were retrieved from our database. The serological tests were considered positive if the circulating autoantibody levels were above the reference values, with the exception of ANA, which was considered positive if the titers were ≥ 320.[17] All patients were negative for the following autoantibodies: anti-double-stranded DNA, anti-Smith, anti-Sclero 70, anti-ribonucleoprotein, anti-histidyl-tRNA synthetase, and anti-centromere antibodies.

HRCT scans were evaluated by a chest radiologist experienced in the interpretation of ILD. The radiological patterns were categorized as UIP, NSIP, or organizing pneumonia patterns as previously described.[18,19]

When PH was suspected, right heart catheterization (RHC) was performed within 7 days of the establishment of a diagnosis of an ILD. Patients were categorized as those without PH (defined as mean pulmonary artery pressure [mPAP] <21 mmHg or mPAP 21–24 mmHg with pulmonary vascular resistance [PVR] <3 wood units [WU]); those with PH (defined as mPAP 21–24 mmHg with PVR >3 WU or mPAP 25–34 mmHg); and those with severe PH (defined as mPAP >35 mmHg or mPAP >25 mmHg with low cardiac index [<2.0 L/min/m^2]) as previously described.[20] During the follow-up period, all pSS-ILD patients who met the proposed diagnostic criteria for the acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF), whether it was idiopathic in origin or triggered (by infection, drug toxicity, or surgery, among other triggers), as previously described, were included.[21]

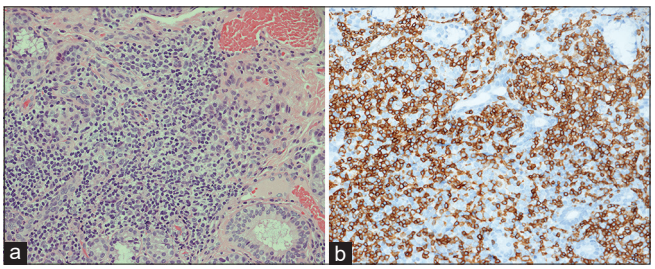

Figure 1: (a) Hematoxylin- and eosin-stained section from the minor salivary gland showing confluent clusters of lymphoplasmacytic infiltration (×200). (b) Immunohistochemical staining for leukocyte common antigen (CD45) highlighting marked lymphoplasmacytic infiltration (×200)

A multidisciplinary approach involving various specialties, including pulmonology, rheumatology, radiology, and pathology, was implemented for all pSS-ILD patients after a thorough analysis of the clinical, radiological, MSGB, surgical lung biopsy (when available), and serological data according to the established guidelines,[16,17] and a management plan was adopted after the multidisciplinary consensus recommendation was made.

Statistical analysis

Data are presented as the means ± standard deviations or numbers (percentages), as appropriate. Between-group differences were compared using *t*-tests, Chi-square tests, or Fisher's exact tests, as appropriate. Survival was compared using Kaplan–Meier estimates and log-rank tests. All survival analyses were performed from the time of pSS-ILD diagnosis to death, loss to follow-up, or the end of the study period (i.e., follow-up duration). Survival status was determined by contacting the patient or consulting the medical records. Survival time was censored on July 31, 2020, or at the date of the last visit if the patient was lost to follow-up. Unadjusted hazard ratios were obtained for all study parameters using Cox proportional hazards regression analysis to determine all-cause mortality. Univariate parameters with $P < 0.1$ were considered for inclusion in multivariate models to identify the independent predictors of mortality in the pSS-ILD patients. $P < 0.05$ was considered statistically significant, and 95% confidence intervals were used to report the precision of our results. SPSS (Statistical Package for the Social Sciences) version 18 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Clinical characteristics and laboratory findings

The present study included 84 patients with pSS-ILD. The mean age of our cohort at the time the diagnosis of pSS-ILD was established was 60 years, and 52 (61.9%) patients were women. The follow-up duration in our pSS-ILD patients was an average of 31.5 months, with a maximum follow-up of 7 years. The mean time between the onset of symptoms and diagnosis was 21 months (range, 1–98 months). In 71 patients, pSS and ILD were simultaneously diagnosed, and in 13 patients (IPF, n = 3, and undifferentiated CTD, n = 10), the diagnosis was changed to pSS-ILD after MSGB was performed. MSGB was performed in 78 patients (92.8%). In total, 72 patients (92.3%) had a focus score ≥1 of lymphoid infiltrates [Figure 1a and b], and the remaining 6 patients were negative [Figure 2]. ANA, RF, SSA, and SSB autoantibodies were negative in 42 (50%) patients [Table 1]. Based on the classification of the HRCT pattern, UIP was the predominant pattern detected (57.1%), followed by NSIP (36.9%) and organizing pneumonia (6%) [Table 1].

