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# Pulmonary involvement in primary Sjögren's syndrome, as measured by the ESSDAI

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**Objective:** Systemic features influence disease prognosis and choice of treatment in primary Sjögren's syndrome (pSS). Our aim was to investigate the prevalence of pulmonary involvement in pSS patients and to classify patients according to the pulmonary domain of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

**Methods:** This retrospective cohort study included consecutive pSS patients, fulfilling American–European Consensus Group/American College of Rheumatology classification criteria, who visited the Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, in 2015. Data on pulmonary complaints and pulmonary tests were obtained from electronic patient records. Pulmonary involvement was recorded if therapy was needed or follow-up was recommended, and when it was possibly or assumed to be related to pSS instead of coincidental factors.

**Results:** Of the 262 included pSS patients, 88 (34%) had pulmonary complaints, mostly cough or dyspnoea on exertion. Pulmonary diagnostics were performed in 225 patients (86%). Pulmonary involvement was present and assumed to be related to pSS in 25 patients (10%) and possibly related to pSS in 14 (5%). Interstitial lung disease (ILD,  $n = 15$ ), especially non-specific interstitial pneumonia ( $n = 7$ ), was present most commonly. In total, 16 patients (6%) were scored as low ( $n = 4$ ), moderate ( $n = 11$ ), or high activity ( $n = 1$ ) on the ESSDAI pulmonary domain.

**Conclusion:** In this cross-sectional study in daily clinical practice, pulmonary involvement was present in 10–15% of pSS patients, of which ILD was most common. Of all pSS patients, 6% were scored as active on the pulmonary domain of the ESSDAI.

Primary Sjögren's syndrome (pSS) is a common systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. Besides sicca symptoms, many patients have extraglandular involvement, e.g. arthritis, cutaneous vasculitis, nephritis, and/or pulmonary involvement.

In previous studies, the estimated prevalence of lung involvement in pSS has varied greatly, ranging from 9% to 75%, mostly depending on differences in the imaging modality used and criteria of pulmonary involvement (1–4). When pulmonary involvement is defined as the presence of pulmonary symptoms with an abnormal pulmonary function test (PFT) or radiograph, the prevalence of pulmonary involvement is reported to be 9–24% (1, 4, 5).

Most pulmonary manifestations in patients with pSS can be categorized as airway abnormalities, interstitial pneumonias, or lymphoproliferative disorders (2). Pleural effusion and pulmonary hypertension also occur in pSS, although

these are far less common in pSS than in other connective tissue diseases, such as scleroderma (6–9). As the patterns of pulmonary lesions are often mixed in pSS, some pulmonary manifestations are difficult to classify (10, 11). Abnormal findings in the lungs of patients with pSS are predominant in the subpleural areas and lower lobes, as is typically seen in connective tissue disease (12–17).

The European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) has been developed to measure systemic disease activity in various organs (5, 18, 19). In the ESSDAI, pulmonary involvement is defined as the presence of pulmonary symptoms (persistent cough and/or dyspnoea) and abnormalities in pulmonary diagnostic tests such as PFTs and/or high-resolution computed tomography (HRCT).

Systemic features, such as pulmonary involvement, clearly mark the prognosis of pSS and can influence the choice of treatment. A retrospective study showed a significant decrease in physical functioning in patients with pulmonary involvement compared to patients without pulmonary involvement which influences the quality of life (20). Previous studies have shown that the prevalence of pulmonary involvement is probably considerable, but the rates are very different in the various studies. Therefore,

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the purpose of this study was to further investigate the prevalence and types of pulmonary involvement in pSS patients and to classify the manifestations according to the pulmonary domain of the ESSDAI.

## Method

### Study population

The study population was selected from the Diagnosis Treatment Combination (DTC) list of all consecutive patients who visited the Sjögren's syndrome expertise centre of the University Medical Center Groningen (UMCG) in 2015. Inclusion criteria were a clinical diagnosis of pSS and fulfilment of the American–European Consensus Group (AECG) (21) and/or American College of Rheumatology (ACR) (22) classification criteria for pSS. Data were obtained retrospectively from electronic patient records.

