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Mixed Airway and Pulmonary Parenchymal Disease in Patients With Primary Sjögren Syndrome: A 6-year Follow-up

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ABSTRACT. ***Objective.*** To assess pulmonary function and chronic obstructive pulmonary disease (COPD) development over time in patients with primary Sjögren syndrome (pSS), as well as the association between pulmonary function, radiographic findings, respiratory symptoms, and clinical features of pSS, taking cigarette consumption into account.

Methods. Forty patients with pSS (mean age 66 yrs; range 42–81 yrs; 39 women), previously participating in a cross-sectional study on pulmonary involvement in pSS, were reassessed by pulmonary function tests after a mean follow-up time of 6 years. At follow-up, patients were also assessed by high-resolution computed tomography of the chest, as well as for pSS disease activity, respiratory symptoms, and cigarette consumption.

Results. Patients with pSS showed significantly decreased percentages of predicted total lung capacity (TLC), residual volume (RV), RV/TLC ratio, and diffusing capacity of the lungs for carbon monoxide, as well as an increase in predicted forced expiratory volume in 1 second/vital capacity (FEV1/VC) ratio from baseline to follow-up. The proportion of COPD in patients with pSS did not change significantly from baseline to follow-up (38% vs 40%, respectively). Radiographic signs of bronchial involvement and interstitial lung disease were each found in 38% of the patients.

Conclusion. Both airway and pulmonary parenchymal disease were commonly found in patients with pSS, with a coexistence of both an obstructive and restrictive pulmonary function pattern, where the latter tended to deteriorate over time. COPD was a common finding. Airway and pulmonary involvement may be underdiagnosed in pSS, which is why special attention to clinical assessment of pulmonary involvement in patients with pSS is mandated.

Key Indexing Terms: diagnostic imaging, radiography, respiratory diseases, Sjögren syndrome

Primary Sjögren syndrome (pSS) is a systemic autoimmune rheumatic disease that typically occurs more often in females and affects various exocrine glands, resulting in the characteristic sicca symptoms[1]. In addition to the symptoms associated with exocrine gland dysfunction, pain, and fatigue in pSS, approximately 1 in 3 patients with pSS demonstrate involvement of several nonexocrine organ systems in a widely heterogeneous pattern[1,2]. Various types of pulmonary parenchymal and airway involvement have been reported in pSS, and respiratory symptoms are common[3]. The prevalence and type of pulmonary involvement differs between studies, possibly due to differences in methodology, pSS classification criteria, and patient selection[3,4,5,6,7]. However, follicular bronchiolitis and peribronchiolar lymphocytic infiltration have been highlighted as histopathological hallmarks of pSS lung disease[5,8,9], and small airway involvement, including airway hyperreactivity, has been reported in several studies[3,4,7,8,9,10,11,12]. Besides pSS-associated airway disease, interstitial lung disease (ILD) is also a recognized manifestation of pSS, and both may coexist in the same patient[3,10]. In a previous study, chronic obstructive lung disease (COPD) was reported in 41% of patients with pSS overall, and, importantly, in 30% of never-smoking patients with pSS, indicating that pSS may be involved in COPD development[13]. Another study reported that COPD commonly developed in pSS patients with respiratory symptoms[11], and a recent registry-based study has demonstrated an increased prevalence of COPD in patients with pSS[14]. Finally, pSS-associated pulmonary disease has been shown to be associated with a decreased quality of life (QOL), as well as increased rates of morbidity and mortality[15,16,17]. Some

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The authors report no conflicts of interest with regard to this manuscript.

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subtypes of ILD in particular are known to be associated with poor prognosis in pSS[18,19]. Globally, COPD is one of the major causes of morbidity and mortality, and smoking is a significant risk factor; however, a substantial proportion of patients with COPD have never smoked[20,21]. Autoimmune mechanisms are important in COPD pathology, aside from cigarette smoking, environmental, and genetic risk factors. Correspondingly, increased rates of COPD among patients with autoimmune rheumatic diseases have been reported[20,21,22,23].

In our study, we therefore aimed to analyze (1) changes in lung volumes, lung function, and COPD development over time in patients with pSS; and (2) the association between pulmonary function, radiographic findings, respiratory symptoms, and clinical features of pSS, taking cigarette consumption into account.

MATERIALS AND METHODS

Patients. Fifty-one consecutive patients with pSS had been previously investigated in a cross-sectional study on pulmonary involvement in pSS at the Department of Rheumatology, Skåne University Hospital in Malmö, Sweden, from 2012 to 2013[13]. In 2018, all patients were alive and invited to a follow-up study; 11 declined participation. Patients declining participation did not significantly differ in baseline characteristics from those included in the follow-up study. Thus, 40 patients with pSS (mean age 66 yrs; range 42–81 yrs; 39 females) were included in this study. All patients fulfilled the American–European Consensus Group classification criteria for pSS[24], as well as the American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria for pSS[25]. Twenty patients were never smokers, 17 were former smokers (mean duration since smoke cessation 30 yrs; range 6–46 yrs), and 3 were current smokers. Patients on inhalation medication had to refrain from using these 24 hours prior to the pulmonary function tests (PFT). Further patient characteristics are presented in Table 1.

PFT controls. The PFT controls consisted of 456 population-based subjects who attended a general health survey in Uppsala, including 186 females [100 never smokers, 86 current smokers (mean age 45 yrs; range 20–70 yrs)] and 270 males [124 never smokers, 146 current smokers (mean age 45 yrs; range 20–70 yrs)][26,27]. Predicted PFT values were calculated based on the controls' PFT results by a linear regression model, into which age, height, weight, and cigarette smoking were added as covariates for females and males separately, thus correcting predicted PFT variables for smoking as well.