Hemodynamic findings

In total, 55 patients (65.4%) underwent RHC, of whom 22 patients (40%) had PH, and 11 patients (20%) had severe PH. The comparisons between patients with and without PH are summarized in Table 2. Regarding age, sex, and smoking status, no significant differences were

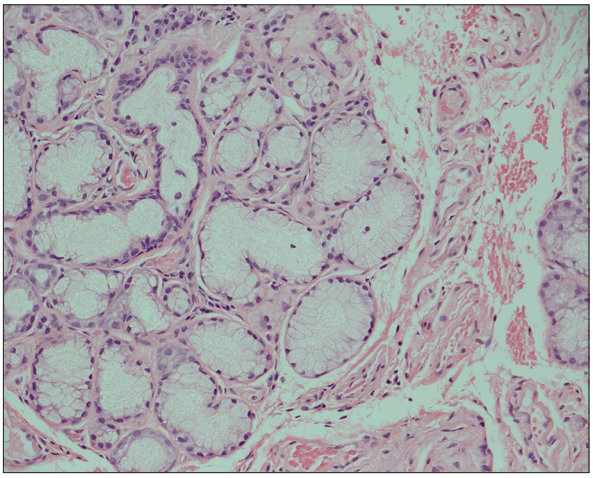

Figure 2: Hematoxylin- and eosin-stained section from the minor salivary gland showing the complete absence of inflammatory cells (×200)

Table 1: Clinical characteristics of the study cohort

Variable (n=84)	n (%)
Age	60.5±13.0
Female sex	52 (61.9)
Ever smoker	16 (19.0)
Autoimmune symptoms (n=74)	
Gastroesophageal reflux	49 (66.2)
Dry eyes or mouth (sicca features)	43 (58.1)
Unexplained weight loss	16 (21.6)
Arthralgia	15 (20.3)
Recurrent unexplained fever	4 (5.4)
Raynaud's phenomenon	3 (4.1)
Minor salivary gland biopsy (n=78)	
Positive	72 (92.3)
Laboratory results†	
ANA	35 (41.6)
Rheumatoid factor	7 (8.3)
Anti-Ro/SSA	19 (22.6)
Anti-La/SSB	4 (4.7)
Negative autoantibodies*	42 (50.0)
HRCT pattern	
UIP	48 (57.1)
NSIP	31 (36.9)
Organizing pneumonia	5 (6.0)

*Negative for ANA, RF, SSA, and SSB autoantibodies, †Positive autoantibody patients could have multiple positive serologic tests. Data are presented as the mean±SD or n (%). ANA=Antinuclear antibody, Anti-Ro/SSA=Anti-Ro/anti-Sjogren's syndrome antigen A, Anti-La/SSB=Anti-La/anti-Sjogren's syndrome-related antigen B, HRCT=High-resolution computed tomography scan, UIP=Usual interstitial pneumonia, NSIP=Nonspecific interstitial pneumonia, SD=Standard deviation, RF=Rheumatoid factor

noted between the groups with and without PH. AE was more frequently observed in the PH group than in patients without PH group ($P = 0.019$). The distribution of autoimmune symptoms was similar between the groups (data not shown). Significant physiological impairments in PFTs and the 6MWT parameters were noted in the pSS-ILD with PH group when compared to the parameters in the group without PH. Furthermore, the UIP pattern was more frequently noted in patients without PH, while the NSIP pattern was more frequently observed in the PH group [Table 2]. In total, 18 patients received PH-specific therapy, and details about the type of PH therapy are shown in Table 2.

Acute exacerbation in the study cohort

The incidence of AE in pSS-ILD patients was 38%. The etiology of AE in the pSS-ILD cohort was classified as idiopathic ($n = 15$) or triggered (infection, $n = 9$), and 8 patients had multiple episodes of AE with different etiologies (i.e., one episode was found to be idiopathic, and another episode at a different time was found to be triggered). No significant differences were noted in demographics, physiological parameters, HRCT patterns, the use of corticosteroids, the use of immunomodulatory therapy, or oxygen supplementation between patients with and without AE [Table 3].

