# Mixed airway and pulmonary parenchymal disease in patients with primary Sjögren's Syndrome - a six-year follow-up

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**Running Head:** Pulmonary involvement in pSS

**Abstract**

*Objective:* To assess pulmonary function and Chronic Obstructive Pulmonary Disease (COPD) development over time in patients with primary Sjögren's Syndrome (pSS) and 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 re-assessed by pulmonary function tests after a mean follow-up time of six years. At follow-up, patients were also assessed by high-resolution computed tomography (HRCT) of the chest and 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 ($D_{L,CO}$), and an increased percentage of predicted forced expiratory volume in one second/vital capacity ($FEV_1$/VC) ratio from baseline to follow-up. The proportion of COPD did not change significantly from baseline to follow-up (38% vs. 40%). Radiographic signs of bronchial involvement and interstitial lung disease were found in 38% of the patients, respectively.

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

## Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune rheumatic disease, classically striking females and affecting various exocrine glands, resulting in the characteristic sicca symptoms (1). Besides the symptoms associated with exocrine gland dysfunction, pain and fatigue in pSS, approximately one third of pSS patients demonstrate involvement of several non-exocrine 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 differ between studies, possibly due to differences in methodology, pSS classification criteria and patient selection (3-7). 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, 7-12). Besides pSS associated airway disease, interstitial lung disease (ILD) is also a recognized manifestation of pSS, both of which may co-exist in the same patient (3, 10). In a previous study, Chronic Obstructive Lung Disease (COPD) was reported in 41% of the pSS patients overall and importantly amongst 30% of never-smoking pSS patients, indicating that pSS *per se* 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 pSS patients (14). Finally, pSS associated pulmonary disease has been shown to be associated with a decreased quality of life (QoL) as well as an increased morbidity and mortality (15-17). Particularly some subtypes of ILD are known to be associated with poor prognosis in pSS (18, 19). Though globally, COPD is one of the major causes of morbidity and mortality and a substantial proportion of patients with COPD have never smoked (20, 21). Besides cigarette smoking, environmental and genetic risk factors, autoimmune mechanisms have

been highlighted in COPD pathology. Correspondingly, increased rates of COPD amongst patients with autoimmune rheumatic diseases have been reported (20-23).

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

### Ethics

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

## Materials and methods

### Patients

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

**Pulmonary function test controls**

The pulmonary function test (PFT) controls consisted of 186 population-based female subjects attending a general health survey in Uppsala, 100 of whom were never smokers and 86 current smokers (mean age 45, range 20-70 years) and 270 population-based male subjects, also attending a general health survey in Uppsala, 124 of whom were never smokers and 146 current smokers (mean age 45, range 20-70 years) (26, 27). Predicted PFT values were calculated based on the PFT results of the controls by a linear regression model, into which age, height, weight and cigarette smoking were added as co-variates for females and males separately, thus correcting predicted PFT variables also for smoking.

**Pulmonary Function Tests**

The PFTs included static and dynamic spirometry, from which the vital capacity (VC), total lung capacity (TLC), residual volume (RV), forced expiratory volume in one second ($FEV_1$), and $FEV_1$/VC ratio and RV/TLC ratio could be calculated. Diffusing capacity of the lungs for carbon monoxide ($D_{L,CO}$) was measured by the single-breath technique. $FEV_1$ and VC were measured before and after 1.0 mg inhaled terbutaline [$FEV_1$ after reversibility test ($FEV_1$rev) and VC after reversibility test (VCrev)] and $FEV_1$ reversibility was calculated.

TLC and RV were measured by body plethysmography. Clinically significant reversibility was defined as $FEV_1$ improvement ≥ 12% and ≥ 200 mL (31). COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, as a $FEV_1$rev/VCrev ratio < 0.70 (20). Lung function tests, including calibration were performed according to current standards (28-30). PFT variables were expressed as percentages of predicted values. Predicted PFT values were calculated based on the PFT results of the controls.

**ESSDAI and ESSPRI**

pSS disease activity was assessed by the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), scoring disease activity in 12 domains, representing different organ systems. The added domain scores compose the ESSDAI total score, with a range between 0-123 points. Patient reported symptoms; 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 between 0-10 points (32, 33).

**SGRQ, CAT, mMRC and questionnaire assessing cigarette smoking**

Evaluation of respiratory and COPD associated symptoms and impact on QoL was conducted, using validated questionnaires; the Swedish versions of the St George's Respiratory Questionnaire (SGRQ) and the COPD assessment test (CAT). The modified Medical Research Council (mMRC) dyspnoea scale was also used. In the SGRQ respiratory symptoms, activity and impact are evaluated. Total scores are calculated and range between 0 to 100 points (34, 35). The CAT assesses and monitors COPD and consists of eight items. Total scores range from 0 to 40 points. CAT scores $< 10$ points indicate less symptomatic COPD while CAT scores $\geq 10$ points indicate more symptomatic COPD (36, 37). The mMRC dyspnoea scale evaluates dyspnoea-associated disability. Total scores range from 0-4 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-years assessment.

