

## Clinical Characteristics of Systemic Sclerosis With Interstitial Lung Disease

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### ABSTRACT

**Objectives:** This study aims to compare the clinical characteristics of systemic sclerosis (SSc) patients with or without interstitial lung disease (ILD), and figure out whether the differences can be useful to suspect ILD in SSc.

**Patients and methods:** We retrospectively collected the clinical data of 108 patients with SSc (13 males, 95 females; mean age 50.1±13.5 years; range 14 to 78 years) and compared them according to the presence of ILD. ILD was confirmed by chest computed tomography, and pulmonary arterial hypertension was suspected when right ventricular systolic pressure was ≥40 mmHg based on echocardiography.

**Results:** Of the 108 patients, 49 (45.4) had diffuse type and 59 (54.6) had limited type SSc. Disease duration, percentages of positive anti-scleroderma 70 (anti-Scl70) antibody and anti-centromere antibody, white blood cell (WBC), platelet, erythrocyte sedimentation rate (ESR), and presence of pulmonary hypertension (PH) differed significantly. On multivariate logistic analysis, positive titer of anti-Scl70 antibody (odds ratio [OR]=15.65,  $p<0.001$ ), platelet (OR=1.01,  $p=0.026$ ), ESR (OR=1.02,  $p=0.037$ ) and PH (OR=21.97,  $p=0.003$ ) were associated with ILD in patients with SSc.

**Conclusion:** In SSc patients with ILD, disease duration was longer and positive titer of anti-Scl70 antibody was more frequent, positive titer of anti-centromere antibody was less frequent, and WBC and platelet counts, ESR levels, and incidence of possible PH were significantly higher than in those without ILD. Positive titer of anti-Scl70 antibody, platelet, ESR, and combination of PH were independently associated with the presence of ILD in SSc patients.

**Keywords:** Interstitial lung diseases; pulmonary hypertension; systemic sclerosis.

Systemic sclerosis (SSc) is a chronic connective tissue disease that causes systemic inflammation and fibrosis, damaging target organs such as skin, lungs, peripheral blood vessels, kidneys, heart, and the digestive system.<sup>1</sup> Although its pathogenesis is complex and remains unclear, fibrosis is caused by vascular endothelial damage, immune activation, autoantibody formation, and excessive collagen and extracellular matrix production.<sup>2,3</sup> The disease is three to eight times more common in females than in males, and occurs mainly in the fifth decade of life.<sup>4,5</sup> SSc is divided into two subtypes according to the extent of skin involvement: a diffuse type involving the proximal limbs or trunk and a limited type involving the distal part limbs.<sup>6</sup>

Among the affected internal organs, respiratory involvement indicates a poor prognosis and is the common cause of death in patients with SSc.<sup>7</sup> Respiratory involvement includes pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD). Pulmonary involvement often develops in patients with a longer duration of SSc.<sup>8</sup> However, this is controversial because the patients may not have any pulmonary symptoms during the early stage of the disease, and they develop typical symptoms such as dyspnea on exertion and cough only after the progression of lung fibrosis or PAH. Most of the data on SSc have been collected retrospectively, and might be biased for clinical reasons.<sup>9,10</sup>

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Although diverse mechanisms in the cellular and humoral pathway are involved in the pathophysiology of ILD and SSc, no drug can stop the progression of fibrosis or organ damage in SSc. An effective treatment to prevent this progression is needed, and substantial recent research has examined this.<sup>11</sup> The presence of ILD in SSc patients determines the severity and expected prognosis of the disease and the early detection of pulmonary disease has been emphasized. Regular assessment has been recommended for ILD and PAH in SSc patients.<sup>12</sup> To detect ILD earlier, regular pulmonary function testing (PFT) is suggested, including the diffusion capacity of the lungs for carbon monoxide and high-resolution computed tomography (HRCT).<sup>13,14</sup> The severity of ILD in SSc ranges from limited involvement and non-progressive to severe and rapid progression, and also the symptoms are diverse.<sup>15</sup> There is no distinct feature that patients with ILD might have, and as an initial and essential symptom, cough was identified to be less frequent and less severe in SSc-associated ILD compared to other fibrotic ILDs.<sup>16</sup> Clinical assessment using HRCT showed good diagnostic performance for ILD in SSc.<sup>15</sup> In this study, we aimed to compare the clinical characteristics of SSc patients with or without ILD, and figure out whether the differences can be useful to suspect ILD in SSc.