Survival analysis of the primary Sjogren's syndrome-interstitial lung disease cohort

There were 20 patients (23.8%) who died during the follow-up period. The estimated survival probabilities in the pSS-ILD cohort at 1, 3, and 5 years were 87%, 70%, and 56%, respectively. When we examined pSS-ILD patients stratified by HRCT pattern, the estimated survival probabilities at 1, 3, and 5 years in patients with the UIP pattern were 83%, 63%, and 39%, respectively, while in the patients with the NSIP pattern, they were 93%, 75%, and 75%, respectively [$P = 0.119$ by log-rank analysis; Figure 3a]. The diagnosis of PH was not associated with a worse outcome [$P = 0.919$ by log-rank analysis; Figure 3b]. The estimated survival probabilities in the pSS-ILD cohort with AE at 1, 3, and 5 years were 79%, 63%, and 46%, respectively, while they were 94%, 74%, and 66%, respectively, in the pSS-ILD cohort without AE [$P = 0.137$ by log-rank analysis; Figure 3c]. A 6MWD <300 m was significantly associated with a worse outcome [$P = 0.006$ by log-rank analysis; Figure 3d].

In univariate Cox regression [Table 4], a number of factors were associated with survival, including age, male sex, smoking status, the percent predicted FVC, the 6MWD, and the use of immunomodulatory therapy.

Table 2: Comparison between primary Sjogren's syndrome-interstitial lung disease patients with and without pulmonary hypertension

Variable	Without PH (*n*=22)	With PH (*n*=33)	*P*
Age	58.5±16.3	63.0±12.7	0.264
Female sex	12 (54.5)	22 (66.6)	0.365
Ever smoker	5 (22.7)	5 (15.1)	0.498
Follow-up duration (months)	32.8±27.6	40.2±21.5	0.270
Acute exacerbation	5 (22.7)	18 (54.5)	0.019
Pulmonary function test (percent predicted)			
FVC	59.8±22.2	49.0±16.8	0.046
DL_{CO}	45.0±20.0$^{\alpha}$	32.7±17.5$^{\beta}$	0.031
6MWT			
Initial SpO_2 (%)	95.7±2.6	93.5±4.2$^{\delta}$	0.032
Final SpO_2 (%)	84.8±7.0	79.8±8.3$^{\delta}$	0.026
Distance (m)	331.1±99.2	259.5±115.7$^{\delta}$	0.023
HRCT pattern			
UIP	16 (72.7)	15 (45.4)	0.046
NSIP	4 (18.1)	17 (51.5)	0.013
Organizing pneumonia	2 (9.0)	1 (3.0)	0.557
Treatment			
PDE-5i		11 (33.3)	
ERA		2 (6.0)	
Combination		5 (15.1)	
PDE-5i+ERA		2 (6.0)	
PDE-5i+prostanoids		1 (3.0)	
PDE-5i+ERA+prostanoids		2 (6.0)	
Oxygen supplementation	9 (40.9)	17 (51.5)	0.440

$^{\alpha}n$=21, $^{\beta}n$=25, $^{\delta}n$=31. Data are presented as the mean±SD or *n* (%). PH=Pulmonary hypertension, FVC=Forced vital capacity, DL_{co}=Diffusion capacity of the lung for carbon monoxide, SpO_2=Oxygen saturation by pulse oximetry, HRCT=High-resolution computed tomography scan, UIP=Usual interstitial pneumonia, NSIP=Nonspecific interstitial pneumonia, PDE-5i=Phosphodiesterase-5 inhibitor, ERA=Endothelin receptor antagonist, SD=Standard deviation, 6MWT=Six-min walk test