PFT. The PFT included static and dynamic spirometry, from which the vital capacity (VC), total lung capacity (TLC), residual volume (RV), forced expiratory volume in 1 second (FEV1), FEV1/VC ratio, and RV/TLC ratio could be calculated. Diffusing capacity of the lungs for carbon monoxide (DLCO) was measured by the single-breath technique. FEV1 and VC were measured before and after 1.0 mg terbutaline was inhaled (FEV1rev and VCrev after reversibility test, respectively), and FEV1 reversibility was calculated. Lung function tests, including calibration, were performed in accordance with current standards[28,29,30]. TLC and RV were measured by body plethysmography. Clinically significant reversibility was defined as FEV1 improvement ≥ 12% and ≥ 200 mL[31]. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and was indicated by a FEV1rev/VCrev ratio < 0.70[20]. PFT variables were expressed as percentages of predicted values. Predicted PFT values were calculated based on the controls' PFT results.

EULAR Sjögren's Syndrome Disease Activity Index and EULAR Sjögren Syndrome Patient Reported Index. pSS disease activity was assessed by the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), scoring disease activity in 12 domains and representing different organ systems. The ESSDAI total score comprises the sum of the 12 domain scores, with a range of 0–123 points. Patient-reported symptoms, including sicca symptoms, pain, and fatigue associated with pSS, were evaluated by the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI). The ESSPRI total score is the mean of the symptom scores, ranging from 0 to 10 points[32,33].

Table 1. Characteristics of patients with pSS.

	Patients, n = 40
Age, yrs, mean (± SD)	66 (± 9)
Sex, n, females/males	39/1
Lower lip biopsy, focus score ≥ 1 (n = 31), %	70
Disease duration, yrs, mean (± SD)	22 (± 12)
Follow-up time, yrs, median (IQR)	6 (5–6)
Smoking status	
Current smokers	3 (8)
Former smokers	17 (43)
Never smokers	20 (50)
Cigarette smoking, pack-yrs, median (IQR)	7.8 (2.5–18.0)
Anti-SSA antibody seropositive, %	83
Anti-SSB antibody seropositive, %	53
ANA seropositive, %	80
RF seropositive, %	65
IgG, g/L, mean (± SD)	13.6 (± 4.9)
C3, g/L, mean (± SD)	0.94 (± 0.24)
C4, g/L, mean (± SD)	0.18 (± 0.07)
ESSDAI total score, median (IQR)	5 (1–8)
ESSPRI total score, mean (± SD)	6 (± 2)
Systemic pSS treatment	13 (33)
Low-dose glucocorticosteroids	9 (23)
Hydroxychloroquine	10 (25)
csDMARD	1 (3)
Inhalation treatment	13 (33)
Combined ICS + LABA	9 (23)
LAMA	2 (5)
SABA or LABA	8 (24)

Values are presented as n (%) unless otherwise specified. Disease characteristics and demographics of the 40 patients with pSS. ANA: antinuclear antibody; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; EULAR: European League Against Rheumatism; ICS: inhaled corticosteroids; LABA: long-acting β2 agonists; LAMA: long-acting muscarinic antagonists; pSS: primary Sjögren syndrome; RF: rheumatoid factor; SABA: short-acting β2 agonists.

St. George's Respiratory Questionnaire, COPD assessment test, modified Medical Research Council, and questionnaire assessing cigarette smoking. Evaluation of respiratory- and COPD-associated symptoms and effect on QOL was conducted using validated questionnaires, including the Swedish versions of the St. George's Respiratory Questionnaire (SGRQ) and the COPD assessment test (CAT). The modified Medical Research Council (mMRC) dyspnea scale was also used. SGRQ total scores are calculated and range between 0–100 points, where lower scores indicate better health[34,35]. The CAT assesses and monitors COPD and consists of 8 items, with total scores ranging from 0 to 40 points. CAT scores < 10 points indicate less symptomatic COPD, while CAT scores ≥ 10 points indicate more symptomatic COPD[36,37]. The mMRC dyspnea scale evaluates dyspnea-associated disability. Total scores range from 0 to 4 points[38]. Cigarette smoking was evaluated by a structured questionnaire assessing smoking status, start and stop year, and mean cigarette consumption for the current and former smokers, which enabled pack-year assessments.

Laboratory tests. Laboratory signs of inflammation were evaluated by assessing levels of C-reactive protein, erythrocyte sedimentation rate, IgG,

IgA, IgM, and complement C3 and C4. Serologies performed in the diagnostic procedures of the disease included anti-SSA and anti-SSB antibodies, antinuclear antibodies, and rheumatoid factor, and were reassessed. Brain natriuretic peptide (NT-ProBNP) was assessed to rule out concomitant congestive heart failure.

High-resolution computed tomography. Thirty-nine patients underwent a high-resolution computed tomography (HRCT) of the chest (1 patient did not consent). The HRCT scan was performed using a multidetector-row scanner (Siemens Somatom Definition Flash; Siemens Healthineers) with a detector configuration of 128 × 0.6, an automated tube voltage selection (Care kV, ref kV 100), tube current modulation (CARE Dose4D 150, ref mAs), a pitch of 1.1, and a rotation time of 0.5 seconds. The following reconstructions were obtained: I70f, 1 mm/0.5 mm (slice thickness/increment), and I70f, 5 mm/5 mm. The images were interpreted visually by a radiologist (HLA), who was blinded to the PFT results and the clinical features of the patients. The findings were defined by the Fleischner Society guidelines for imaging studies[39]. Presence of emphysema, cysts, nodules, signs of bronchial involvement (defined as central bronchiectasis or bronchial wall thickening), and signs of ILD (defined as ground-glass attenuation, a reticular pattern, traction bronchiectasis, or honeycombing) were registered.