### Pulmonary involvement

Primary study parameters were the number and type of pulmonary complaints, the number of pulmonary tests performed, and the outcomes of these tests. The following pulmonary complaints were recorded: persistent cough, dyspnoea during exercise, dyspnoea at rest, and recurrent lower respiratory infections. Pulmonary tests were performed only when there was a clinical suspicion of lung involvement, and included conventional chest radiography, computed tomography (CT), PFTs, and pulmonary biopsy ( $n = 6$ ). The most recently performed tests were recorded. Some radiological tests (five chest radiographs and seven CTs) were performed in and imported from other hospitals.

Pulmonary involvement was recorded when imaging of the lungs, PFTs, or pulmonary biopsies showed abnormalities and both of the following conditions applied: (i) therapy was needed and/or follow-up was recommended; and (ii) there was an assumed or possible relation with pSS. The investigator (AH) defined pulmonary manifestations as

'assumed to be related to pSS' when the pulmonary condition was known to occur in association with pSS, such as interstitial lung disease (ILD), and other causes could be excluded, such as drug-induced ILD. In addition, pulmonary manifestations were defined as 'assumed to be related to pSS' when the treating pulmonologist or rheumatologist, who has the overall clinical picture, interpreted the pulmonary manifestations as assumed to be related to pSS. Pulmonary manifestations were defined as 'possibly related to pSS' when it was not evident whether pulmonary manifestations were caused by pSS or by coincidental factors. In uncertain cases, the association with pSS was determined by an experienced pulmonologist (GDN). Pulmonary manifestations were assumed not to be related to pSS when, for example, chronic obstructive pulmonary disease (COPD) was present in current or previous smokers. COPD was noted as possibly related to pSS when it was present in non-smokers.

Active pulmonary involvement was classified according to the pulmonary domain of the ESSDAI (18, 19).

### Other assessments

Secondary study parameters included demographic and clinical data (gender, age, time since diagnosis of pSS, and duration of symptoms of pSS), smoking status, EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), ESSDAI, parotid or labial salivary gland focus score, laboratory parameters [anti-Sjögren's syndrome antigen A and B (anti-SSA, anti-SSB), antinuclear antibodies (ANAs), immunoglobulin G (IgG), rheumatoid factor (RF), complement C3, complement C4, cryoglobulin, and paraprotein] and current use of drugs to treat pulmonary conditions and systemic drugs with potential influence on the lungs.

### Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). Results were expressed as number of patients (%), mean  $\pm$  sd, or median [interquartile range (IQR)] for categorical, normally distributed, and non-normally distributed data, respectively. To compare differences between patients with and without pulmonary involvement, we used the chi-squared and Fisher's exact tests for categorical data, and the independent samples t-test and Mann–Whitney U-test for continuous data. A  $p$ -value  $< 0.05$  was considered statistically significant.

## Results

### Patient characteristics

In total, 360 patients with Sjögren's syndrome (SS) or clinical suspicion of SS visited the UMCG in 2015. Of these patients, 14 patients had secondary SS, most commonly in combination with rheumatoid arthritis, 69 patients

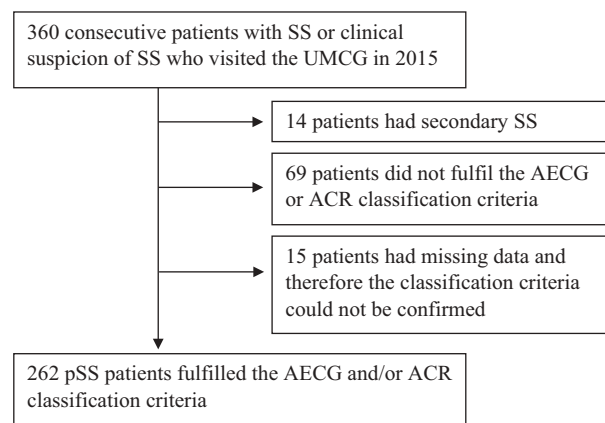


Figure 1. Flowchart of primary Sjögren's syndrome (pSS) patients included in the analyses. SS, Sjögren's syndrome; UMCG, University Medical Center Groningen.

did not fulfil the AECG or ACR classification criteria, and 15 patients had missing data and therefore the classification could not be confirmed (Figure 1).