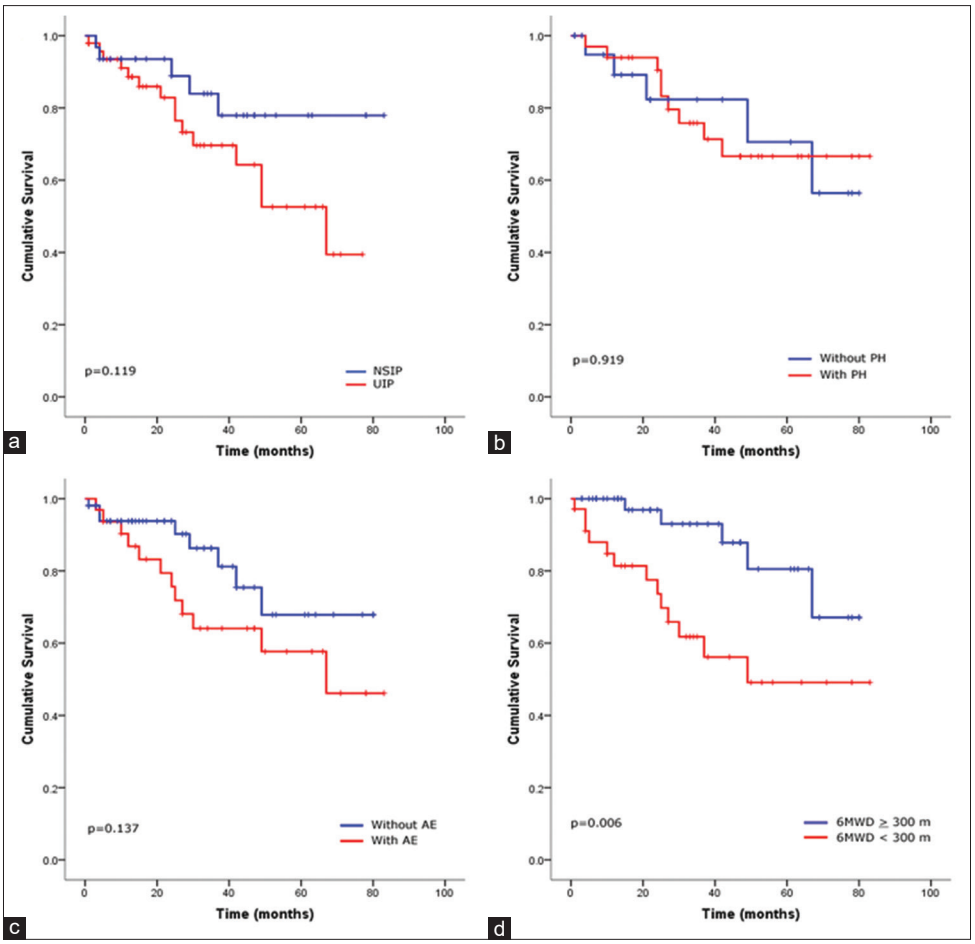

Figure 3: Kaplan–Meier survival estimates for the relationships with (a) the usual interstitial pneumonia pattern and nonspecific interstitial pneumonia pattern, (b) pulmonary hypertension and without pulmonary hypertension, (c) acute exacerbation and no acute exacerbation, and (d) the 6-min walk distance at a threshold of 300 m in primary Sjogren's syndrome-associated interstitial lung disease patients

However, in the multivariable analysis, male sex, the UIP pattern, and the percent predicted FVC were the only independent predictors of survival [Table 4].

Discussion

The present study describes the clinical characteristics and outcomes in pSS-ILD patients from one center with variable degrees of parenchymal fibrosis. We found that 60% of the pSS-ILD patients had PH, and 38% of the patients experienced AE during follow-up. The 5-year survival rate of the cohort was 56%, and the diagnosis of UIP was independently associated with an increased risk of mortality.

In this study, we describe the largest cohort of pSS-ILD patients from this region. Importantly, we show that pSS and ILD were simultaneously diagnosed in 84.5% of the patients and that the diagnosis was changed to pSS-ILD after we implemented MSGB in our center, implying that pSS is significantly underestimated and overlooked among patients with ILD. Furthermore, we show that a substantial number of our ILD patients have no autoimmune symptoms and/or lack autoantibodies related to pSS; thus, our study confirms the findings of other studies, which have shown that ILD can develop before the onset of pSS, highlighting the importance of a thorough evaluation of patients with ILD of unknown etiology.[1,7,8,22-25]

