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The Anti-Ro52 Antibody as a Protective Factor for Pulmonary Fibrosis in Primary Sjögren's Syndrome

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ABSTRACT

Background: Pulmonary fibrosis is common in primary Sjögren's syndrome (pSS)-related interstitial lung disease (ILD). However, research is lacking on the diagnostic immunological examination of pSS-related pulmonary fibrosis. Particularly, the value of detecting anti-Ro52 antibody in pulmonary fibrosis is unclear.

Objective: To evaluate the potential diagnostic value of anti-SSA, anti-SSB, and anti-Ro52 autoantibodies as markers of pSS-related pulmonary fibrosis.

Methods: One-hundred seventy-nine patients with pSS were analyzed retrospectively at our hospital. They were divided into the fibrosis and non-fibrosis groups. Pulmonary fibrosis was classified as mild, moderate, or severe based on the patients' computed tomography (CT) findings. Laboratory examinations, including anti-SSA, anti-SSB, and anti-Ro52 antibody evaluations, were performed. The influencing factors of pulmonary fibrosis were analyzed using logistic regression.

Results: Chest CT revealed pulmonary fibrosis in 45 patients with pSS (25.1%). The positive rates of anti-SSA and anti-Ro52 antibodies in the fibrosis group were lower than in the non-fibrosis group (P=0.04, P=0.001). The frequency of anti-Ro52 antibody showed no significant differences between mild-to-moderate (53.8%) and severe (47.3%) pulmonary fibrosis. The anti-Ro52 antibody was identified as a potentially protective factor against pSS (P=0.041).

Conclusion: Patients with pSS and pulmonary fibrosis had a low frequency of anti-SSA and anti-Ro52 antibodies. In patients with pSS and negative anti-Ro52 antibody, a chest CT is recommended to further understand the patients' condition.

Keywords: Anti-Ro52 antibody, Computed tomography, Primary Sjögren's syndrome, Pulmonary fibrosis

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INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disease secondary to rheumatoid arthritis, with a prevalence ranging from 0.1% to 4.8% (1), being common in women aged 40 to 60 years (2). The disease is characterized by lymphocyte infiltration, often accompanied by symptoms such as a dry mouth, dry eyes, and keratoconjunctivitis. The primary target organs of the autoantibodies are the exocrine glands (e.g., lacrimal and salivary glands), however, various organs and systems throughout the body are also affected (3). The lungs are rich in blood vessels and connective tissues, and they commonly present extra-glandular manifestations of SS (4). Primary Sjögren's syndrome (pSS) lung involvement mainly includes interstitial lung disease (ILD), lymphoproliferative disease, and airway disease (5). Pulmonary fibrosis is common in pSS-related ILD and often leads to scarring and structural destruction of the lung tissue (6). In severe cases, pulmonary fibrosis can impair respiratory function and cause respiratory failure, or even death (7).

Studies have demonstrated that antinuclear antibody (ANA), present in most patients with SS, contributes to the lung involvement in SS (8). Rocca et al. reported that there was no significant correlation between either anti-SSB or anti-SSA antibody levels and pulmonary involvement in the two groups (lung involvement and control) of patients with SS (9). Conversely, Gao et al. (4) found a low rate of anti-SSA antibody positivity in patients with both SS and lung involvement compared with the controls. In recap, the outcomes of these studies on the risk factors associated with pSS were varied, with no strong consensus. At the same time, there are few reports on the value of ANA in pulmonary fibrosis in patients with pSS. Therefore, in this study, we included a certain number of pSS cases to evaluate the clinically relevant factors (with emphasis on ANA) of pSS-related pulmonary fibrosis and to provide more references for the early detection, intervention, and reduction of the risk of lung damage.

MATERIAL AND METHODS

Patients

This retrospective study was approved by the local institutional review board of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology in Wuhan, Hubei, China, but the demand to acquire written informed consent from the participants was rejected. This study was conducted according to the guidelines of the Declaration of Helsinki. The selection of patients is shown in Figure 1. A total of 1,013 patients with SS who were admitted to our rheumatology or respiratory medicine departments between January 2012 and December 2019 were screened. Patients with secondary SS and other lung diseases (such as lung malignancies, infection, tuberculosis, chronic bronchitis, asthma, etc.) were excluded from this study. Finally, 179 patients were included. All cases met the criteria of the 2002 International Classification Standard for Sjögren's syndrome (10) or the 2016 American-European Consensus Group (AECG) SS classification standard (11).