Of the 262 included pSS patients, the mean age was  $56 \pm 15$  years, and most patients were female (93%) and anti-SSA positive (93%). Median time since diagnosis was 6 years (IQR 2–11 years). Additional patient characteristics are shown in Supplementary table S1.

### Pulmonary complaints

One or more pulmonary complaints were present in 88 patients (34%). Cough was reported most often; this was present in 70 pSS patients (27%). Dyspnoea on exertion was present in 42 patients (16%) and recurrent lower airway infections in 17 patients (7%). Dyspnoea at rest was not mentioned by any of the patients.

### Pulmonary involvement related and possibly related to pSS

Pulmonary involvement was found in 25–39 pSS patients (10–15%). This range is composed of pulmonary manifestations assumed to be related to pSS (10%) and pulmonary

manifestations possibly related to pSS (5%) (Figure 2). Overall, ILD was most common, being present in 15 patients; in particular, non-specific interstitial pneumonia (NSIP) was present in seven patients, of whom four had fibrotic NSIP. Usual interstitial pneumonia (UIP) was not found in any of the patients (Table 1). A mucosa-associated lymphoid tissue (MALT) lymphoma in the lung was seen in two patients, who also had MALT lymphomas in other parts of the body: in the submandibular and parotid glands (both patients), in the conjunctiva of the right eye (one patient), and in lymph nodes in the neck (the other patient).

Undefined features were seen in three patients. For one patient, these included dyspnoea during exercise and abnormal PFT with slightly reduced diffusing capacity of the lungs for carbon monoxide (DLCO) and restrictive abnormalities. Another patient had recurrent lower respiratory infections without bronchiectasis or bronchopathy, with a solid globular lesion of 7 mm and a second smaller lesion in the lung. The third patient had also a stationary solid globular nodule of 5 mm on CT.

An overview of all clinically relevant pulmonary manifestations, defined as not related, possibly related, or assumed to be related to pSS, is shown in Figure 2.