Previous studies in pSS-ILD cohorts reported an average age at presentation ranging from 58 to 68 years, a female predominance, and a smoking history in 13%–31% of the patients, depending on the studied population.[2-4,6-8,10,23,24] In agreement with the cited studies, our cohort had a mean age at presentation of 60 years, 62% were women, and the majority were nonsmokers. Considerable variation among studies was noted regarding the prevalence of autoimmune symptoms and signs in pSS-ILD patients. For instance, the prevalence of Raynaud's phenomenon was found to be 8% in one study, whereas in another study, it was noted in 57% of their studied patients.[7,23] Similarly, dry eyes was reported to have a prevalence of 43% in one study, while in another study, it was as high as 93%.[3,8] Furthermore, gastroesophageal reflux was reported in 2% of the patients in one study, while

Table 3: Comparison between primary Sjogren's syndrome-interstitial lung disease patients with and without acute exacerbation

Variable	Without AE (*n*=52)	With AE (*n*=32)	*P*
Age	59.9±13.5	61.6±12.4	0.555
Female sex	32 (61.5)	20 (62.5)	0.930
Ever smoker	11 (21.1)	5 (15.6)	0.575
Follow-up duration (months)	28.7±22.3	36.0±24.4	0.163
Pulmonary function test (percent predicated)‡			
FVC	60.2±21.2	53.1±18.0	0.123
DL_{CO}	48.0±21.3[α]	41.7±21.3[β]	0.239
6MWT¥			
Initial SpO_2 (%)	95.2±3.1	94.8±3.7	0.540
Final SpO_2 (%)	84.7±8.2	83.8±8.4	0.634
Distance (m)	314.1±107.6	288.0±117.7	0.316
HRCT pattern			
UIP	30 (57.6)	18 (56.2)	0.897
NSIP	17 (32.6)	14 (43.7)	0.308
Organizing pneumonia	5 (9.6)	0	0.151
Treatment			
Corticosteroids	17 (32.6)	14 (43.7)	0.308
Immunomodulatory therapy†	34 (65.3)	26 (81.2)	0.118
PH specific therapy	9 (17.3)	13 (40.6)	0.018
Antifibrotic therapy*	4 (7.6)	7 (21.8)	0.094
Oxygen supplementation	15 (28.8)	12 (37.5)	0.410

*Either nintedanib or pirfenidone, †In the group without acute exacerbation, patients received azathioprine (*n*=2), mycophenolate mofetil (*n*=24), tacrolimus (*n*=2), mycophenolate mofetil+rituximab (*n*=4), tacrolimus+mycophenolate mofetil (*n*=2), In the group with acute exacerbation, patients received azathioprine (*n*=1), mycophenolate mofetil (*n*=16), mycophenolate mofetil+rituximab (*n*=8), mycophenolate mofetil+tacrolimus (*n*=1), [β]*n*=45, [β]*n*=25. Data are presented as the mean±SD or *n* (%). AE=Acute exacerbation, FVC=Forced vital capacity, DL_{co}=Diffusion capacity of the lung for carbon monoxide, SpO_2=Oxygen saturation by pulse oximetry, HRCT=High-resolution computed tomography scan, UIP=Usual interstitial pneumonia, NSIP=Nonspecific interstitial pneumonia, SD=Standard deviation, 6MWT=6-min walk test, PH=Pulmonary hypertension, ‡In the group without acute exacerbation, *n*=51; in the group with acute exacerbation, *n*=31, ¥In the group without acute exacerbation, *n*=49; in the group with acute exacerbation, *n*=30

in another report, it was noted in 23.8% of the pSS-ILD patients.[7,23] In the current study, gastroesophageal reflux was the most common symptom (66%), followed by dry eyes or mouth (58%), while Raynaud's phenomenon was the least common finding (4%). Different methodologies, sample sizes, environmental factors, ethnicities, and other factors may explain the observed variations between the cited studies and our study.

Regarding HRCT patterns, most studies have shown that NSIP is the most common ILD pattern in pSS patients, ranging between 26% and 66%, followed by the UIP pattern, ranging between 2% and 33%.[2-4,7-10,23] However, recent studies reported a higher prevalence of the UIP pattern, ranging between 42% and 92%, implying that significant heterogeneity occurs among pSS patients and among studied populations.[6,24] In the present study, UIP was the most common pattern, followed by NSIP. Regarding the serological test results, we showed that autoantibodies against SSA and SSB were positive in only 22% and 5% of the patients, respectively. Previous studies in pSS-ILD patients showed that autoantibodies against SSA and SSB were positive in 36% to 57% and 13% to 36% of the patients, respectively, emphasizing that the diagnosis of pSS in ILD patients is complex and requires a high index of suspicion.[2,7,8,23,24] Importantly, 50% of our pSS-ILD patients were negative for ANA, RF, SSA, and SSB; thus, such patients would have been misdiagnosed with IPF or idiopathic NSIP if MSGB was not performed. Therefore, our study highlights the importance of MSGB and emphasizes that clinicians should not rely solely on serological tests to diagnose pSS in ILD patients.