**Laboratory tests**

Laboratory signs of inflammation were evaluated by assessing levels of: CRP, ESR, IgG, IgA, IgM, C3 and C4. Serologies performed in the diagnostic procedures of the disease included anti-SS-A, anti-SS-B antibodies as well as ANA and RF and were re-assessed. 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, Forchheim, Germany) with a detector configuration of 128 × 0.6, automated tube voltage selection (Care kV, ref kV 100), tube current modulation (CareDose 4D 150 ref mAs), pitch 1.1 and a rotation time of 0.5 seconds. The following reconstructions were obtained: I70f, 1 mm slice thickness/0.5 mm increment and I70f, 5 mm/5 mm. The images were interpreted visually by a radiologist (HLA), who was blinded with regard to the PFT results and the clinical features of the patients. The findings were defined by the Fleischner society's guidelines for imaging studies (39). Presence of emphysema, cysts, nodules, signs of bronchial involvement (defined as central bronchiectasis or bronchial wall thickening) and ILD signs (defined as ground glass attenuation, a reticular pattern, traction bronchiectasis or honeycombing) were registered.

**Statistics**

When comparing measured and predicted PFT results as well as when comparing previous with the actual PFT results the paired samples Student's t-test and the Wilcoxon Signed Rank Test were used. For comparison between independent groups, the Student's t-test and the

Mann Whitney U-test were used. Differences in categorical data were analyzed by the Chi-square test and Fisher's exact test. The McNemars test was used when comparing pairwise frequencies of categorical data. For correlations, Pearson's correlation coefficient and Spearman's correlation coefficient were calculated as appropriate. P-values <0.05 were considered statistically significant.

## Results

*Pulmonary function test results - changes over time*

Patients with pSS showed significantly decreased percentages of predicted TLC, RV, RV/TLC ratio and $D_{L,CO}$ and an increased percentage of predicted $FEV_1$/VC ratio at follow-up compared to percentages of predicted values at baseline. There was no statistically significant difference in prevalence of COPD between baseline and follow-up (38% vs. 40%; p=1.000) (TABLE 2A). At baseline 15 patients demonstrated COPD and at follow-up 16 of 40; thus, 2 patients did not fulfill GOLD criteria for COPD at follow-up, and 3 patients developed COPD from baseline to follow-up. A statistically non-significant shift from mild towards moderate COPD from baseline to follow-up was observed, both amongst pSS patients in general as well as amongst never- and ever-smoking pSS patients respectively (FIGURE 1). Amongst patients with symptomatic COPD (mMRC≥1) at baseline, 43% and 57% fulfilled GOLD 1 and 2 criteria at baseline, respectively, whilst 29% and 71% fulfilled GOLD 1 and 2 criteria at follow-up, respectively, and 29% progressed in GOLD class during follow-up. Amongst patients without symptomatic COPD at baseline, 13% progressed in GOLD class during follow-up.

When comparing never- and ever-smoking pSS patients at follow-up, no significant differences in percentages of predicted PFT results were found between groups (data not shown). Although the proportion of COPD was numerically increased in the latter the

differences did not reach statistical significance (55% vs. 25%; p=0.053). However, cigarette consumption, as evaluated by pack-years, was significantly increased in the pSS patients with COPD at follow-up compared to patients without COPD at follow-up (4 (0; 21) vs. 0 (0; 3); p=0.034).

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

*PFT results - 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 SS-A and SS-B seropositivity and levels of C3, C4 and IgG (data not shown).

Besides the SGRQ Activity score, which was significantly increased in pSS 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, as was pSS associated pulmonary disease activity as evaluated by the ESSDAI respiratory domain score. Of note, the majority of the pSS patients with COPD did not demonstrate activity in the ESSDAI respiratory domain (TABLE 3). Comparing pSS patients with and without COPD at follow-up, the frequency of activity in the ESSDAI domains were as follows: constitutional (25% vs. 17%), lymphadenopathic (0% vs. 4%), glandular (13% vs. 13%), articular (13% vs. 17%), cutaneous (6% vs. 4%), respiratory (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-SS-A positivity, ESSDAI and ESSPRI total scores, 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=0.170) and COPD at follow-up (64% vs. 31%; p=0.080) were numerically more common amongst the former. Finally, comparing patients with and without hydroxychloroquine treatment at baseline, no statistically significant difference in COPD prevalence or respiratory symptoms, at follow-up, were found (data not shown).

*HRCT findings*

Radiographic abnormalities at follow-up were found in 82% of the 39 pSS patients. Both signs of bronchial involvement [represented by central bronchiectasis (28%) and bronchial wall thickening (10%)] as well as ILD signs [represented by ground glass attenuation (18%), a reticular pattern (18%) and traction bronchiectasis (13%)] were equally common in proportions, namely 38% each (TABLE 3). One-third within both pSS patients with signs of bronchial involvement and patients with ILD signs showed a mixed pattern with both bronchial and ILD associated findings (data not shown). Cysts, emphysema and nodules were observed in 36%, 21% and 8% of the pSS patients respectively (TABLE 3).