Clinical Data Collection

Clinical data of all the patients with pSS, including sex, age, disease duration, main symptoms and signs, laboratory examinations, and pulmonary function test (PFT), were obtained from the hospital's electronic medical records at the time of the first hospitalization. Seventy-six patients followed up. Laboratory data included white blood cell count (WBC), C-reactive protein (CRP), anti-Ro52, anti-SSA and anti-SSB antibodies, ANA, immunoglobulin G (IgG), A (IgA), and M (IgM), complement C3 and C4, and rheumatoid factor (RF). ANA detection was performed using an indirect immunofluorescence method. Anti-SSA, anti-SSB, and anti-Ro52 antibodies were detected

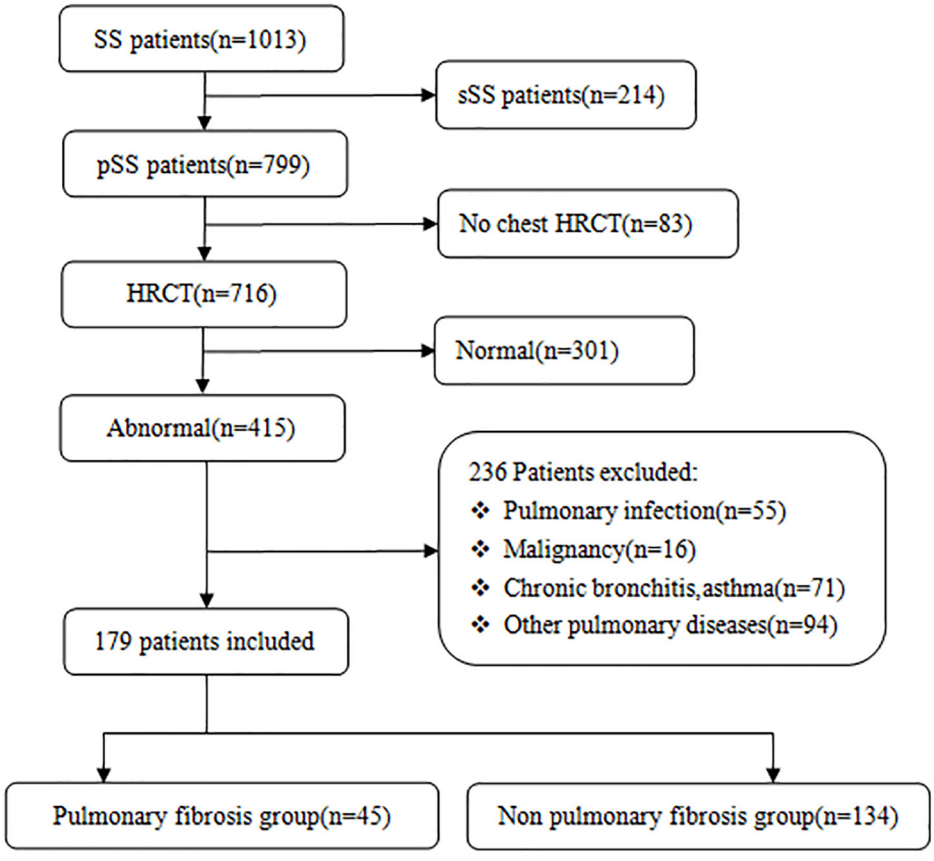

Figure 1. Flowchart depicting the case selection procedure for this study.

by enzyme-linked immunosorbent assay following the manufacturer's instructions (Sany Biotechnology Company, Buffalo, NY).

Imaging Characteristics and Evaluation

Scans were procured utilizing any of the CT scanners enumerated below: Optima 660 (GE, America), uCT 780 (United Imaging, China), or Somatom Definition AS+ (Siemens Healthineers, Germany). The main parameters for the CT scan were: automatic tube current modulation=30–80 mAs, tube voltage=120 kV, layer thickness=5 mm, matrix=512×512, pitch=0.9–1.2 mm, and scanning field=350×350 mm. Reconstruction was made with a bone algorithm as follows: reconstruction layer thickness=0.625–1.250 mm, lung window level=−600 HU, window width=1500–1600 HU, mediastinal window level=40 HU, and window width=350 HU. The patients were scanned in the supine position with breath-holding after inhalation. The upper and lower boundaries of the scan were the apex and the bottom of the lung respectively (the posterior costophrenic angle needed to be scanned).