PH secondary to CTD is a well-established complication that is classified as Group 1 PH.[26] PH data in pSS-ILD patients (Group 3 PH) are limited, and the published studies have mainly derived findings from systemic sclerosis (SSc) patients, showing that SSc-ILD with PH is far worse than SSc-PH without ILD.[27,28] In the current study, we noted that the incidence of PH in pSS-ILD patients was 40%, and 20% met the definition of severe PH. Surprisingly, despite the significant impairments in physiological parameters, including DLco and 6MWD, noted in the PH group, our study failed to show a difference in survival between those with and without PH. Potential explanations include the relatively small number of patients enrolled in both the groups, which meant that the analysis was underpowered. Furthermore, the advanced state of lung fibrosis noted in our cohort precluded us from capturing such differences.

Table 4: Cox proportional hazards regression analysis showing the variables predicting survival in the study cohort

Variable	Unadjusted		Adjusted	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.040 (1.003-1.079)	0.035		
Male sex	3.661 (1.465-9.150)	0.005	6.085 (1.299-28.506)	0.022
Ever smoker	3.089 (1.216-7.847)	0.018		
UIP	2.255 (0.816-6.230)	0.117	3.997 (1.022-15.638)	0.046
NSIP	0.529 (0.192-1.460)	0.219		
Acute exacerbation	2.276 (0.930-5.571)	0.072	2.858 (0.923-8.852)	0.069
FVC (percent predicted)	0.967 (0.939-0.995)	0.023	0.962 (0.928-0.997)	0.036
DL_{CO} (percent predicted)	0.995 (0.970-1.022)	0.730		
6MWD (m)	0.995 (0.991-0.999)	0.019		
6MWT final SpO_2<88%	0.836 (0.323-2.159)	0.711		
sPAP (mmHg)	1.008 (0.984-1.032)	0.537		
PVR (wood units)	1.015 (0.881-1.170)	0.835		
CI (L/min/m^2)	1.157 (0.782-1.712)	0.465		
PH specific therapy	0.032 (0.000-2.946)	0.135		
Corticosteroid	0.787 (0.313-1.977)	0.610		
Antifibrotic therapy	0.749 (0.173-3.236)	0.699		
Immunomodulatory therapy	0.326 (0.135-0.787)	0.013		
Oxygen supplementation	0.650 (0.235-1.802)	0.408		

UIP=Usual interstitial pneumonia, NSIP=Nonspecific interstitial pneumonia, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=6-min walk distance, 6MWT=6-min walk test, SpO_2=Oxygen saturation by pulse oximetry, sPAP=Systolic pulmonary artery pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index, PH=Pulmonary hypertension, CI=Confidence interval, HR=Hazard ratio

In our cohort, the average percent predicted FVC during the initial evaluation was 57%, which is significantly lower than the values reported in any of the published studies on pSS-ILD, which ranged between 65% and 93%.[2-4,6-8,10] Such an advanced state of lung fibrosis at presentation is likely due to the significant delays in diagnosis and in referring these patients to specialized centers. For instance, dyspnea and cough are common complaints in ILD patients; thus, the misdiagnosis of these patients with more common conditions that have similar symptoms, such as asthma, chronic obstructive lung disease, heart failure and others, is quite common, resulting in a delay in diagnosis and the initiation of the appropriate treatment.[29,30] Alhamad *et al*.[31] noted that the mean delay between the onset of symptoms and the diagnosis of IPF ranged between 1 and 4 years. In agreement with that study, we found that the mean delay between the onset of symptoms and the diagnosis of pSS-ILD was nearly 2 years, and in some patients, it was as long as 8 years. Therefore, it is of paramount importance for clinicians to make a correct diagnosis of pSS-ILD as early as possible, which can be achieved by increasing the awareness of this condition among clinicians and expediting referrals to specialized ILD centers.