Only emphysema was significantly more common amongst the pSS 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 amongst 45% of never- and 32% of ever-smoking pSS patients, and of note, 50 % of the pSS patients with emphysema and 67% of the patients with both emphysema and COPD, at follow-up, were never-smokers.

Studying associations between radiographic signs of bronchial involvement and percentages of predicted PFT results, only a significantly decreased percentage of predicted $FEV_1$ was found when comparing patients with vs. without radiographic signs of bronchial involvement

(87 (74; 95) vs. 97 (87; 101); p=0.030). Amongst pSS patients with vs. without radiographic ILD signs no significant differences in PFT results were found. Comparing patients with COPD with and without concomitant CT signs of emphysema and/or bronchiectasis, at baseline, no significant differences in obstructive PFT variables were found (data not shown). Comparing pSS 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%). Of note, anti-SS-A seropositivity was significantly more common amongst pSS patients with radiographic ILD signs in comparison to those without (100% vs. 71%; p=0.031). Furthermore, in pSS patients with radiographic ILD signs, C4 was significantly decreased and IgG significantly increased compared to patients without such findings (0.13 (0.08; 0.19) vs. 0.20 (0.17; 0.24); p=0.044) and (15.7 (13.5; 19.9) vs. 11.0 (8.3; 14.8); p=0.010), respectively. Finally, comparing patients with and without hydroxychloroquine treatment at baseline, a numerically lower prevalence of radiographic ILD signs at follow-up was found amongst the former (20% vs. 45%; p=0.263).

The CAT total score was significantly increased amongst the pSS patients with radiographic bronchial signs compared to patients without (11 (9; 21) vs. 8.5 (5.3; 12.5); p=0.047). Also amongst pSS patients with HRCT findings, the CAT total score was significantly increased (10 (7.3; 16) vs. 6 (2; 7); p=0.022) and the proportion of patients with CAT total score > 10 points was significantly higher (63% vs. 14%; p= 0.035) in comparison to patients without HRCT findings. 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 this study patients with pSS demonstrated a mixed pattern of both airway and pulmonary parenchymal disease. During a median follow-up time of six years pSS patients significantly decreased percentages of predicted TLC, RV, RV/ TLC ratio and $D_{L,CO}$ and increased percentage of predicted $FEV_1$/VC ratio at follow-up compared to baseline. COPD was a common finding in pSS patients, although numerically more common amongst ever-smokers. However, the proportions 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 signs were common HRCT findings, affecting 38% of the patients respectively. Limited associations between respiratory symptoms, pSS disease features, PFT variables and HRCT findings were observed, in accord with previous reports (11, 13, 40).

The mixed and heterogeneous findings, both with regard to pulmonary function and radiographic findings, representing signs of both bronchial involvement and ILD, emphysema, cysts and noduli, are in line with the previously described pleomorphic pSS pulmonary features (3-5, 11, 13, 41). Few previous studies have studied pulmonary function changes over time, and results are difficult to compare, due to use of various classification criteria for pSS, modalities when assessing pulmonary function and study design (11, 41-43). The pSS patients in this study demonstrated mild and moderate COPD. Although the proportions of COPD did not increase over time, a statistically non-significant shift from mild towards 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 showed a significantly increased prevalence of COPD during follow-up, but the pSS patients were in that study all investigated due to presence of respiratory symptoms (11), whilst the current study included consecutive pSS outpatients. COPD was more common amongst ever-smokers. However, the mean duration, amongst former smokers, between smoking cessation and inclusion in this study was 30 years. Furthermore, as a mainly obstructive pulmonary function pattern was found, even after taking smoking into account, and as COPD still was found amongst 25% of never-smoking patients, this suggests that pSS *per se* may result in COPD development. Neither inhalation treatment nor use of hydroxychloroquine seemed to impact the development of COPD over time.

In line with the current study, several prior studies, including a large longitudinal study from Greece, report a predominance of small airway obstruction in pSS patients (4, 8, 9, 12, 44), with a suggested superimposed restrictive component (11, 13, 43), that may progress during follow-up (41). In this study the only radiographic abnormalities being significantly associated with any of the pulmonary function variables were emphysema with COPD and signs of bronchial involvement with decreased percentage of predicted $FEV_1$. The limited association between PFT results and radiographic findings in pSS has previously been reported (11, 13, 16). In the current study a significant decrease of $D_{L,CO}$ over time was found, a finding also previously described in a longitudinally study of PFT variables in pSS (43). $D_{L,CO}$ reduction may be observed both as a sign of pulmonary parenchymal disease, as a consequence of loss of alveolar area in emphysema and might as well be associated with the 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 $D_{L,CO}$, 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, in whom signs of at least a systolic dysfunction and pulmonary hypertension were ruled out.