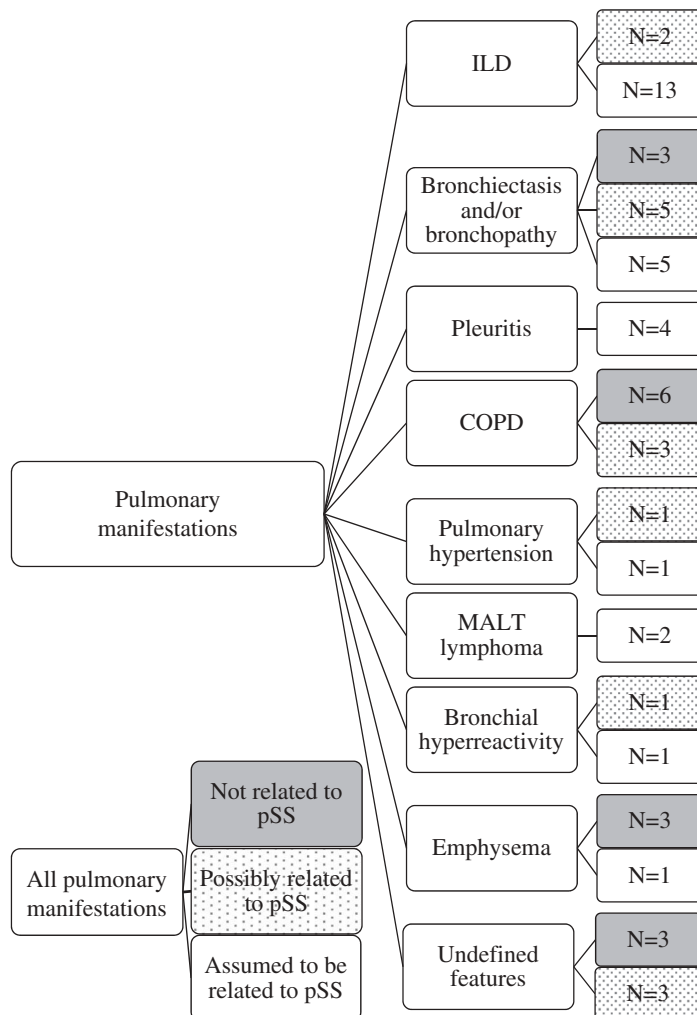


Figure 2. Flowchart of pulmonary manifestations related and not related to primary Sjögren's syndrome (pSS): all manifestations (26% of the pSS patients), not related to pSS (11%), possibly related to pSS (5%), and assumed to be related to pSS (10%). COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; MALT, mucosa-associated lymphoid tissue.

### Diagnostic abnormalities

Pulmonary diagnostics had been performed in 225 (86%) patients, of which chest radiography was most frequently performed (Table 2). Chest radiography was performed in 24 (96%) and 13 (93%) patients with pulmonary involvement assumed to be or possibly related to pSS, respectively. In 18 (46%) of the patients in both groups, abnormalities were seen on the radiographs, including bronchopathy, atelectasis, reticular opacities, fibrotic residual features, and pleural effusion.

CT or HRCT was performed in 24 (96%) and in 10 (71%) of the patients with pulmonary involvement assumed to be or possibly related to pSS, respectively. The (HR)CT scans of both groups showed the following features: ground-glass opacities (n = 10; 29%), nodular thickening (n = 8; 24%), thin-walled air cysts (n = 6; 18%), atelectasis (n = 5; 15%), reticular interstitial pattern (n = 4; 12%), pleural thickening (n = 4; 12%), pleural effusion (n = 3; 9%), and thickening of interlobular septa (n = 2; 6%). Honeycombing was not seen in any of the patients. Ground-glass opacities were predominantly present in the lower lobes of the lungs. When air cysts were present, there were often 10 cysts or more (n = 4), with a diffuse distribution. Three examples of interstitial pneumonia on HRCT seen in this cohort are shown in Figure 3.

PFTs were performed in 24 (96%) and in 10 (71%) of the patients with pulmonary involvement assumed to be or possibly related to pSS, respectively. PFTs of

patients with possible or assumed pulmonary involvement in pSS showed restriction more often than obstruction: n = 10 (36%) and n = 7 (21%) respectively.

### Pulmonary manifestations not related to pSS

Current pulmonary manifestations which were supposed not to be related to pSS were present in 29 patients (11%) (Figure 2). Most common was asthma (n = 14), followed by smoking-related conditions: COPD (n = 6), emphysema (n = 3), and bronchiectasis and/or bronchopathy (n = 3). One patient, with bronchiectasis and bronchopathy, had residual defects after a lobectomy for lung cancer. Three patients had undefined features: isolated mildly reduced DLCO with a history of smoking, atelectasis with pleural effusion, and one patient with a stable hyperdense structure in the mediastinum.

### Pulmonary domain of the ESSDAI

In total, 16 patients (6%) had a positive ESSDAI for the pulmonary domain: four patients with low, 11 patients with moderate, and one patient with high activity. Pulmonary involvement in pSS was not scored in the ESSDAI of patients with long-lasting features (> 1 year) which were assumed to be related to damage (n = 15), MALT lymphoma which was rated in another domain (lymphadenopathy and lymphoma; n = 2), or

Table 1. Number and types of pulmonary manifestations which are possibly or assumed to be related to primary Sjögren's syndrome (pSS).

Pulmonary manifestations	Possibly + assumed to be related to pSS (n = 39)	Assumed to be related to pSS (n = 25)
ILD	15	13
NSIP	4	4
Status after NSIP	2	2
LIP	3	3
OP	1	0
Status after OP	1	1
Combined NSIP/OP	1	1
ILD undefined	3	2
Bronchiectasis and/or bronchopathy†	10	5
Bronchiectasis	8	3
Bronchopathy	8	4
Pleuritis	4	4
Active pleuritis	1	1
Status after pleuritis	3	3
COPD (in non-smoker)	3	0
Pulmonary hypertension	2	1
MALT lymphoma in the lung	2	2
Bronchial hyperreactivity	2	1
Emphysema (not defined as COPD)	1	0
Undefined features	3	0

In three patients, multiple pulmonary manifestations occurred next to each other.