The chest imaging data of patients with pSS were extracted from our hospital's Radiology Information System workstation, and two thoracic radiologists with 10–15 years of diagnostic experience, unaware of the patients' clinical data, independently evaluated the CT images. If the radiologists' conclusions varied widely, they discussed the image until they reached a settlement. All patients with abnormal chest CT findings were observed for pulmonary fibrosis and divided into the fibrosis (45 cases, 25.1%) and non-fibrosis (134 cases, 74.9%) groups. According to the Interstitial lung disease-CT (ILD-CT) standard recommended by the Fleischner Society Nomenclature Committee (12), if a reticular pattern (including a honeycomb shadow) was observed on the CT image, it was considered indicative of pulmonary fibrosis. The lobes were divided into inner, middle, and outer layers from the inside to the outside, and the presence,

range, and distribution of reticular structures were recorded. The effects of ground-glass attenuation, consolidation, nodules, bronchial wall thickening, bronchiectasis, mosaic perfusion, lung emphysema, interlobular septal thickening, pleural line, lung cysts, pleural effusion, and pericardial effusion were also observed. According to Gunnarsson et al. (13), the reticular shadow of each lung lobe was scored according to the percentage of reticular changes per the affected lung: 0 points, no involvement; 1 point, affected area 1%–4%; 2 points, 5%–14%; 3 points, 15%–29%; 4 points, 30%–49%; and 5 points, >50%. Then, the area scores of each lobe were added to calculate the total score. The severity of fibrosis was classified as mild (total score: 1–2 points), moderate (total score: 3–4 points), and severe (total score: >5 points).

Statistical Analysis

Data analysis was performed with the SPSS version 25.0 software package (SPSS Inc., Chicago, IL). The mean standard deviation and median (Q1, Q3) were used to express continuous variables. Categorical variables were expressed as counts (N) and percentages (%). Comparisons between the groups included the Mann–Whitney U test, independent samples t-test, chi-square test, or Fisher's exact test. Logistic regression was used to analyze the influence of potential influencing factors on pulmonary fibrosis. The potential influencing variables were analyzed by univariate regression. If it was a clinically important variable or a variable with a P value of <0.1 in the univariate analysis, it was included in the multivariate logistic regression analysis. A P value<0.05 for comparison between the groups indicated statistical significance.

RESULTS

Patients' Characteristics

A total of 179 patients with pSS-related

Table 1. Clinical characteristics of 179 patients with primary Sjögren's syndrome (pSS)

	Fibrosis CT changes, n=45	Non-fibrosis CT changes, n=134	P value
Female，n（%）	34 (75.6)	119 (88.8)	
Male，n（%）	11 (24.4)	15 (11.2)	
			0.029
Age at disease onset (years)	53.9±10.1	51.6±12.2	0.268
Disease duration (months)	30 (7.8, 69)	48 (24, 99)	0.001
Signs and symptoms, n (%)			
Cough	31 (68.9)	37 (27.6)	<0.001
Wheeze	21 (46.7)	17 (12.7)	<0.001
Raynaud phenomenon	5 (11.1)	17 (12.7)	0.781
Oral dryness	21 (46.7)	101 (75.4)	<0.001
Ocular dryness	17 (37.8)	80 (59.7)	0.011
Arthralgias	9 (20.0)	43 (32.1)	0.122
Lack of strength	6 (13.3)	14 (10.4)	0.595
Rampant caries	4 (8.9)	26 (19.4)	0.102
Morning stiffness	3 (6.7)	14 (10.4)	0.649
Chest tightness	3 (6.7)	16 (11.9)	0.475
Chest pain	4 (8.9)	7 (5.2)	0.598
Dyspnea	4 (8.9)	3 (2.2)	0.122
Pulmonary hypertension	2 (4.4)	3 (2.2)	0.799
Rash	3 (6.7)	2 (1.5)	0.194
Fever	18 (40.0)	20 (14.9)	<0.001
Physical decline	12 (26.7)	25 (18.7)	0.251

Data are n (%), average ±standard deviation (SD) or median (Q1, Q3) as appropriate.

chest CT abnormalities, including 153 women (85.4%) and 26 men (14.6%), were enrolled. The median disease duration was 36 months (ranging from 1 to 480 months), and the average age at first diagnosis was 52.2±11.8 years (ranging from 16 to 81 years). There were 45 cases (25.1%) in the fibrosis group and 134 cases (74.9%) in the non-fibrosis group. The duration of disease was shorter in the fibrosis group compared with the non-fibrosis group (median duration=30 months, Q1=7.8, Q3=69, P=0.001), and the frequency was higher in male patients (24.4%, P=0.029). Cough, wheezing, and fever were more pronounced in the fibrosis group (P<0.05) while dry mouth and eyes were less frequent (P<0.05). There were no significant differences in age, frequency of chest pain, dyspnea, chest tightness, Raynaud's phenomenon, rash, and arthralgia between the two groups (P>0.05) (Table 1).