Radiographic cysts were a common finding amongst the pSS patients in this study, which is in accordance with previous studies reporting radiographic cystic lesions to be a characteristic pulmonary radiographic pSS feature (3, 16, 45-47). Also emphysema was commonly demonstrated. Of note, half of the pSS patients with emphysema were never smokers, suggesting that the disease *per se* may be involved in the demonstrated airway and parenchymal pulmonary manifestations, including emphysema and COPD. Of note, the majority of the pSS 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 recent 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 this study were the study of well characterized consecutive pSS patients, as well as the use of population-based PFT controls, predicted PFT values taking 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 pSS patients not including pSS 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 older PFT controls than 70 years of age, as well as the lack of pulmonary function variables specifically reflecting small airways.

In conclusion, both airway and pulmonary parenchymal disease were commonly found in pSS patients, with a coexistence of both obstructive and restrictive pulmonary function

findings, where the latter tended to progress over time. Also the HRCTs demonstrated a heterogeneous pulmonary pattern with a mix of both bronchial and pulmonary parenchymal findings. COPD was still 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 carefully assessment and monitoring of pulmonary involvement, even in patients without respiratory symptoms.

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## Table and Figure Legends

### TABLE 1

### CHARACTERISTICS OF pSS PATIENTS

Disease characteristics and demographics of the 40 pSS patients. Values are presented as mean (± S.D.), median (IQR) and proportions with findings as percentages.

ACR = American College of Rheumatology, AECG = American European Consensus Group, EULAR = European League Against Rheumatism, ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index, ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index, csDMARD = conventional synthetic Disease Modifying Anti-Rheumatic Drugs, ICS = Inhaled Corticosteroids, LABA = Long-Acting β2 Agonists, LAMA = Long-Acting Muscarinic Antagonists, SABA = Short -Acting β2 Agonists

### TABLE 2A

### PULMONARY FUNCTION TEST RESULTS IN pSS PATIENTS

Results of the PFTs presented as percentage of predicted values in 40 pSS patients at baseline 2012 compared to follow-up 2018. Clinically significant reversibility was defined as $FEV_1$ improvement ≥12% and ≥ 200 mL after 1.0 mg inhaled terbutaline. Results are presented as mean percentages of predicted (± S.D.), median percentages of predicted (IQR) and proportional findings as numbers and percentages. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ vs. predicted values, respectively, whereas p-values refer to baseline vs. follow-up.

PFT = pulmonary function tests, VC = Vital capacity, TLC = Total lung capacity, RV = Residual volume, $FEV_1$ = Forced expiratory volume in one second, $D_{L,CO}$ = Diffusing capacity of the lungs for carbon monoxide, COPD = Chronic obstructive pulmonary disease, NA = not assessed

**TABLE 2B**

**PULMONARY FUNCTION TEST RESULTS IN pSS PATIENTS WITH COPD AT FOLLOW-UP AND IN pSS PATIENTS WITH ILD SIGNS AT FOLLOW-UP**

Results of the PFTs at baseline 2012 compared to follow-up 2018, presented as percentages of predicted values, amongst the 16 patients with pSS and COPD and 15 patients with pSS and radiographic ILD signs at follow-up.

Results are presented as median percentages of predicted (IQR) and proportional findings as percentages. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ vs. predicted values, respectively, whereas p-values refer to baseline vs. follow-up.

PFT = Pulmonary function test, COPD = Chronic obstructive pulmonary disease, ILD = interstitial lung disease, VC = Vital capacity, TLC = Total lung capacity, RV = Residual volume, $FEV_1$ = Forced expiratory volume in one second, $D_{L,CO}$ = Diffusing capacity for carbon monoxide, FU = Follow-up, NA = not assessed

**TABLE 3**

**RESPIRATORY AND RADIOGRAPHIC FINDINGS IN pSS PATIENTS**

Results of the ESSDAI respiratory domain and respiratory symptoms evaluated by Swedish versions of the CAT, mMRC and SGRQ in all the 40 patients with pSS as well as the 16 pSS patients with (+) and the 24 pSS patients without (-) COPD at follow-up.

Results of HRCT of the chest in 39 of the pSS patients, as well as in the 16 pSS patients with (+) and the 23 pSS patients without (-) COPD. Bronchial involvement includes central bronchiectasis or bronchial thickening and ILD signs ground glass attenuation, a reticular pattern, traction bronchiectasis or honeycombing. Results are presented as medians (IQR) and proportional findings as percentages.

COPD = chronic obstructive pulmonary disease, EULAR = European League Against Rheumatism, ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index, NA = not assessed, CAT = COPD assessment test, mMRC = modified Medical Research Council dyspnoea scale, SGRQ = St George's Respiratory Questionnaire, HRCT = high-resolution computed tomography, ILD = interstitial lung disease

**FIGURE 1**

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

**TABLE 1**

**CHARACTERISTICS OF pSS PATIENTS**

Disease characteristics and demographics of the 40 pSS patients. Values are presented as mean (± S.D.), median (IQR) and proportions with findings as percentages.