Statistics. The paired samples *t* test and the Wilcoxon signed-rank test were used when comparing measured and predicted PFT results, and when comparing previously reported and actual PFT results. For comparisons between independent groups, the *t* test and the Mann-Whitney U test were used. Differences in categorical data were analyzed by the chi-square test and Fisher exact test. The McNemar test was used in pairwise comparisons of categorical data. For correlations, Pearson correlation coefficient and Spearman correlation coefficient were calculated as appropriate. *P* values < 0.05 were considered statistically significant.

Ethics. The study was approved by the Regional Ethical Review Board at Lund (LU 2018/26). All patients gave written informed consent, in accordance with the Declaration of Helsinki.

RESULTS

Changes over time. At the follow-up, patients with pSS showed significantly decreased percentages of predicted TLC, RV, RV/TLC ratios, and DLCO, as well as an increased percentage of predicted FEV1/VC ratios, compared to percentages of predicted values at baseline. There was no statistically significant difference in the prevalence of COPD between baseline and follow-up (38% vs 40%; $P > 0.99$; Table 2A). Out of 40 patients, 15 demonstrated COPD at baseline compared to 16 at follow-up. Two patients did not fulfill GOLD criteria for COPD at follow-up, and 3 patients developed COPD from baseline to follow-up. A statistically nonsignificant shift from mild to moderate COPD from baseline to follow-up was observed, both among patients with pSS in general, and among never- and ever-smoking (i.e., current and former cigarette smokers) patients with pSS (Figure 1). Among patients with symptomatic COPD (mMRC ≥ 1) at baseline, 43% and 57% fulfilled GOLD 1 and 2 criteria at baseline, respectively. At follow-up, 29% and 71% fulfilled GOLD 1 and 2 criteria, respectively, and 29% progressed in GOLD class during follow-up. Among patients without symptomatic COPD at baseline, 13% progressed in GOLD class during follow-up.

When comparing never- and ever-smoking patients with pSS at follow-up, no significant differences in percentages of predicted PFT results were found between groups (data not shown). Although the proportion of COPD numerically increased in ever-smoking patients, the differences did not reach statistical significance (55% vs 25%; $P = 0.05$). However, cigarette consumption, as evaluated by pack-years and represented as median (IQR), was significantly increased in patients with COPD at follow-up compared to patients without COPD at follow-up [4 (0–21) vs 0 (0–3); $P = 0.03$; data not shown].

Table 2A. Pulmonary function test (PFT) results in patients with pSS (n = 40).

	Baseline	Follow-up	*P*
VC	97 (± 14)	96 (± 14) *	0.47
TLC	101 (± 12)	97 (± 10)	< 0.001
RV	113 (± 20) **	101 (± 18)	< 0.001
RV/TLC ratio	112 (100–120) ***	103 (92–112)	< 0.001
FEV1	91 (± 15) ***	91 (± 16) ***	0.99
FEV1/VC ratio	96 (89–100) **	98 (89–104)	0.01
DLCO	95 (± 13) *	92 (± 15) **	0.02
COPD, n (%)	15 (38)	16 (40)	> 0.99
Mild COPD	10 (67)	7 (44)	0.38
Moderate COPD	5 (33)	9 (56)	0.13
Severe and very severe COPD	0 (0)	0 (0)	N/A
Clinically significant reversibility	3 (8)	2 (5)	> 0.99

Results are presented as mean percentages of predicted values (± SD), median percentages of predicted values (IQR), and proportional findings as numbers and percentages. Results of the PFT presented as percentage of predicted values in 40 patients with pSS at baseline in 2012 compared to follow-up in 2018. Clinically significant reversibility was defined as FEV1 improvement ≥ 12% and ≥ 200 mL after 1.0 mg inhaled terbutaline. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ vs predicted values, respectively, whereas *P* values refer to baseline vs follow-up. COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: forced expiratory volume in 1 s; N/A: not assessed; pSS: primary Sjögren syndrome; RV: residual volume; TLC: total lung capacity; VC: vital capacity.

Among the patients with COPD at follow-up, the percentages of predicted TLC, RV, and RV/TLC ratios decreased significantly from baseline to follow-up. Among the patients with radiographic ILD signs at follow-up, the percentages of predicted TLC, RV, and RV/TLC ratios decreased significantly from baseline to follow-up (Table 2B).

pSS features and respiratory symptoms. PFT results were generally poorly associated with pSS disease features (e.g., disease duration, presence of focal sialadenitis in lower lip biopsy, anti-SSA and anti-SSB seropositivity, and levels of C3, C4, and IgG; data not shown).

Besides the SGRQ activity score, which was significantly increased in patients with COPD at follow-up, respiratory symptoms, as evaluated by the CAT, mMRC, and remaining SGRQ scores, were similar between patients with and without COPD. pSS-associated pulmonary disease activity, evaluated by the ESSDAI respiratory domain score, was also similar between patients with and without COPD. Of note, the majority of patients with COPD did not demonstrate activity in the ESSDAI respiratory domain (Table 3). The frequency of activity in the ESSDAI domains, comparing pSS patients with and without COPD at follow-up, were as follows: constitutional (25% vs 17%), lymphadenopathic (0% vs 4%), glandular (13% vs 13%), articular (13% vs 17%), cutaneous (6% vs 4%), respiratory