## PATIENTS AND METHODS

The study included 108 patients with SSc (13 males, 95 females; mean age 50.1±13.5 years; range 14 to 78 years) who were treated in the Ajou University Hospital Rheumatology Department between September 1999 and December 2015. The diagnosis of SSc was based on the 1980 American College of Rheumatology criteria for SSc.<sup>17</sup> The study protocol was approved by the Ajou University Hospital Ethics Committee (BMR-SMP-16-387). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical records were collected retrospectively. The clinical features collected included SSc-related symptoms, such as Raynaud's phenomenon, scleroderma, skin ulcers, skin rashes, arthritis, and symptoms associated with the digestive system. Clinical examinations included chest radiography, chest computed tomography (CT), and echocardiography. Laboratory data comprised complete blood cell counts including white blood cells (WBCs), platelets, inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The presence and titers of autoantibodies, including antinuclear antibody (ANA), anti-scleroderma 70 (anti-Scl70) antibody, and anti-centromere antibody were gathered. The involvement of each organ was defined as

**Table 1.** Characteristics of patients with systemic sclerosis (n=108)

	n	%	Mean±SD
Age (year)			50.1±13.5
Gender			
Female	95		
Male	13		
Duration (year)			5.3±4.3
Subtype			
Diffuse	49		
Limited	59		
Positive antinuclear antibody	104	96.3	
Anti-scleroderma 70	36	33.3	
Anti-centromere Ab	42	38.9	
White blood cells (μL)			6944.5±2283.0
Platelet (×10 <sup>3</sup> /μL)			257.6±75.3
Erythrocyte sedimentation rate (mm/h)			31.6±24.9
C-reactive protein (mg/dL)			0.69±2.3
Raynaud's phenomenon	106	98.1	
Sclerodactyly	97	89.8	
Skin rash	28	25.9	
Digital ulcers	27	25.0	
Arthritis	57	52.8	
Gastrointestinal involvement	44	40.7	
Interstitial lung disease	43	39.8	
Pulmonary hypertension	13	12.0	

SD: Standard deviation.

**Table 2.** Comparison of systemic sclerosis patients with interstitial lung disease and those not

Clinical features	SSc with ILD (n=43)			SSc without ILD (n=65)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			51.34±14.55			49.23±13.51	0.49
Gender							0.92
Female	38			57			
Male	5			8			
Duration (year)			6.72±5.02			4.28±3.50	0.012*
Subtype							0.33
Diffuse	22			27			
Limited	21			38			
Antinuclear antibody (+)	42	97.7		62	95.4		0.54
Anti-scleroderma 70 (+)	27	62.8		10	15.4		<0.001
Anti-centromere (+)	4	9.3		33	50.8		<0.001
White blood cells (μL)			7650.9±2656.2			6469.0±1858.1	0.022*
Platelet (×10 <sup>3</sup> /μL)			282.1±81.7			241.3±66.5	0.007*
Erythrocyte sedimentation rate (mm/h)			39.4±27.3			26.5±22.0	0.008*
C-reactive protein (mg/dL)			1.2±3.1			0.3±1.4	0.1
Raynaud's phenomenon	42	97.7		64	98.5		0.77
Sclerodactyly	38	88.4		59	90.8		0.69
Skin rash	11	25.6		17	26.2		0.95
Digital ulcer	15	34.9		12	17.9		0.06
Arthritis	23	53.5		34	52.3		0.91
Gastrointestinal involvement	21	48.8		23	35.4		0.17
Pulmonary hypertension	11	25.6		2	3.1		<0.001*

SSc: Systemic sclerosis; ILD: Interstitial lung disease; SD: Standard deviation; \* p-value <0.05.

follows: arthritis was defined as the presence of joint tenderness and swelling or arthritic changes on radiography of the musculoskeletal system. ILD was confirmed by chest CT, and PAH was suspected when right ventricular systolic pressure was  $\geq 40$  mmHg based on echocardiography.

### Statistical analysis

Patients with or without ILD were compared using the two sample t-test, Mann-Whitney nonparametric tests, and chi-square analysis for categorical variables. To identify associations

between clinical factors and the development of ILD, we calculated Spearman's correlation coefficient. Two-sided p-values <0.05 were considered statistically significant. All calculations were performed using IBM SPSS Statistics version 22.0 software (IBM Corp., Armonk, NY, USA).