ACR = American College of Rheumatology, AECG = American European Consensus Group, EULAR = European League Against Rheumatism, ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index, ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index, csDMARD = conventional synthetic Disease Modifying Anti-Rheumatic Drugs, ICS = Inhaled Corticosteroids, LABA = Long-Acting β2 Agonists, LAMA = Long-Acting Muscarinic Antagonists, SABA = Short -Acting β2 Agonists

| Characteristics | pSS patients, n = 40 |
|---|---|
| Age (yrs) | 66 ± 9 |
| Gender, n females/males | 39/ 1 |
| Lower lip biopsy – focus score ≥ 1 (n=31), (%) | 70 |
| Disease duration (yrs) | 22 ± 12 |
| Follow up time (yrs) | 6 (5; 6) |
| Current/prior/never smokers, n (%) | 3 (8) / 17 (43) / 20 (50) |
| Cigarette smoking (pack-yrs) | 7.8 (2.5; 18.0) |
| Anti-SS-A antibody seropositives (%) | 83 |
| Anti-SS-B antibody seropositives (%) | 53 |
| ANA seropositives (%) | 80 |
| RF seropositives (%) | 65 |
| IgG (g/L) | 13.6 ± 4.9 |
| C3 (g/L) | 0.94 ± 0.24 |
| C4 (g/L) | 0.18 ± 0.07 |
| ESSDAI Total score | 5 (1; 8) |
| ESSPRI Total score | 6 ± 2 |
| Systemic pSS treatment, n (%) | 13 (33) |
| Low-dose glucocorticosteriods, n (%) | 9 (23) |
| Hydroxychlorquine, n (%) | 10 (25) |
| csDMARD, n (%) | 1 (3) |
| Inhalation treatment, n (%) | 13 (33) |
| Combined ICS + LABA, n (%) | 9 (23) |
| LAMA, n (%) | 2 (5) |
| SABA or LABA, n (%) | 8 (24) |

**TABLE 2A**

**PULMONARY FUNCTION TEST RESULTS IN pSS PATIENTS**

Results of the PFTs presented as percentage of predicted values in 40 pSS patients at baseline 2012 compared to follow-up 2018. Clinically significant reversibility was defined as $FEV_1$ improvement ≥12% and ≥ 200 mL after 1.0 mg inhaled terbutaline. Results are presented as mean percentages of predicted (± S.D.), median percentages of predicted (IQR) and proportional findings as numbers and percentages. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ vs. predicted values, respectively, whereas p-values refer to baseline vs. follow-up.

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| PFT results in pSS patients, n=40 | Baseline | Follow-up | p-values |
|---|---|---|---|
| VC (% of predicted) | 97 ± 14 | 96 ± 14* | 0.472 |
| TLC (% of predicted) | 101 ± 12 | 97 ± 10 | 0.000 |
| RV (% of predicted) | 113 ± 20** | 101 ± 18 | 0.000 |
| RV/TLC ratio (% of predicted) | 112 (100; 120)*** | 103 (92; 112) | 0.000 |
| $FEV_1$ (% of predicted) | 91 ± 15*** | 91 ± 16*** | 0.989 |
| $FEV_1$/VC ratio (% of predicted) | 96 (89; 100)** | 98 (89; 104) | 0.012 |
| $D_{L,CO}$ (% of predicted) | 95 ± 13* | 92 ± 15** | 0.016 |
| COPD, n (%) | 15 (38) | 16 (40) | 1.000 |
| - Mild COPD, n (% of the above) | 10 (67) | 7 (44) | 0.375 |
| - Moderate COPD, n (% of the above) | 5 (33) | 9 (56) | 0.125 |
| - Severe and very severe COPD, n | 0 | 0 | NA |
| Clinically significant reversibility, n (%) | 3 (8) | 2 (5) | 1.000 |

**TABLE 2B**

**PULMONARY FUNCTION TEST RESULTS IN pSS PATIENTS WITH COPD AT FOLLOW-UP AND IN pSS PATIENTS WITH ILD SIGNS AT FOLLOW-UP**

Results of the PFTs at baseline 2012 compared to follow-up 2018, presented as percentages of predicted values, amongst the 16 patients with pSS and COPD at follow-up and 15 patients with pSS and radiographic ILD signs at follow-up.

Results are presented as median percentages of predicted (IQR) and proportional findings as percentages. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ vs. predicted values, respectively, whereas p-values refer to baseline vs. follow-up.