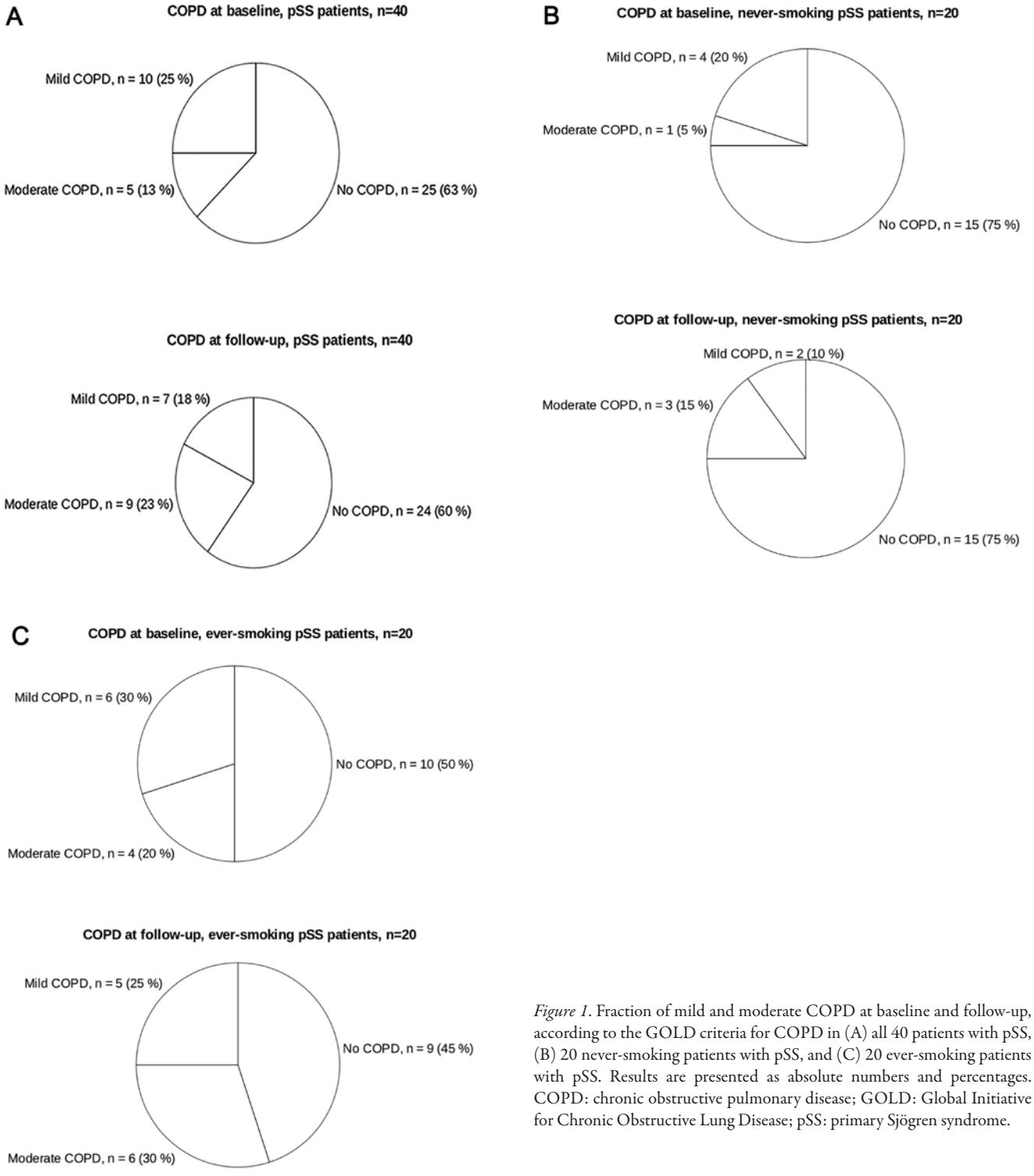

Figure 1. Fraction of mild and moderate COPD at baseline and follow-up, according to the GOLD criteria for COPD in (A) all 40 patients with pSS, (B) 20 never-smoking patients with pSS, and (C) 20 ever-smoking patients with pSS. Results are presented as absolute numbers and percentages. COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; pSS: primary Sjögren syndrome.

(31% vs 38%), renal (6% vs 13%), muscular (0% vs 0%), peripheral nervous system (0% vs 4%), central nervous system (0% vs 0%), hematological (31% vs 29%), and biological (31% vs 58%). In addition, age, disease duration, proportions of lower lip biopsy positivity, anti-SSA positivity, ESSDAI and ESSPRI total scores, and levels of C3, C4, and IgG for pSS did not significantly differ between the patients with and without COPD (data not shown). Comparing patients with and without inhalation treatment at baseline, COPD at baseline (55% vs 31%; $P = 0.17$) and at follow-up (64% vs 31%; $P = 0.08$) were numerically more common among the former. Finally, when comparing patients with and without hydroxychloroquine (HCQ) treatment at baseline, no statistically significant difference in COPD prevalence or respiratory symptoms were found at follow-up (data not shown).

Table 2B. Pulmonary function test (PFT) results in pSS patients with COPD (n = 16) and ILD signs (n = 15) at follow-up.