CT Findings

The distribution of abnormalities observed in the chest CT was asymmetrical (Figure 2). Abnormal changes were common in the lower and outer bands of the lungs. Forty-five patients (25.1%) had reticular patterns consistent with pulmonary fibrosis. Other chest CT abnormalities included ground-glass attenuation (58.1%), bronchial wall thickening (35.8%), and interlobular septal thickening (30.2%) (Table 2). The reticular patterning in the fibrosis group often had ground-glass attenuation (40/45, 88.9%), interlobular septal thickening (35/45, 75.6%),

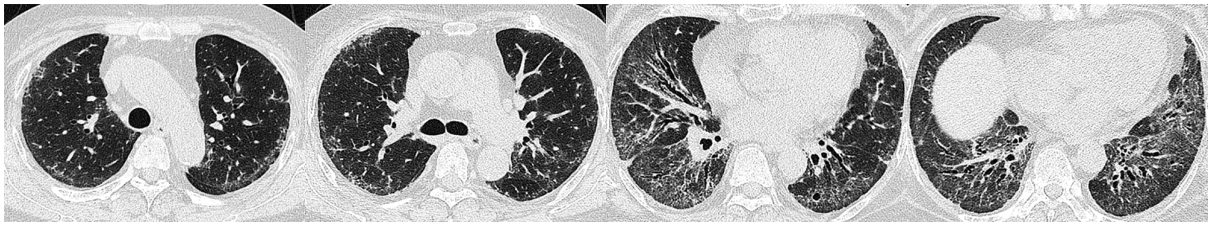

Figure 2. A 56-year-old woman with a 2-year history of dry mouth and a 2-day fever with a diagnosis of primary Sjögren's syndrome (pSS). On CT images, ground-glass shadows and grid shadows are observable in both lungs. These are distributed asymmetrically and mainly under the pleura. The lower lung is larger than the upper lung, accompanied by traction bronchiectasis.

Table 2. Imaging manifestations of 179 patients

	Patients with abnormal chest n=179 (%)	Fibrosis CT changes n=45 (%)	Non-fibrosis CT changes n=134 (%)	P value
Reticular pattern	45 (25.1)	45 (100)	0	/
Ground-glass attenuation	104 (58.1)	40 (88.9)	64 (47.8)	<0.001
Consolidation	49 (27.4)	21 (46.7)	28 (20.9)	0.001
Interlobular septal thickening	54 (30.2)	34 (75.6)	20 (14.9)	<0.001
Pleural line	18 (10.1)	9 (20.0)	9 (6.7)	0.010
Nodules	34 (19.0)	10 (22.2)	24 (17.9)	0.523
Lung cysts	50 (27.9)	9 (20.0)	41 (30.6)	0.170
Emphysema	28 (15.6)	4 (8.9)	24 (17.9)	0.149
Bronchial wall thickening	64 (35.8)	33 (73.3)	31 (23.1)	<0.001
Bronchiectasis	33 (18.4)	16 (35.6)	17 (12.7)	0.010
Mosaic perfusion	11 (6.1)	3 (6.7)	8 (6.0)	1.000
Pericardial effusion	23 (12.8)	7 (15.6)	16 (11.9)	0.531
Pleural effusion	12 (6.7)	2 (4.4)	10 (7.5)	0.722

The P value is the comparison between the fibrosis and non-fibrosis groups.

thickened bronchial walls (33/45, 73.3%), bronchiectasis (16/45, 35.6%), and other signs (Table 2). According to the pulmonary fibrosis scoring system, among the 45 patients with pulmonary fibrosis, eight cases (17.8%) were mild, 18 were moderate (40.0%), and 19 were severe (42.2%). Mild pulmonary fibrosis mainly affected the outer area of the lower lung, moderate fibrosis affected the middle and outer areas of the lower lung, and severe fibrosis had a wide range of impacted regions.