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; LIP, lymphocytic interstitial pneumonia; MALT, mucosa-associated lymphoid tissue; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia.

†Excluding traction bronchiectasis, secondary to ILD.

Table 2. Pulmonary diagnostics.

Pulmonary diagnostics	All patients (n = 262)	Possibly + assumed to be related to pSS (n = 39)	Assumed to be related to pSS (n = 25)
Performed pulmonary diagnostics	225 (86)	39 (100)	25 (100)
Chest radiography	203 (78)	37 (95)	24 (96)
CT (CT/HRCT/PET-CT)	87 (33)	34 (87)	24 (96)
CT	44 (51)	10 (26)	5 (20)
HRCT	38 (44)	22 (56)	17 (86)
PET-CT	5 (6)	2 (5)	2 (8)
PFT	147 (56)	34 (87)	24 (96)

Data are shown as n (%).

CT, computed tomography; HRCT, high-resolution computed tomography; PET, positron emission tomography; PFT, pulmonary function tests.

when (HR)CT and/or PFTs had not been recently performed (n = 6).

#### Comparison of patients with and without pulmonary involvement

Patients with pulmonary involvement were significantly older, had a longer disease duration and higher ESSDAI score, and more often had a positive salivary gland biopsy (focus score  $\geq 1$ ) than patients without pulmonary involvement. Patients with pulmonary involvement less often had positive ANAs. No significant differences in gender, smoking status, or other laboratory parameters were found (Table 3). When analysing only patients with activity for the pulmonary domain of the ESSDAI, comparable results were found, except that no significant difference was found in time since diagnosis and a significant difference was found in paraproteinaemia (Table 3). Additional patient characteristics of pSS patients with and without ILD are shown in Supplementary table S2.

#### Prevalence of COPD

COPD was clinically diagnosed in nine (3.4%) of the entire population, of which six cases (2.3%) were smoking related and three (1.1%) were non-smoking related. In the 147 patients who underwent a PFT, forced expiratory volume in 1 second ( $FEV_1$ )/forced vital capacity (FVC)  $< 0.70$  was present in 22 (15%) of patients.

#### Discussion

In this large cross-sectional retrospective cohort study, we investigated the prevalence of different types of pulmonary involvement in pSS in daily clinical practice and rated them according to the pulmonary domain of the ESSDAI.

We found pulmonary involvement assumed to be related to pSS in 10% of patients and pulmonary manifestations possibly related to pSS in 5% of patients. This prevalence is in line with two reviews reporting pulmonary involvement in approximately 10–20% of the pSS patients (1, 23). However, our prevalence of 10–15% is probably an underestimation. Pulmonary