	Baseline	Follow-up	*P*
Patients with pSS and COPD at follow-up, n = 16			
VC	96 (85–106)	97 (81–109)	0.78
TLC	101 (87–113)	98 (86–108)	0.01
RV	110 (98–134)*	101 (88–114)	0.001
RV/TLC ratio	116 (99–129)*	107 (92–123)	< 0.001
FEV1	85 (70–88)***	77 (67–94)***	0.53
FEV1/VC ratio	86 (79–98)***	87 (79–95)***	0.98
DLCO	88 (78–99)**	92 (71–99)*	0.67
COPD, n (% of COPD+ at FU)	13 (81)	16 (100)	0.25
Mild COPD, n (% of COPD+ at FU)	8 (50)	7 (44)	> 0.99
Moderate COPD, n (% of COPD+ at FU)	5 (31)	9 (56)	0.13
Severe and very severe COPD, n (% of COPD+ at FU)	0 (0)	0 (0)	N/A
Patients with pSS and radiographic ILD signs at follow-up, n = 15			
VC	88 (82–102)*	91 (83–97)*	0.87
TLC	97 (87–107)	95 (86–103)	0.03
RV	113 (98–140)*	101 (87–127)	0.001
RV/TLC ratio	117 (104–131)**	109 (92–122)	0.001
FEV1	81 (74–91)**	78 (74–96)**	> 0.99
FEV1/VC ratio	95 (85–99)**	96 (79–102)	0.65
DLCO	91 (78–103)*	85 (76–98)*	0.28

Values are presented as median % of predicted values (IQR) unless otherwise specified. Results of PFT at baseline in 2012 compared to follow-up in 2018, presented as percentages of predicted values, among the 16 patients with pSS and COPD at follow-up and the 15 patients with pSS and radiographic ILD signs at follow-up. * $P < 0.05$, actual vs predicted values. ** $P < 0.01$, actual vs predicted values. *** $P < 0.001$, actual vs predicted values. COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in 1 second; FU: follow-up; N/A: not assessed; PFT: pulmonary function test; pSS: primary Sjögren syndrome; RV: residual volume, TLC: total lung capacity; VC: vital capacity.

HRCT findings. Radiographic abnormalities at follow-up were found in 82% of the 39 patients with pSS who consented to the HRCT tests. Signs of both bronchial involvement [represented by central bronchiectasis (28%) and bronchial wall thickening (10%)] and ILD [represented by ground-glass attenuation (18%), a reticular pattern (18%), and traction bronchiectasis (13%)] were equally common in proportions, each affecting 38% of patients (Table 3). Among pSS patients with signs of bronchial involvement, one-third had a mixed pattern, also demonstrating ILD-signs. Equally, among patients with ILD signs, one-third showed signs of bronchial involvement. Cysts (36%), emphysema (21%), and nodules (8%) were observed in the patients, with only emphysema being significantly more common among the patients with COPD (38% vs 9%; $P = 0.045$; Table 3).

The proportions of never- and ever-smoking pSS patients were similar in pSS patients with and without any of the HRCT findings. However, ILD signs were found among 45% of never-smoking patients, compared to 32% of ever-smoking patients. Notably, 50% of the patients with emphysema and 67% of the patients with both emphysema and COPD at follow-up were never smokers (data not shown).

Studying associations between radiographic signs of bronchial involvement and percentages of predicted PFT results, a significantly decreased percentage of predicted FEV1 was found when comparing patients with and without radiographic signs of bronchial involvement [87 (74–95) vs 97 (87–101), respectively; $P = 0.03$; data not shown]. Among patients with and without radiographic ILD signs, no significant differences in PFT results were found. No significant differences in obstructive PFT variables were found when comparing patients with COPD, with and without concomitant CT signs of emphysema and/or bronchiectasis, at baseline (data not shown). Comparing patients with and without radiographic ILD signs at follow-up, the frequency of activity in the ESSDAI domains were as follows: constitutional (27% vs 17%), lymphadenopathic (7% vs 0%), glandular (14% vs 13%), articular (13% vs 17%), cutaneous (14% vs 0%), respiratory (60% vs 21%), renal (20% vs 4%), muscular (0% vs 0%), peripheral nervous system (0% vs 4%), central nervous system (0% vs 0%), hematological (40% vs 21%), and biological (67% vs 33%; data not shown). Notably, anti-SSA seropositivity was significantly more common among patients with radiographic ILD signs in comparison to those without (100% vs 71%; $P = 0.03$; data not shown). Further, when comparing patients with and without radiographic ILD signs, C4 was significantly lower [0.13 (0.08–0.19) vs 0.20 (0.17–0.24); $P = 0.04$], while IgG was significantly elevated [15.7 (13.5–19.9) vs 11.0 (8.3–14.8); $P = 0.01$]. Finally, comparing patients with and without HCQ treatment at baseline, a numerically lower prevalence of radiographic ILD signs at follow-up was found among the former (20% vs 45%; $P = 0.26$).

Table 3. Respiratory and radiographic findings in patients with pSS.