PFT = Pulmonary function test, COPD = Chronic obstructive pulmonary disease, ILD = interstitial lung disease, VC = Vital capacity, TLC = Total lung capacity, RV = Residual volume, $FEV_1$ = Forced expiratory volume in one second, $D_{L,CO}$ = Diffusing capacity for carbon monoxide, FU = Follow-up, NA = not assessed

| PFT results in patients with pSS and COPD at follow-up, n=16 | Baseline | Follow-up | p-values |
|---|---|---|---|
| VC (% of predicted) | 96 (85; 106) | 97 (81; 109) | 0.782 |
| TLC (% of predicted) | 101 (87; 113) | 98 (86; 108) | 0.013 |
| RV (% of predicted) | 110 (98; 134)* | 101 (88, 114) | 0.001 |
| RV/TLC ratio (% of predicted) | 116 (99; 129)* | 107 (92; 123) | 0.000 |
| $FEV_1$ (% of predicted) | 85 (70; 88)*** | 77 (67; 94)*** | 0.528 |
| $FEV_1$/VC ratio (% of predicted) | 86 (79; 98)*** | 87 (79; 95)*** | 0.980 |
| $D_{L,CO}$ (% of predicted) | 88 (78; 99)** | 92 (71; 99)* | 0.669 |
| COPD, n (% of pSS with COPD at FU) | 13, (81) | 16, (100) | 0.250 |
| - Mild COPD, n (% of pSS with COPD at FU) | 8, (50) | 7, (44) | 1.000 |
| - Moderate COPD, n (% of pSS with COPD at FU) | 5, (31) | 9, (56) | 0.125 |
| - Severe and very severe COPD, n | 0 | 0 | NA |
| PFT results in patients with pSS and radiographic ILD signs at follow-up, N=15 | Baseline | Follow-up | p-values |
| VC (% of predicted) | 88 (82; 102)* | 91 (83; 97)* | 0.865 |
| TLC (% of predicted) | 97 (87; 107) | 95 (86; 103) | 0.027 |
| RV (% of predicted) | 113 (98; 140)* | 101 (87, 127) | 0.001 |
| RV/TLC ratio (% of predicted) | 117 (104; 131)** | 109 (92; 122) | 0.001 |
| $FEV_1$ (% of predicted) | 81 (74; 91)** | 78 (74; 96)** | 1.000 |
| $FEV_1$/VC ratio (% of predicted) | 95 (85; 99)** | 96 (79; 102) | 0.650 |
| $D_{L,CO}$ (% of predicted) | 91 (78; 103)* | 85 (76; 98)* | 0.281 |

**TABLE 3**

**RESPIRATORY AND RADIOGRAPHIC FINDINGS IN pSS PATIENTS**

Results of the ESSDAI respiratory domain and respiratory symptoms evaluated by Swedish versions of the CAT, mMRC and SGRQ in all the 40 patients with pSS as well as the 16 pSS patients with (+) and the 24 pSS patients without (-) COPD at follow-up.

Results of HRCT of the chest in 39 of the pSS patients, as well as in the 16 pSS patients with (+) and the 23 pSS patients without (-) COPD. Bronchial involvement includes central bronchiectasis or bronchial thickening and ILD signs ground glass attenuation, a reticular pattern, traction bronchiectasis or honeycombing. Results are presented as medians (IQR) and proportional findings as percentages.

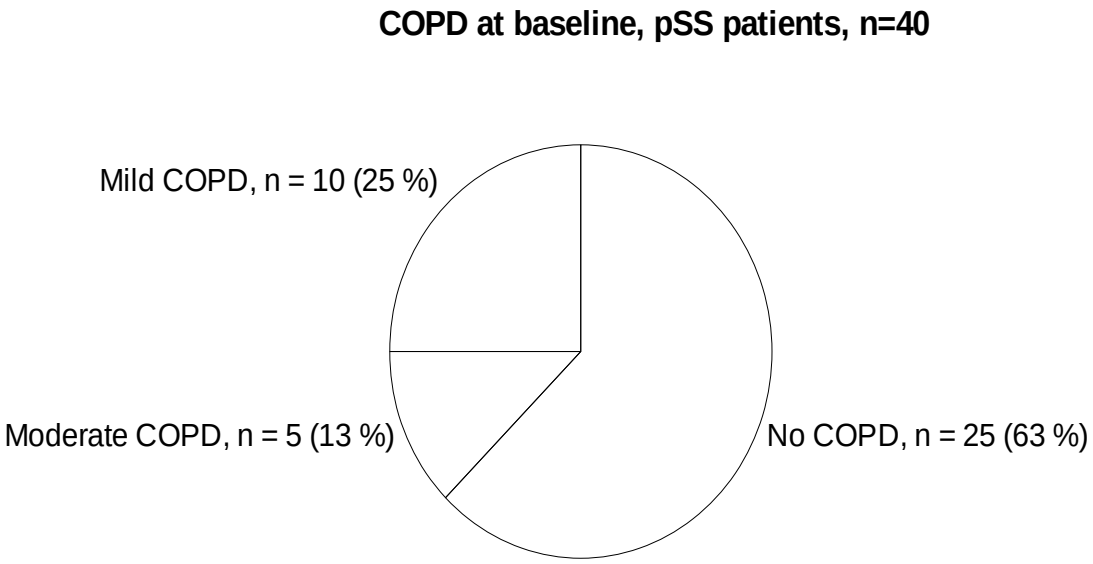
COPD = chronic obstructive pulmonary disease, EULAR = European League Against Rheumatism, ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index, NA = not assessed, CAT = COPD assessment test, mMRC = modified Medical Research Council dyspnoea scale, SGRQ = St George's Respiratory Questionnaire, HRCT = high-resolution computed tomography, ILD = interstitial lung disease