## RESULTS

The mean duration of disease was  $5.3 \pm 4.3$  years (Table 1). Of the patients, 49 (45.4%)

**Table 3.** Logistic regression analysis of clinical features to interstitial lung disease in patients with systemic sclerosis

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Duration	1.14	1.04-1.25	0.007*		NA	
Anti-scleroderma 70 (+)	4.99	1.85-13.43	0.001*	15.65	4.59-52.79	<0.001*
Anti-centromere (+)	0.1	0.032-0.31	<0.001*		NA	
White blood cells	1.00	1.00-1.00	0.012*	1.00	1.00-1.00	0.09
Platelet	1.01	1.00-1.01	0.01*	1.01	1.00-1.02	0.026*
Erythrocyte sedimentation rate	1.02	1.01-1.04	0.01*	1.02	1.0-1.04	0.037*
Digital ulcer	2.37	0.98-5.74	0.057		NA	
Pulmonary hypertension	10.83	2.26-51.82	0.003*	21.97	2.9-166.41	0.003*

OR: Odds ratio; CI: Confidence interval; NA: Not available; \* p-value <0.05.

had diffuse SSc, 59 (54.6%) had limited SSc, and 104 (96.3%) were ANA-positive. ANA was speckled in 45 (40.9%), homogenous in 19 (17.3%), nucleolar in 16 (14.5%), centromeric in 13 (11.8%), and mixed in 12 (10.9%). Thirty six patients (33.3%) had positive titers of anti-Scl70 antibody, and 42 patients (38.9%) had positive titers of anti-centromere antibody. Patients' manifestations included Raynaud's phenomenon in 106 (98.1%), sclerodactyly in 97 (89.8%), arthritis in 57 (52.8%), gastrointestinal symptoms in 44 (40.7%), skin rash in 28 (25.9%), and digital ulcers in 27 (25.0%) (Table 1). ILD developed in 43 patients (39.8%) and pulmonary hypertension (PH) was suspected in 13 (12.0%).

The duration of disease was significantly longer in SSc patients with ILD than in those without ILD ( $6.72 \pm 5.02$  vs.  $4.28 \pm 3.50$  years,  $p=0.009$ ) (Table 2). In SSc patients with ILD, more patients had positive titers of anti-Scl70 antibody (62.8 vs. 15.4%,  $p<0.001$ ) and less patients had positive titers of anti-centromere antibody (9.3 vs. 50.8%,  $p<0.001$ ) compared to those without ILD. SSc patients with ILD had significantly higher WBC ( $7,650.93 \pm 2,656.22$  vs.  $6,468.96 \pm 1,858.12/\mu\text{L}$ ,  $p=0.022$ ) and platelet ( $282,100 \pm 81,730$  vs.  $241,300 \pm 66,500/\mu\text{L}$ ,  $p=0.007$ ) counts and ESR levels ( $39.4 \pm 27.3$  vs.  $26.5 \pm 22.0$  mm/hour,  $p=0.008$ ) than those without ILD. Possible PAH was also more common in SSc patients with ILD (25.6% vs. 3.1%,  $p<0.001$ ). Considering the subtypes of ILD, 21 patients had usual interstitial pneumonia (48.8%), while 20 patients had non-specific interstitial pneumonia (46.5%).

On univariate logistic analysis, disease duration (odds ratio [OR]=1.14,  $p=0.007$ ), positive titer of anti-Scl70 antibody (OR=4.99,  $p=0.001$ ), positive titer of anti-centromere antibody (OR=0.1  $p=0.007$ ), WBC (OR=1.00,  $p=0.012$ ), platelet (OR=1.01,  $p=0.01$ ), ESR (OR=1.02,  $p=0.01$ ) and PH (OR=10.83,  $p=0.003$ ) were associated with ILD in patients with SSc (Table 3). On multivariate logistic analysis, positive titer of anti-Scl70 antibody (OR=15.65,  $p<0.001$ ), platelet (OR=1.01,  $p=0.026$ ), ESR (OR=1.02,  $p=0.037$ ), and PH (OR=21.97,  $p=0.003$ ) were associated with ILD in patients with SSc.