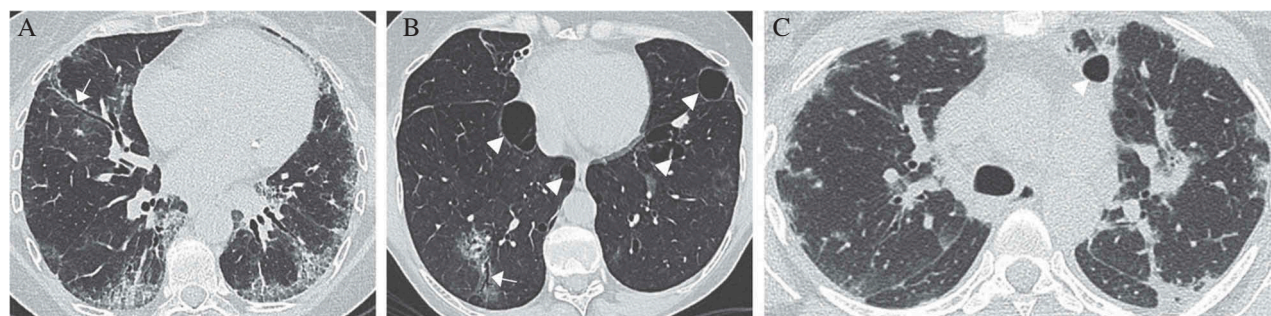


Figure 3. Types of interstitial pneumonia on high-resolution computed tomography (HRCT). (A) A primary Sjögren's syndrome (pSS) patient with fibrotic non-specific interstitial pneumonia. HRCT shows reticular abnormalities with traction bronchiolectasis (white arrow), ground-glass opacity and lymphadenopathy. (B) A pSS patient with lymphocytic interstitial pneumonia. HRCT shows multiple air cysts (white arrowheads), ground-glass opacity, and traction bronchiolectasis (white arrow). (C) A pSS patient with organizing pneumonia. HRCT shows bilateral patchy consolidations with peripheral and peribronchial predominance and an air cyst (white arrowhead).

Table 3. Characteristics of primary Sjögren's syndrome (pSS) patients with and without pulmonary involvement and with active pulmonary involvement according to the pulmonary domain of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

Patient characteristics	No pulmonary involvement (n = 223)	Pulmonary involvement (n = 39)	p†	Active pulmonary ESSDAI domain (n = 16)	p‡
Age (years)	55 ± 16	61 ± 13	0.037*	66 ± 11	0.002*
Gender, female	207 (93)	37 (95)	1.000	15 (94)	1.000
Time since diagnosis (years)	6 (2–11)	10 (4–17)	0.012*	8 (3–15)	0.478
Time since start of symptoms (years)	13 (8–18)	18 (9–25)	0.173	13 (6–21)	0.805
Smoking			0.282		0.384
Current smoker	23 (11)	1 (3)		0 (0)	
Previous smoker	47 (22)	10 (27)		4 (25)	
Non-smoker	144 (67)	26 (70)		12 (75)	
ESSPRI	6 (5–8)	7 (5–7)	0.611	7 (5–7)	0.577
ESSDAI	3 (1–6)	5 (2–18)	0.001*	12 (8–21)	0.000*
Salivary gland biopsy, focus score ≥ 1	169 (88)	34 (100)	0.030*	15 (100)	0.226
Laboratory parameters					
Anti-SSA positive	207 (94)	35 (92)	0.722	13 (81)	0.096
Anti-SSB positive	129 (59)	20 (54)	0.601	8 (53)	0.687
ANAs	212 (96)	33 (87)	0.038*	11 (69)	0.001*
IgG titre (g/L)	16.0 (12.2–20.5)	15.2 (9.4–18.3)	0.051	15.6 (9.7–25.2)	0.672
RF (kU/L)	32 (14–68)	23 (7–44)	0.369	30 (6–45)	0.672
Complement C3 (g/L)	1.14 ± 0.24	1.12 ± 0.23	0.598	1.19 ± 0.20	0.493
Complement C4 (g/L)	0.20 ± 0.073	0.21 ± 0.090	0.590	0.22 ± 0.096	0.300
Cryoglobulinaemia	33 (21)	11 (36)	0.090	5 (36)	0.312
Paraproteinaemia	9 (5)	4 (13)	0.106	3 (21)	0.045*
Current medication use					
Biologic DMARDs	3 (1)	3 (8)	0.045*	2 (13)	0.038*
Synthetic DMARDs	53 (24)	12 (31)	0.350	2 (13)	0.375
Corticosteroids	14 (6)	11 (28)	< 0.001*	4 (25)	0.023*
NSAIDs	73 (33)	13 (33)	0.942	6 (38)	0.696
Inhalation corticosteroids	18 (8)	11 (28)	< 0.001*	5 (31)	0.011*
β <sub>2</sub> -Sympathomimetics	9 (4)	5 (13)	0.041*	1 (6)	0.508

Data are shown as mean ± sd, n (%), or median (interquartile range).

†Comparison of patients with pulmonary involvement with patients without pulmonary involvement. ‡Comparison of patients with pulmonary involvement according to the ESSDAI with patients without pulmonary involvement.