	All Patients, n = 40	COPD+, n = 16	COPD−, n = 24	*P*
ESSDAI respiratory domain score > 0, n (%)	14 (35)	5 (31)	9 (38)	0.69
Low activity	9 (23)	3 (19)	6 (25)	0.72
% of ESSDAI score	64%	60%	67%	> 0.99
Moderate activity	5 (13)	2 (13)	3 (13)	> 0.99
% of ESSDAI score	36%	40%	33%	> 0.99
High activity	0 (0)	0 (0)	0 (0)	N/A
CAT total score, median (IQR)	10 (6.00–15.75)	10 (7.00–18.25)	10 (4.00–12.5)	0.17
CAT < 10, n (%)	19 (48)	8 (50)	11 (46)	0.80
CAT ≥ 10, n (%)	21 (52)	8 (50)	13 (54)	0.80
mMRC, median (IQR)	2 (1–2)	2 (2–3)	2 (0–2)	0.13
SGRQ total score, median (IQR)	22.0 (11.4–31.6)	27.8 (18.2–34.0)	18.3 (8.1–30.8)	0.13
SGRQ symptom score	27.0 (9.3–42.4)	34.4 (14.6–46.4)	20.6 (7.2–39.5)	0.28
SGRQ activity score	41.5 (23.3–55.0)	50.7 (37.6–66.2)	35.6 (13.5–50.7)	0.02
SGRQ impact score	8.0 (1.6–18.5)	9.0 (3.6–18.6)	7.2 (0.4–18.5)	0.47
HRCT findings, n (%)	n = 39	n = 16	n = 23	
HRCT abnormalities, any of the below	32 (82)	13 (81)	19 (83)	> 0.99
Cysts	14 (36)	6 (38)	8 (35)	0.86
Central bronchiectasis	11 (28)	7 (44)	4 (17)	0.15
Emphysema	8 (21)	6 (38)	2 (9)	0.045
Ground-glass attenuation	7 (18)	2 (13)	5 (22)	0.68
Reticular pattern	7 (18)	5 (31)	2 (9)	0.10
Traction bronchiectasis	5 (13)	2 (13)	3 (13)	> 0.99
Bronchial wall thickening	4 (10)	1 (6)	3 (13)	0.63
Nodules	3 (8)	3 (19)	0 (0)	0.06
Honeycombing	0 (0)	0 (0)	0 (0)	N/A
Bronchial involvement	15 (38)	8 (50)	7 (30)	0.22
Central bronchiectasis, % of bronchial involvement	73	88	57	0.28
Bronchial wall thickening, % of bronchial involvement	27	13	43	0.28
ILD signs	15 (38)	7 (44)	8 (35)	0.57
Mixed bronchial and ILD signs	5 (13)	4 (25)	1 (4)	0.14

Results are presented as n (%) unless otherwise specified. Results of the ESSDAI respiratory domain and respiratory symptoms evaluated by Swedish versions of the CAT, mMRC, and SGRQ in all 40 patients with pSS, including 16 patients with COPD (COPD+) and 24 patients without COPD (COPD−) at follow-up. Bronchial involvement includes central bronchiectasis or bronchial thickening. ILD signs include ground-glass attenuation, a reticular pattern, traction bronchiectasis, or honeycombing. CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; ESSDAI: EULAR Sjögren Syndrome Disease Activity Index; EULAR: European League Against Rheumatism; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; mMRC: modified Medical Research Council dyspnea scale; N/A: not assessed; pSS: primary Sjögren syndrome; SGRQ: St. George's Respiratory Questionnaire.

The CAT total score was significantly increased among patients with radiographic bronchial signs compared to patients without [11 (9–21) vs 8.5 (5.3–12.5); P = 0.047]. Among patients with HRCT findings, the CAT total score was significantly increased [10 (7.3–16) vs 6 (2–7); P = 0.02] and the proportion of patients with CAT total score > 10 points was significantly higher (63% vs 14%; P = 0.04) compared to patients without HRCT findings (data not shown). When comparing patients with any positive CT findings at baseline, with and without respiratory symptoms (mMRC ≥ 1), the prevalence of ILD signs and COPD at follow-up did not significantly differ between the groups.

DISCUSSION

In our study, patients with pSS demonstrated a mixed pattern of both airway and pulmonary parenchymal disease. During a median follow-up time of 6 years, the percentages of predicted TLC, RV, RV/TLC ratios, and DLCO decreased significantly, while percentages of predicted FEV1/VC ratios increased significantly at follow-up compared to baseline. COPD was a common finding in patients with pSS, although it was numerically more common among ever-smokers. The proportion of patients with COPD did not change significantly during follow-up. On the contrary, changes in pulmonary function over time demonstrated mainly a progression of restrictive variables. Both signs of bronchial involvement and ILD were common HRCT findings, each affecting 38% of the patients. Limited association between respiratory symptoms, pSS disease features, PFT variables, and HRCT findings were observed, in accordance with previous reports[11,13,40].

The heterogeneous results relating to pulmonary function and radiographic findings, including signs of bronchial involvement, ILD, emphysema, cysts, and noduli, are in line with the previously described pleomorphic pSS pulmonary features[3,4,5,11,13,41]. Few previous studies have examined pulmonary function changes over time, and results are difficult to compare due to

the use of various classification criteria for pSS, modalities when assessing pulmonary function, and study designs[11,41,42,43].

The patients with pSS in our study demonstrated mild and moderate COPD. Although the proportions of COPD did not increase over time, a statistically nonsignificant shift from mild to moderate COPD at follow-up was observed. Only a few studies have previously reported COPD as a common finding in patients with pSS[11,13,14]. The previous longitudinal study of COPD prevalence in pSS by our group found a significantly increased prevalence of COPD during follow-up; however, the patients with pSS in that study were all investigated due to presence of respiratory symptoms[11], whereas the current study included consecutive pSS outpatients. COPD was more common among ever-smoking patients, although the mean duration among former smokers between smoking cessation and inclusion in this study was 30 years. Further, because a mainly obstructive pulmonary function pattern was found even after taking smoking into account, and because COPD was still found in 25% of never-smoking patients, our study suggests that pSS may result in COPD development. Neither inhalation treatment nor use of HCQ seemed to affect the development of COPD over time.