## DISCUSSION

In patients with SSc, pulmonary involvement is related to poor prognosis and it is important to diagnose ILD or PAH quickly to intervene. However, this detection is frequently delayed when cases develop gradually without symptoms such as dyspnea or cough and the typical findings in PFT or on chest radiography.<sup>13,14,18</sup> This study investigated the clinical characteristics of patients with SSc accompanied by ILD to identify the parameters suggesting some clues in asymptomatic patients with SSc with ILD.

The incidence of ILD is higher in patients with the diffuse type of SSc than in those with the limited type of SSc. In 3,656 patients with SSc, the European Scleroderma Trials and Research group reported that the incidence of ILD was 53% in patients with diffuse type SSc and 35% in patients with limited type.<sup>18</sup> Our results for the incidence of ILD according to subtype were similar.

Pulmonary involvement was reported to be related with specific ethnic, socioeconomic, and behavioral factors in SSc.<sup>19</sup> Patients with SSc with accompanying cardiopulmonary disease had frequent significant abnormalities on nailfold videocapillaroscopy.<sup>20</sup> This is consistent with the increased incidence of digital ulcers due to peripheral vascular abnormalities in patients with pulmonary involvement in our study. Therefore, clinicians should suspect pulmonary involvement if a patient with SSc has abnormal nailfold videocapillaroscopy patterns or digital ulcers. In a recent report about severity and outcome of ILD in SSc, neither subtype of SSc nor specificity of autoantibodies was associated with severity of ILD in SSc, but digital ulcer and PH were closely related with deterioration of diffusing capacity of the lungs for carbon monoxide in SSc patients with ILD.<sup>21</sup>

In this study, SSc patients with ILD had higher positive values of anti-Scl70 antibody and lower positive values of anti-centromere antibody compared to those without ILD, and positivity of anti-Scl70 antibody was an independent risk factor for ILD in SSc patients. In line with other studies demonstrating a strong association between anti-Scl70 antibody and ILD, we found similar results among Korean SSc patients.<sup>22,23</sup>

The SSc patients with ILD had blood cell counts and inflammatory marker levels that differed from those in patients without ILD. Our patients had no secondary infections such as pneumonia, but the WBC and ESR were significantly elevated in SSc patients with ILD compared to those without ILD. Therefore, increased WBC and ESR might represent chronic inflammation status in pulmonary tissue without infection. A large cohort showed that baseline CRP was correlated with shorter survival and decline in forced vital capacity in SSc patients with ILD.<sup>24</sup> CRP is used commonly as other inflammatory markers including ESR, and such data represented circulating markers that might predict inflammation in lung interstitium. CRP level was elevated in patients with ILD in this study without a statistical power. Moreover, several pro-inflammatory cytokines were reported higher in ILD progression in SSc.<sup>25</sup>

Pulmonary arterial hypertension in SSc leads to right heart failure and mortality, although its correlation has not been reported.<sup>26</sup> In our series, the incidence of PAH was significantly higher in SSc patients with ILD. As predictive factors for PAH, its incidence was higher in SSc patients with ILD.<sup>27</sup> Conversely, another study reported no association between the severity of ILD and the right atrial pressure measured via right catheterization in SSc patients, suggesting that the pulmonary fibrotic changes in the ILD of SSc differ from those of the pulmonary vascular pathophysiology in PAH.<sup>28</sup> Clinically, combined PAH in SSc patients with ILD leads to a large difference in the prognosis compared to that in SSc patients with ILD only.<sup>29</sup>

This study is limited in that it was a cross-sectional and retrospective study from a single center, resulting in enrolment of a small number of patients and a lack of data related with progression or survival of SSc. In addition, there was no data of right catheterization for PH and gastrointestinal involvement. Nevertheless, to our knowledge, it is the first to analyze the clinical data of patients with SSc with pulmonary involvement in South Korea, and it shows the differences of SSc patients with ILD for further evaluations regarding ILD.

In conclusion, we analyzed the characteristics of SSc patients with ILD, and found that SSc

patients with ILD had longer disease duration, positive value of anti-Scl70 antibody more frequently, positive value of anti-centromere antibody less frequently, higher WBC and platelet counts and ESR compared to those without ILD. The incidence of probable PAH suspected by echocardiography was significantly higher in patients with ILD than those without ILD. After adjustment, positive anti-Scl70 antibody, platelet count, ESR, and the development PH were significantly associated with ILD in SSc patients.

#### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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