PFT

We conducted PFTs on 33 patients, of whom 21 were from the fibrosis group and 12 from the non-fibrosis group. Compared with the average, restrictive ventilatory dysfunction was observed in 12 (57.1%) and 6 (50%) cases, and the diffusing capacity of the lungs for carbon monoxide (DLCO) decreased in 10 (47.6%) and 7 (58.3%) cases, and the maximum ventilation decreased in 8 (38.1%) and 5 (41.7%) cases, in the fibrosis and non-fibrosis groups, respectively. Airway resistance increased in 5 (23.8%) and 3 (25.0%) cases, in the fibrosis and non-fibrosis groups, respectively. Moreover, there were two cases of reduced lung capacity and one case of respiratory failure in the fibrosis group. In the non-fibrosis group, there were two cases of normal lung function. No significant differences were found between the fibrosis and non-fibrosis groups for each of these PFTs mentioned above (P>0.05).

Laboratory Test

WBC and CRP levels increased significantly in the fibrosis group compared with those in the non-fibrosis group (P<0.001), and the frequency of positive anti-SSA and anti-Ro52 antibodies was lower (P=0.04 and P=0.001, respectively). The differences in RF, IgG, IgA, IgM, C3, C4, ANA, and anti-SSB antibody levels between the two groups were not statistically significant (P>0.05) (Table 3). Among the 45 patients in the fibrosis group, 53.8% (14/26) of the patients with mild-to-moderate pulmonary fibrosis and 47.3% (9/19) of those with severe pulmonary fibrosis were positive for the anti-Ro52 antibody. However, these subsets did not differ significantly from each other (P=0.668). Given that majority of the patients with pulmonary fibrosis showed ground-glass attenuation, we also analyzed its relationship with immunological indicators. Among 179 patients, with and without ground-glass attenuation, the difference in the frequency of anti-SSA, anti-SSB, and anti-Ro52 antibody positivity was not significant, except for a significant difference in ANA positivity (96/104 vs. 61/75, P=0.027). Additionally, we also found no significant difference in the frequency of positive ANA, anti-SSA, anti-SSB, and anti-Ro52 antibodies

Table 3. Comparison of laboratory test results between primary Sjögren's syndrome (pSS) patients with and without fibrosis

	Fibrosis CT changes, n	Non-fibrosis CT changes, n	P value
WBC $\times 10^9$/L	45 6.9 (4.6, 11.7)	134 4.8 (3.7, 6.4)	<0.001
CRPmg/L	33 5.0 (2.7, 17.2)	101 1.2 (0.5, 4.3)	<0.001
RF,IU/mL	20 35.0 (22.9, 61.6)	87 46.5 (11.8, 98.3)	0.723
IgG, g/L	36 16.1 (11.2,23.4)	118 16.5 (12.0, 18.9)	0.710
IgA, g/L	36 2.7 (2.0, 3.2)	118 2.6 (2.0, 3.2)	0.396
IgM, g/L	36 1.5 (1.2, 1.8)	118 1.1 (0.8, 1.5)	0.084
C3, g/L	36 0.95 (0.85, 1.10)	118 0.9 (0.78, 1.1)	0.129
C4, g/L	36 0.25 (0.17, 0.29)	118 0.23 (0.17,0.27)	0.328
ANA, positive	39 (86.7)	118 (88.1)	0.805
Anti-SSA antibody, positive	32 (71.1)	116 (86.6)	0.018
Anti-Ro52 antibody, positive	23 (51.1)	103 (76.9)	0.001
Anti-SSB antibody, positive	17 (37.8)	72 (53.7)	0.064

Data are n (%), median (Q1, Q3) as appropriate. WBC, white blood cells; CRP, C reactive protein; IgG/IgA/IgM, immunoglobulin; RF, rheumatoid factor; ANA, antinuclear antibody

Table 4. Analysis of risk factors of pulmonary fibrosis in patients with primary Sjögren's syndrome (pSS)

Variables	β	SE	Wals	P	OR	95% CI of OR
Male	0.943	0.442	4.547	0.033	2.567	1.079-6.104
Age at disease onset	0.017	0.015	1.229	0.268	1.017	0.987-1.047
Disease duration	-0.011	0.005	5.672	0.017	0.989	0.98-0.998
Anti-SSA antibody	-0.962	0.415	5.374	0.02	0.382	0.169-0.862
Anti-Ro52 antibody	-1.156	0.362	10.214	0.001	0.315	0.155-0.639
Anti-SSB antibody	-0.649	0.353	3.377	0.066	0.523	0.262-1.044

β, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval

Table 5. Logistic regression analysis of multiple factors for pulmonary fibrosis in patients with primary Sjögren's syndrome (pSS)

Variables	β	SE	Wals	P	OR	95% CI of OR
Male	0.638	0.477	1.793	0.181	1.894	0.744-4.821
Disease duration	-0.009	0.005	3.384	0.066	0.991	0.982-1.001
Anti-SSA antibody	-0.441	0.499	0.783	0.376	0.643	0.242-1.709
Anti-Ro52 antibody	-0.869	0.424	4.194	0.041	0.419	0.183-0.963
Anti-SSB antibody	-0.022	0.435	0.003	0.959	0.978	0.417-2.293

β, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval

among the 45 patients in the pulmonary fibrosis group with and without ground-glass attenuation (P>0.05).

Multivariate Logistic Regression Analysis

In the multivariate analysis, anti-Ro52 antibody positivity was identified as a protective factor for pSS-related pulmonary fibrosis (P=0.041) (Tables 4 and 5).

Follow-up of pSS-related Pulmonary Fibrosis

The median follow-up period was 21.1 months (ranging from 1 to 84 months). Thirty-two patients (71.1%) in the fibrosis group followed up with an average of three (ranging from 1 to 11) chest CT reassessments. Twenty-one patients (65.6%) with pulmonary fibrosis received hormonal and immunosuppressive therapy, three (9.3%) received anti-fibrosis therapy, and 11 (34.4%) with pulmonary fibrosis showed progress in varying degrees.

DISCUSSION

ILD is common in pSS (14-18), though there have been few research papers on pSS-associated pulmonary fibrosis. We retrospectively analyzed the presence, distribution, degree, and influencing factors of pulmonary fibrosis in a pSS cohort at our hospital.

In this study, the abnormal chest CT findings were mainly distributed in the lower lobes and outer bands of the lungs and were distributed asymmetrically, which were consistent with the findings of the previous studies (4). In the present study, the most common abnormality on the chest CT of patients with pSS was ground-glass attenuation. Conversely, the network structure consistent with pulmonary fibrosis observed in this study is relatively rare. In the previous studies, the specificity of high-resolution (HR) CT in diagnosing pSS-ILD was as high as 90% (19) and could well reflect the pathological changes in pSS-ILD (16). Some reports described a reticular pattern as the most common manifestation of pSS-ILD observed by HRCT (9, 14). The relatively few reticular structures identified in this study may be ascribed to the different inclusion criteria and CT scan parameters. On the one hand, we used thick-scan and thin-bone reconstruction schemes to perform CT scans on patients,

which may not be conducive to visualizing more network structures. On the other hand, the significance of ground-glass attenuation in pulmonary fibrosis remains unclear. Ground-glass attenuation is regarded as part of the fibrosis process when coexisting with traction bronchiectasis and/or reticular abnormalities (20). The ground-glass attenuation may also be related to parenchymal inflammation/exudative infiltration (21). Therefore, we did not consider ground-glass opacity as a component of pulmonary fibrosis.

In this study, as in the previous studies (14), the PFT abnormalities observed in patients with lung involvement were mainly DLCO reduction and restrictive ventilatory dysfunction. However, an abnormal lung function is generally detectable only when morphological changes sufficient to cause lung-function decline have occurred, and it is difficult for PFT to detect small changes in the lungs displayed on CT (22). Furthermore, extrapulmonary factors, such as obesity (23) and neuromuscular diseases (24), can also affect the PFT results. Further to that, the majority of patients' lung function here seems to be unlikely to be affected over time. Therefore, under appropriate circumstances, chest CT can be used to elucidate lung involvement in pSS patients.

Data on pSS-related pulmonary fibrosis immune markers are limited. A study from China demonstrated that the frequency of anti-SSA antibody positivity was low in 165 patients with pSS lung involvement (4). Interestingly, a study on SS patients with bronchiectasis also found that the frequency of anti-SSA antibody positivity was low (25). Traction bronchi and bronchiectasis are well-known signs of pulmonary fibrosis on chest CT images (20). These results are similar to the findings of our research. Yazisiz et al. (26) found that the positive rates of ANA, anti-SSB, and anti-SSA antibodies in the lungs were higher in patients with pSS than in patients without pSS, but the difference was not significant. Roca et al. reported that the rates of ANA, anti-SSB, anti-Ro60, and anti-Ro52 antibody positivity were not significantly different between pSS non-ILD and pSS-ILD (9), being inconsistent with our research finding.