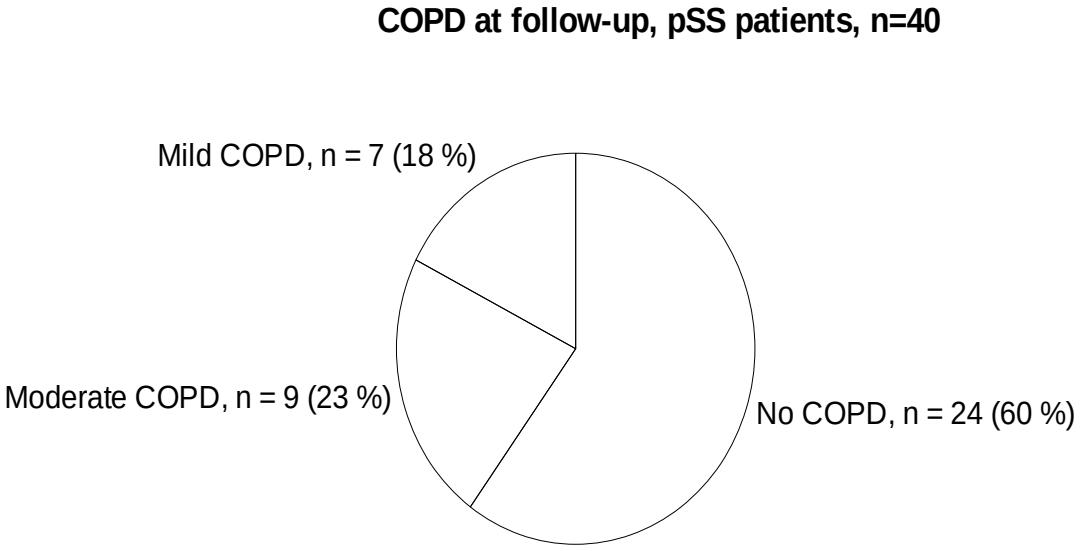
| Respiratory and radiographic findings | All pSS patients, n=40 | pSS patients + COPD, n=16 | pSS patients – COPD, n=24 | p-values pSS + vs. – COPD |
|---|---|---|---|---|
| ESSDAI respiratory domain score > 0, n (%) | 14 (35) | 5 (31) | 9 (38) | 0.685 |
| Low activity, n (%), | 9 (23) | 3 (19) | 6 (25) | 0.717 |
| % of above | 64% | 60% | 67% | 1.000 |
| Moderate activity, n (%), | 5 (13) | 2 (13) | 3 (13) | 1.000 |
| % of above | 36% | 40% | 33% | 1.000 |
| High activity, n | 0 | 0 | 0 | NA |
| CAT total score | 10 (6.00; 15.75) | 10 (7.00; 18.25) | 10 (4,00; 12.5) | 0.174 |
| CAT <10 | 19 (48) | 8 (50) | 11 (46) | 0.796 |
| CAT ≥ 10 | 21 (52) | 8 (50) | 13 (54) | 0.796 |
| mMRC | 2 (1, 2) | 2 (2; 3) | 2 (0; 2) | 0.126 |
| SGRQ Total score | 22.0 (11.4; 31.6) | 27.8 (18.2; 34.0) | 18.3 (8.1; 30.8) | 0.134 |
| - SGRQ Symptom score | 27.0 (9.3; 42.4) | 34.4 (14.6; 46.4) | 20.6 (7.2; 39.5) | 0.279 |
| - SGRQ Activity score | 41.5 (23.3; 55.0) | 50.7 (37.6; 66.2) | 35.6 (13.5; 50.7) | 0.017 |
| - SGRQ Impact score | 8.0 (1.6; 18.5) | 9.0 (3.6; 18.6) | 7.2 (0.4; 18.5) | 0.469 |
| HRCT findings assessed in 39 patients | n=39 | n=16 | n=23 | |
| HRCT abnormalities, any of the below, n (%) | 32 (82) | 13 (81) | 19 (83) | 1.000 |
| Cysts, n (%) | 14 (36) | 6 (38) | 8 (35) | 0.862 |
| Central bronchiectasis, n (%) | 11 (28) | 7 (44) | 4 (17) | 0.146 |
| Emphysema, n (%) | 8 (21) | 6 (38) | 2 (9) | 0.045 |
| Ground glass attenuation, n (%) | 7 (18) | 2 (13) | 5 (22) | 0.678 |
| Reticular pattern, n (%) | 7 (18) | 5 (31) | 2 (9) | 0.101 |
| Traction bronchiectasis, n (%) | 5 (13) | 2 (13) | 3 (13) | 1.000 |
| Bronchial wall thickening, n (%) | 4 (10) | 1 (6) | 3 (13) | 0.631 |
| Nodules, n (%) | 3 (8) | 3 (19) | 0 (0) | 0.061 |
| Honeycombing, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |
| Bronchial involvement, n (%) | 15 (38) | 8 (50) | 7 (30) | 0.217 |
| Central bronchiectasis (% of the above) | 73 | 88 | 57 | 0.282 |
| Bronchial wall thickening (% of the above) | 27 | 13 | 43 | 0.282 |
| ILD signs, n (%) | 15 (38) | 7(44) | 8 (35) | 0.571 |