In line with our current study, several previous studies, including a large longitudinal study from Greece[9], reported a predominance of small airway obstruction in patients with pSS[4,8,12,44], with a suggested superimposed restrictive component[11,13,43] that may progress during follow-up[41]. In our study, the only radiographic abnormalities found to be significantly associated with any of the pulmonary function variables were emphysema with COPD, and signs of bronchial involvement with a decreased percentage of FEV1 compared to predicted FEV1. The limited association between PFT results and radiographic findings in pSS has been previously reported[11,13,16]. In our current study, a significant decrease in DLCO over time was found, a result that was previously described in a longitudinal study of PFT variables in pSS[43]. DLCO reduction may be observed as a sign of pulmonary parenchymal disease and as a consequence of loss of alveolar area in emphysema. DLCO reduction may also be associated with bronchiolitis, with bronchiolar wall thickening and obliteration secondary to lymphocytic infiltration and structural changes in small airways observed in pSS[5,8,9]. Other non-parenchymal explanations for the reduced DLCO often found in rheumatic diseases could be diastolic dysfunction or development of pulmonary arterial hypertension. However, echocardiographic assessment was only performed in patients with significantly increased NT-proBNP, and in whom signs of systolic dysfunction and pulmonary hypertension were ruled out.

Radiographic cysts were a common finding among the patients with pSS in our study, which is in line with previous studies reporting radiographic cystic lesions to be a characteristic pulmonary radiographic feature in pSS[3,16,45,46,47]. Emphysema was also commonly demonstrated. Notably, half of the patients with emphysema were never-smokers, suggesting that the disease may be involved in the demonstrated airway and parenchymal pulmonary manifestations, including emphysema and COPD. The majority of the patients with COPD did not demonstrate disease activity in the ESSDAI respiratory domain[48]. Considering the limited associations between respiratory symptoms, pulmonary function, and HRCT findings, as well as previous studies showing an increased morbidity and mortality in pSS patients with pulmonary disease[15,16], we recommend that evaluation of pulmonary involvement in pSS should be liberally performed.

The strengths of our study include the analysis of well-characterized, consecutive patients with pSS, as well as the use of population-based PFT controls, predicted PFT values that took cigarette consumption into account, and the use of different modalities assessing both airway and pulmonary parenchymal disease.

The limitations were the relatively small number of patients with pSS, the exclusion of patients with more severe forms of ILD, the limited number of never-smoking patients, HRCT images being obtained only at follow-up, the lack of a control group for the HRCT images, the lack of PFT controls older than 70 years of age, and the lack of pulmonary function variables specifically reflecting small airways.

In conclusion, both airway and pulmonary parenchymal disease were commonly found in patients with pSS, with a coexistence of both obstructive and restrictive pulmonary function findings, in which the latter tended to progress over time. Additionally, the HRCT demonstrated a heterogeneous pulmonary pattern with a mix of both bronchial and pulmonary parenchymal findings. COPD was a common finding. Airway and pulmonary involvement may be underdiagnosed in pSS and special attention in the clinical assessment of patients with pSS is needed, with careful assessment and monitoring of pulmonary involvement, even in patients without respiratory symptoms.

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REFERENCES

1. Mariette X, Criswell LA. Primary Sjogren's syndrome. N Engl J Med 2018;379:97.
2. Ramos-Casals M, Brito-Zerón P, Solans R, Camps MT, Casanovas A, Sopeña B, et al. Systemic involvement in primary Sjogren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology 2014;53:321-31.
3. Hatron PY, Tillie-Leblond I, Launay D, Hachulla E, Fauchais AL, Wallaert B. Pulmonary manifestations of Sjogren's syndrome. Presse Med 2011;40:e49-64.
4. Bellido-Casado J, Plaza V, Díaz C, Geli C, Domínguez J, Margarit G, et al. Bronchial inflammation, respiratory symptoms and lung function in primary Sjogren's syndrome. Arch Bronconeumol 2011;47:330-4.
5. Shi JH, Liu HR, Xu W, Feng RE, Zhang ZH, Tian XL, et al. Pulmonary manifestations of Sjogren's syndrome. Respiration 2009;78:377-86.
6. Yazisiz V, Arslan G, Ozbudak IH, Turker S, Erbasan F, Avci AB, et al. Lung involvement in patients with primary Sjogren's syndrome: what are the predictors? Rheumatol Int 2010;30:1317-24.
7. Kampolis CF, Fragkioudaki S, Mavragani CP, Zormpala A, Samakovli A, Moutsopoulos HM. Prevalence and spectrum of symptomatic pulmonary involvement in primary Sjogren's syndrome. Clin Exp Rheumatol 2018;36 Suppl 112:94-101.
8. Amin K, Lúdvíksdóttir D, Janson C, Nettelbladt O, Gudbjörnsson B, Valtysdottir S, et al. Inflammation and structural