\*Significant difference ( $p < 0.05$ ).

ANAs, antinuclear antibodies; DMARDs, disease-modifying anti-rheumatic drugs; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; IgG, immunoglobulin G; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SSA, Sjögren's syndrome antigen A; SSB, Sjögren's syndrome antigen B.

tests, other than chest radiography, were usually only performed when pulmonary symptoms were present. Symptoms are not always correlated with abnormalities on HRCT (14). Therefore, pulmonary involvement in asymptomatic patients was not included.

In the present study, ILD was the most prevalent pulmonary manifestation related to pSS, being slightly more common than airway abnormalities. The most common type of ILD was NSIP, in concordance with previous studies in pSS (2, 23–27). Fibrotic NSIP was present in four of the seven patients with NSIP, also in concordance with previous studies which showed that fibrotic NSIP was more common than non-fibrotic NSIP (23, 26). Some studies suggested that airway abnormalities are more common in pSS but are often subclinical (1, 28). When we include traction bronchiectasis secondary to ILD, we also found a higher prevalence of airway abnormalities than ILD. Airway abnormality is a broad concept and it can be difficult to

differentiate whether it is related to pSS or other causes of airway abnormality, such as recurrent pneumonia.

In our cohort, we found a COPD prevalence of only 3.4%. However, in many patients no recent PFTs had been performed, and in patients who did undergo a PFT, FEV<sub>1</sub>/FVC < 0.70 was present in 15% of patients. These data suggest that the prevalence of COPD is probably underestimated, and that even in patients with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, COPD is often not clinically diagnosed. Two studies by one research group, including one longitudinal study in which a PFT was performed in all participants, showed a COPD prevalence of 37–41% in pSS patients, which was much higher compared to the general population (29, 30). Even in never-smokers, the prevalence of COPD was 30% (30). This high prevalence could partly be explained by the large number of subclinical



COPD patients when performing a PFT in all patients. In addition, a cut-off of  $FEV_1/FVC < 0.70$  probably leads to an overestimation of COPD in elderly patients (31). Despite these limitations, it is likely that COPD is common in pSS patients. In line with these findings, a retrospective cohort study showed that the incidence of COPD was 1.4-fold greater in pSS patients than in non-SS patients (32). A 2017 study showed no significant difference in pulmonary symptoms in pSS patients with or without concomitant COPD, suggesting that other factors, such as airway sicca, are more important in eliciting such symptoms in pSS patients (33). Another study showed an increase in specific cytokines in sputum of never-smoking pSS patients, suggesting a specific ongoing inflammatory process in the airways among pSS patients (34).

In previous studies, the prevalence of obstruction and restriction in PFT in pSS patients with pulmonary involvement has varied. Some studies reported that the most common finding is restriction (35), while others suggested that obstruction may be more common (12, 28, 30). We found restriction more often than obstruction, which can be explained by the high prevalence of ILD in pSS.

The ESSDAI was developed to measure systemic disease activity in pSS patients (18, 19). In our cohort, 6% of the 262 pSS patients had a positive ESSDAI on the pulmonary domain: 2% had low, 4% moderate, and 0% (one patient) high activity. In the study by Nilsson et al, including 51 consecutive pSS patients with pulmonary tests, 55% had a positive ESSDAI on the pulmonary domain: 39% had low, 14% moderate, and 2% high activity (30). This large difference in pulmonary activity according to the ESSDAI scores is probably based on similar reasons to the difference in pulmonary involvement in pSS. In their study, all patients were assessed by PFT and (HR)CT, while in the current study additional pulmonary tests were performed only when there was a clinical suspicion of lung involvement. Furthermore, the ESSDAI was calculated retrospectively in almost all patients from our cohort. This may have resulted in an underestimation of the ESSDAI scores.