| | | | | |
|---|---|---|---|---|
| Mixed bronchial and ILD signs, n (%) | 5 (13) | 4 (25) | 1 (4) | 0.139 |

**FIGURE 1**

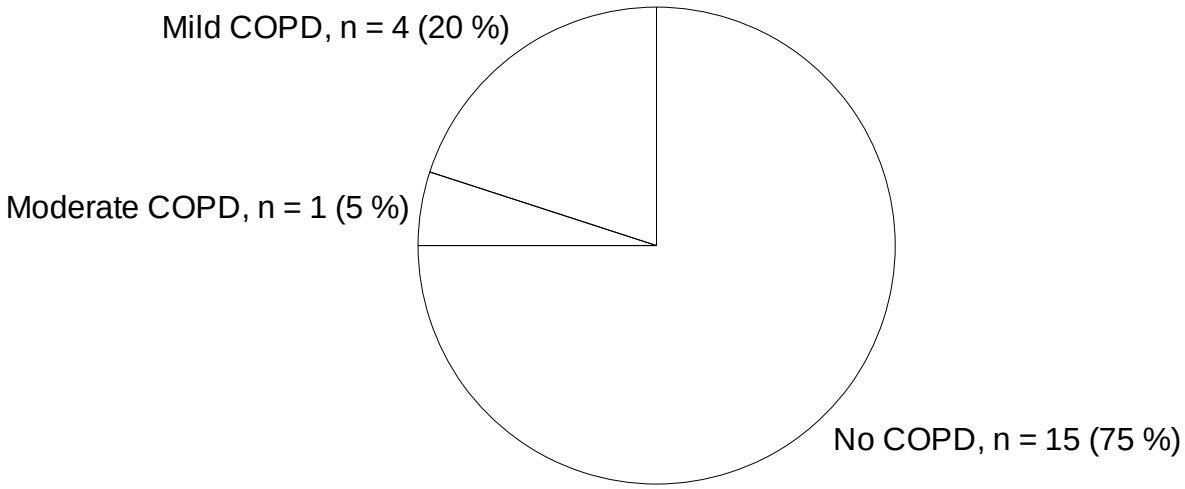
**A**



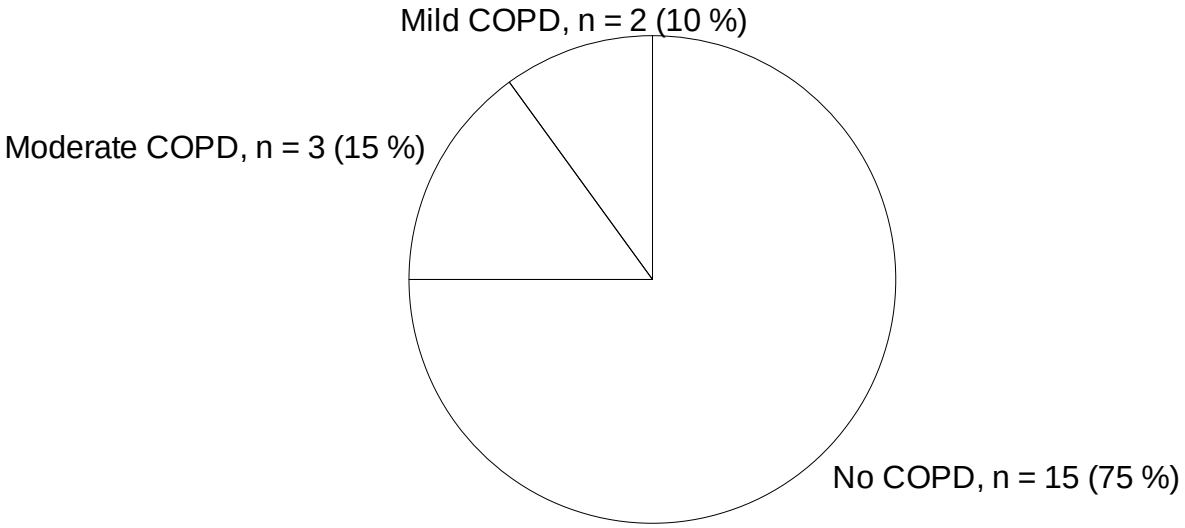



**B**

**COPD at baseline, never-smoking pSS patients, n=20**




**COPD at follow-up, never-smoking pSS patients, n=20**



C