changes in the airways of patients with primary Sjogren's syndrome. Respir Med 2001;95:904-10.
9. Papiris SA, Maniati M, Constantopoulos SH, Roussos C, Moutsopoulos HM, Skopouli FN. Lung involvement in primary Sjogren's syndrome is mainly related to the small airway disease. Ann Rheum Dis 1999;58:61-4.
10. Nilsson AM, Theander E, Hesselstrand R, Piitulainen E, Wollmer P, Mandl T. The forced oscillation technique is a sensitive method for detecting obstructive airway disease in patients with primary Sjogren's syndrome. Scand J Rheumatol 2014;43:324-8.
11. Mandl T, Diaz S, Ekberg O, Hesselstrand R, Piitulainen E, Wollmer P, et al. Frequent development of chronic obstructive pulmonary disease in primary SS--results of a longitudinal follow-up. Rheumatology 2012;51:941-6.
12. Lúdvíksdóttir D, Valtysdottir ST, Hedenström H, Hällgren R, Gudbjörnsson B. Eight-year follow-up of airway hyperresponsiveness in patients with primary Sjogren's syndrome. Ups J Med Sci 2017;122:51-5.
13. Nilsson AM, Diaz S, Theander E, Hesselstrand R, Piitulainen E, Ekberg O, et al. Chronic obstructive pulmonary disease is common in never-smoking patients with primary Sjogren syndrome. J Rheumatol 2015;42:464-71.
14. Shen TC, Wu BR, Chen HJ, Lin CL, Wei CC, Chen CH, et al. Risk of chronic obstructive pulmonary disease in female adults with primary Sjogren syndrome: a nationwide population-based cohort study. Medicine 2016;95:e3066.
15. Palm O, Garen T, Berge Enger T, Jensen JL, Lund MB, Aaløkken TM, et al. Clinical pulmonary involvement in primary Sjogren's syndrome: prevalence, quality of life and mortality--a retrospective study based on registry data. Rheumatology 2013;52:173-9.
16. Chen MH, Chou HP, Lai CC, Chen YD, Chen MH, Lin HY, et al. Lung involvement in primary Sjogren's syndrome: correlation between high-resolution computed tomography score and mortality. J Chin Med Assoc 2014;77:75-82.
17. Brito-Zerón P, Kostov B, Solans R, Fraile G, Suárez-Cuervo C, Casanovas A, et al. Systemic activity and mortality in primary Sjogren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. Ann Rheum Dis 2016;75:348-55.
18. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjogren syndrome. Chest 2006;130:1489-95.
19. Roca F, Dominique S, Schmidt J, Smail A, Duhaut P, Lévesque H, et al. Interstitial lung disease in primary Sjogren's syndrome. Autoimmun Rev 2017;16:48-54.
20. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2019 Report. [Internet. Accessed November 6, 2020]; Available from: goldcopd.org/gold-reports
21. Hagstad S, Ekerljung L, Lindberg A, Backman H, Rönmark E, Lundbäck B. COPD among non-smokers - report from the obstructive lung disease in Northern Sweden (OLIN) studies. Respir Med 2012;106:980-8.
22. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2016;138:16-27.
23. Gergianaki I, Tsiligianni I. Chronic obstructive pulmonary disease and rheumatic diseases: A systematic review on a neglected comorbidity. J Comorb 2019;9:2235042X18820209.
24. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
25. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017;76:9-16.
26. Hedenström H, Malmberg P, Agarwal K. Reference values for lung function tests in females. Regression equations with smoking variables. Bull Eur Physiopathol Respir 1985;21:551-7.
27. Hedenström H, Malmberg P, Fridriksson HV. Reference values for lung function tests in men: regression equations with smoking variables. Ups J Med Sci 1986;91:299-310.
28. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720-35.
29. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
30. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511-22.
31. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.
32. Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T, et al. Validation of EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis 2015;74:859-66.
33. Seror R, Bowman SJ, Brito-Zerón P, Theander E, Bootsma H, Tzioufas A, et al. EULAR Sjogren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015;1:e000022.
34. Engström CP, Persson LO, Larsson S, Sullivan M. Reliability and validity of a Swedish version of the St George's Respiratory Questionnaire. Eur Respir J 1998;11:61-6.
35. Ferrer M, Villasante C, Alonso J, Sobradillo V, Gabriel R, Vilagut G, et al. Interpretation of quality of life scores from the St George's Respiratory Questionnaire. Eur Respir J 2002;19:405-13.
36. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34:648-54.
37. Lanza FC, Castro RA, de Camargo AA, Zanatta DJ, Rached S, Athanazio R, et al. COPD Assessment Test (CAT) is a valid and simple tool to measure the impact of bronchiectasis on affected patients. COPD 2018;15:512-9.
38. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581-6.
39. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697-722.
40. Strevens Bolmgren V, Olsson P, Wollmer P, Hesselstrand R, Mandl T. Respiratory symptoms are poor predictors of concomitant chronic obstructive pulmonary disease in patients with primary Sjogren's syndrome. Rheumatol Int 2017;37:813-8.
41. Pertovaara M, Korpela M, Saarelainen S, Laitinen J, Järvenpää R, Laippala P, et al. Long-term follow-up study of pulmonary findings in patients with primary Sjogren's syndrome. Scand J Rheumatol 2004;33:343-8.
42. Davidson BK, Kelly CA, Griffiths ID. Ten year follow up of pulmonary function in patients with primary Sjogren's syndrome. Ann Rheum Dis 2000;59:709-12.
43. Kelly C, Gardiner P, Pal B, Griffiths I. Lung function in primary Sjogren's syndrome: a cross sectional and longitudinal study. Thorax 1991;46:180-3.
44. Skopuli FN, Dafi U, Ioannidis JP, Mousopulos HM. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000;29:296-304.

45. Koyama M, Johkoh T, Honda O, Mihara N, Kozuka T, Tomiyama N, et al. Pulmonary involvement in primary Sjogren's syndrome: spectrum of pulmonary abnormalities and computed tomography findings in 60 patients. J Thorac Imaging 2001;16:290-6.
46. Lohrmann C, Uhl M, Warnatz K, Ghanem N, Kotter E, Schaefer O, et al. High-resolution CT imaging of the lung for patients with primary Sjogren's syndrome. Eur J Radiol 2004;52:137-43.
47. Egashira R, Kondo T, Hirai T, Kamochi N, Yakushiji M, Yamasaki F, et al. CT findings of thoracic manifestations of primary Sjogren syndrome: radiologic-pathologic correlation. Radiographics 2013;33:1933-49.
48. Retamozo S, Acar-Denizli N, Rasmussen A, Horvath IF, Baldini C, Priori R, et al. Systemic manifestations of primary Sjogren's syndrome out of the ESSDAI classification: prevalence and clinical relevance in a large international, multi-ethnic cohort of patients. Clin Exp Rheumatol 2019;37 Suppl 118:97-106.