No significant difference in the frequency of anti-Ro52 antibody was observed between patients with mild-to-moderate pulmonary fibrosis and patients with severe pulmonary fibrosis. This has also been confirmed in a study on mixed connective tissue disease (MCTD) and pulmonary fibrosis (27). Of the 113 patients with MCTD assessed, 38 (34%) developed pulmonary fibrosis. The positivity rate was comparable in patients with mild-to-moderate fibrosis (8/17; 44%) and those with severe fibrosis (11/21, 52%).

Multivariate regression analysis revealed that anti-Ro52 antibody positivity is a potentially protective factor against pSS-related pulmonary fibrosis. The anti-Ro52 antibody is commonly found in several systemic autoimmune rheumatic (e.g., inflammatory myopathies, pSS, systemic lupus erythematosus, and systemic sclerosis), autoimmune liver, and non-autoimmune (e.g., viral infections or neoplastic diseases) diseases (28). The anti-Ro52 antibody may be associated with the specific phenotype of the disease or may be a precursor of lung infection. Additionally, the position of the Ro52 antigen on human chromosome 11 may determine the relationship between anti-Ro52 antibodies and pulmonary infections (28). Recently, Buvry et al. (29) studied 68 patients with pSS and found that ILD was significantly higher in the anti-Ro52 antibody-positive group (41.9%, n=13) than in the negative group (16.2%, n=6). Hence, they proposed anti-Ro52 antibody positivity as a predictor of ILD (P=0.01), in sharp contrast with the findings of our study. However, Buvry et al.'s study had a small number of patients with ILD (only 19 cases) and focused more on ILD, and not a specific study on pulmonary fibrosis. In another retrospective study, the researchers did not find a difference in the frequency of anti-Ro52 antibody positivity between pSS-ILD (85 cases) and non-ILD (85

cases) groups. Patients with ILD were further divided into a usual interstitial pneumonia (UIP) group (after 10 cases) and a non-UIP group (75 cases); the frequency of anti-Ro52 antibody positivity was lower in the UIP group than in the non-UIP group (n=6; 60.0% vs. n=66; 88.0%; P=0.042) (30).

Some researchers hypothesize that patients with UIP have a poor prognosis, while those with nonspecific interstitial pneumonia (NSIP) have a better prognosis (31). In contrast, a study on the relationship between ILD and collagenous vascular disease showed that the prognoses of patients with UIP and NSIP were not significantly different (32). Enomoto et al. (33) reported that $PaCO_2$, degree of HRCT reticular pattern abnormality, and the severity of fibroblast lesions are prognostic factors of pSS-ILD. They proposed that the prognosis of patients with UIP is no worse than that of patients with NSIP, and it is more important to evaluate the pathological, radiological, and clinical data in detail as opposed to identifying UIP. Therefore, understanding the reticular pattern of HRCT and/or the severity of cellular shadow in patients with PSS helps determine patient prognosis.

In addition, we also did a preliminary study on the correlation between ground-glass shadow and anti-Ro52 antibody and found no correlation between them. The anti-Ro52 antibody may be associated with the specific phenotype of the disease or the precursor of lung infection (28). In this study, most of the ground-glass shadows may be thickened pulmonary interstitium (12), representing cellular ILD rather than an infectious disease (34), thus, these two may not be related. However, this may need to be confirmed by further studies involving multiple centers and a large number of cases.

There are, however, some drawbacks to our findings. First, this was a single-center retrospective study, which may have caused an analysis bias. Second, few patients in our cohort had undergone PFT. Third, fewer patients followed up in this study, and the length of follow-up varied. Finally, we did not perform pathological examinations. Bronchoalveolar lavage, transbronchial biopsy, and surgical lung biopsy are all invasive procedures, which are unacceptable for most patients.

In conclusion, patients with pSS and pulmonary fibrosis had high WBC and CRP levels and a low frequency of anti- Ro52 and anti- SSA antibody positivity. The anti-Ro52 antibody positivity may be a protective factor against pulmonary fibrosis. When patients with pSS and anti-Ro52 antibody negativity present with the above conditions, chest CT may help physicians understand the patients' pulmonary fibrosis.

Conflict of Interest: None declared.

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