The ESSDAI is a good instrument for rating active pulmonary involvement, but the ESSDAI score is not a complete reflection of pulmonary complaints caused by pulmonary involvement in pSS. A history of active pulmonary involvement in pSS can also cause stable pulmonary complaints as a result of residual defects such as fibrosis. These defects are not rated in the ESSDAI, because stable, long-lasting features present for > 1 year are assumed to be no longer active. However, it can be difficult to determine whether pulmonary involvement is stable, when no previous tests are available. Longitudinal, prospective studies are needed to accurately determine the percentage of patients with active and progressive pulmonary involvement according to the ESSDAI. MALT lymphomas in the lungs and lymphadenopathy in the mediastinum

are not included in the pulmonary domain of the ESSDAI (since they are scored in the lymphadenopathy domain), even though they can cause pulmonary complaints.

In the current study, older age and longer disease duration were found to be associated with pulmonary involvement in pSS. Three previous studies also reported that older age at disease onset and/or longer disease duration were associated with a higher risk of pulmonary involvement in pSS (13, 36, 37). A prospective study published in 2017 found that age of non-sicca onset was higher in pSS patients with pulmonary involvement (38). No clear explanation can be given. However, in the general population the prevalence of bronchiectasis and interstitial lung abnormalities seems to increase with age (39). Another prospective study showed a male predominance in pSS patients with ILD (40). We could not confirm this finding.

Unexpectedly, we found a significantly lower prevalence of ANA positivity and lower RF levels in patients with active pulmonary involvement, while paraproteinaemia was more common in this group. There were no significant differences in other laboratory parameters between patients with and without pulmonary involvement. In contrast, Palm et al found that anti-La/SSB positivity, hypergammaglobulinaemia, RF positivity, and lymphopenia were more prevalent in patients with pulmonary involvement (20). We cannot explain these different results. In the current study, the IgG titre was lower in patients with pulmonary involvement than in patients with no pulmonary involvement, and this difference almost reached statistical significance. A possible explanation may be that the higher use of immunosuppressive medication in patients with pulmonary involvement influenced the IgG titre in patients with pulmonary involvement.

In this study, clinical data from visits in 2015 were used. However, we also included the results of the most recently performed diagnostic tests. Patients who were asymptomatic in 2015 therefore may have had symptoms in the past, when the radiographies or PFTs were performed. In addition, all chest radiographs were included, regardless of the indications. For example, some patients underwent X-rays to screen for infectious diseases prior to immunosuppressive treatment, or as part of preoperative screening.

The strength of this study is the inclusion of a large number of consecutive pSS patients from daily clinical practice, resulting in a cohort that is representative of the general pSS population. Our hospital has a multidisciplinary SS expertise centre. The main limitation of the present study is the retrospective design, which resulted in some missing data. Not all radiographs and (HR)CT were uniformly reported by different radiologists and various indications. Sometimes, there was no report at all, in the case of imported external diagnostics from other hospitals. However, an experienced pulmonologist (GDN) specializing in

ILD reviewed the diagnostics of those cases, to limit the influence of interobserver variability.

Based on our results, we would like to underline the clinical relevance of early recognition for treatment of pulmonary involvement in pSS. Based on the high prevalence reported in our study and the possible consequences for treatment of pulmonary involvement in pSS, we strongly recommend screening for pulmonary involvement in pSS patients in daily clinical practice. Our advice for screening is to perform a pulmonary anamnesis, PFT, and chest radiograph in every pSS patient, and HRCT if indicated. More prospective studies are needed to accurately determine the proportion of patients with active and progressive pulmonary involvement in pSS and the cost-effectiveness of screening for pulmonary involvement.

## Conclusion

In this large cross-sectional study, pulmonary involvement was found in 10–15% of the patients, comprising 10% assumed to be related to pSS and 5% possibly related to pSS. Most common was ILD, especially NSIP, followed by lymphocytic interstitial pneumonia and organizing pneumonia. UIP was not seen in any of the patients. Of all pSS patients, 6% were scored as active on the pulmonary domain of the ESSDAI, most with moderate activity. These findings underline the need for awareness of pulmonary involvement in patients with pSS in daily clinical practice.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article.

**Supplementary table S1.** Characteristics of the pSS study population.

**Supplementary table S2.** Characteristics of pSS patients with and without ILD.

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