AE was originally described in IPF patients; however, studies have shown that AE can also occur in patients with CTD-ILD and other forms of chronic fibrotic ILDs.[32-38] To date, there are no consensus recommendations regarding the definition of AE in patients with non-IPF ILD; however, it has been proposed that applying the same definition used in patients with IPF in patients with non-IPF ILD may be beneficial.[39] To the best of our knowledge, this is the first study to describe in detail the clinical characteristics and outcomes in pSS-ILD patients experiencing AE. We found that the incidence of AE in our cohort was 38%. This is in agreement with the findings reported by Cao *et al*.,[32] in which pSS patients represented 35.7% of those with AE in their CTD-ILD cohort. The risk factors for AE in non-IPF ILD patients include a reduced FVC%, reduced total lung capacity percentage, and reduced DLco%.[32,36] Therefore, the advanced state of lung fibrosis observed in our cohort at baseline may explain the higher risk of developing AE. Importantly, the 5-year survival rate in the AE group was 46%, while it was 66% in the group without AE, highlighting the importance of recognizing AE as a serious complication and the urgent need to develop effective preventive measures that would have a positive impact on pSS-ILD patient survival.

Survival studies in pSS-ILD patients have shown a 5-year survival rate ranging between 84% and 89.9%.[3,9-11] In the present study, we found that the 5-year survival rate was 56%, which is significantly worse than those in previous studies. However, the findings in the previous studies and our study should be interpreted in the context of the studied populations. Our cohort had an advanced state of lung fibrosis at presentation; these patients predominantly had the UIP pattern and had high incidences rates of PH and AE, which may have

collectively contributed to the poor survival observed in the present study.

Previous studies in patients with various types of ILD have shown that the parameters obtained from the 6MWT are important physiological markers associated with increased mortality.[31,40-42] In agreement with previous studies, we found that a 6MWD <300 m was significantly associated with reduced survival, highlighting the importance of the 6MWT as a surrogate marker of disease severity in pSS-ILD patients. In univariate Cox regression analysis, a number of factors were associated with the survival of patients with pSS-ILD; however, in multivariate analysis, we found that male sex, UIP pattern, and a reduced percent predicted FVC were the only independent predictors of increased mortality. Therefore, our study complements the findings in cohorts of other ethnicities with regard to the prognostic factors in pSS-ILD patients.[3,9,10]

The present study had several strengths and limitations. The strengths include the enrollment of a large cohort of pSS-ILD patients in one center. Moreover, 93% of the pSS-ILD patients underwent MSGB, which added useful information and avoided misclassification, particularly among patients who were negative for autoantibodies. Last, each patient in the pSS-ILD cohort received rigorous evaluations and was subsequently discussed in a multidisciplinary meeting to ensure that all patients received a correct diagnosis and management. The limitations included the retrospective nature of the study, which may have led to unexpected bias, although the data were collected prospectively. All patients in the present study were from the Saudi population; thus, our results may not be generalizable to other populations. A limited number of patients underwent surgical lung biopsy; thus, UIP may have been missed in patients with HRCT-based diagnoses of NSIP. However, a difference in survival was noted between NSIP and UIP patients, and the UIP pattern was independently associated with a 4-fold increased risk of mortality, indicating that these patients received the correct diagnosis. Finally, institutional bias may have occurred due to fact that the most severe cases were referred to our center, which may have contributed to the poor survival noted in our pSS-ILD patients.

Conclusions

We have described a large cohort of pSS-ILD patients diagnosed in one center and highlighted a number of important aspects. We found a significant delay between the onset of symptoms and the diagnosis of pSS-ILD. Moreover, we observed that 15.5% of the pSS-ILD patents were misclassified as having either IPF or undifferentiated CTD before the implementation of MSGB in our center. Furthermore, nearly 50% of the pSS-ILD patients lacked sicca features and were negative for autoantibodies related to pSS; thus, a high index of suspicion is needed on the part of clinicians managing ILD patients. Importantly, we report high incidence rates of PH and AE, both of which are associated with serious complications. Our study clearly demonstrates that the UIP pattern and a reduced percent predicted FVC are important surrogate markers of mortality in pSS-ILD patients.

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Conflicts of interest

There are no conflicts of interest.

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