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Original Article

Clinical characteristics and prognostic risk factors for interstitial lung disease in patients with systemic sclerosis

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Abstract: Objective: Investigate the clinical characteristics, treatment effects, and prognostic factors for interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). Methods: This retrospective study examined the records of 320 patients with SSc. Presence of ILD, extent of skin involvement, effect of treatment (based on high-resolution computed tomography), and prognostic risk factors were examined. Results: One hundred and sixty-nine patients (52.8%) had ILD. Patients with SSc-ILD had greater average age (51.30±10.86 vs. 48.58±12.52 years); longer (9.5 vs. 6.5 months); higher prevalence of cough, exertional dyspnea, chest tightness and pain, and pulmonary hypertension; higher levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); and anti-Scl-70 antibody positivity. In males, ILD is more common in patients with dcSSc than in patients with lcSSc. All patients received immunosuppressants and/or glucocorticoids for at least 12 months. Follow-up data were available for 71 SSc-ILD patients. Based on HRCT scores, 34 (47.9%) patients experienced deterioration, 18 (25.3%) remained stable, and 19 (26.8%) improved. Those who deteriorated were older, had a higher prevalence of exertional dyspnea, and higher ESR. Multivariate logistic regression showed that disease duration was independently associated with ILD. Age and exertional dyspnea were independent risk factors for SSc-ILD deterioration. After immunosuppressive therapy, disease progression occurred in 47.9% of patients. Conclusion: ILD in SSc correlated with prolonged disease duration, presence of cough and pulmonary hypertension, active inflammation, and anti-Scl70 antibody positivity. Age and exertional dyspnea were associated with deterioration of SSc-ILD.

Keywords: Systemic sclerosis, interstitial lung disease, high-resolution computed tomography

Introduction

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease that is characterized by limited or diffuse cutaneous fibrosis, vasculopathy, and inflammation. Patients can present with clinical characteristics that range in severity, from involvement restricted to the skin, to peripheral angiopathy, and even to rapidly progressive forms affecting the internal organs. The lungs are one of the most commonly affected organs, and involvement of parenchyma and pulmonary vessels is typical [1]. Interstitial lung disease is a common manifestation and the leading cause of death in patients with systemic sclerosis [2]. The mainstay of treatment for systemic sclerosis is immunosuppression, including low-dose corticosteroids, cyclophosphamide, mycophenolate mofetil, etc. SSc patients with lung fibrosis have a mortality risk nearly three times greater than SSc patients without lung fibrosis and the median survival times of 5 to 8 years [3, 4].

The manifestations of ILD are progressive exertional dyspnea, dry cough, and “velcro” rales in both lower lungs. High-resolution computed tomography (HRCT) results typically indicate diffuse ground-glass and reticular dense shadows in both lungs, conditions that eventually lead to severe lung fibrosis and respiratory failure, making it necessary to regularly monitor chest HRCT findings. Previous studies showed that clinical treatments had relatively poor efficacy in SSc-ILD patients. In particular, the combination of glucocorticoids and immunosup-

pressants may be effective in patients with early-stage ILD, but patients with severe respiratory dysfunction in late-stage disease have poorer responses [5]. The severity of ILD is graded by clinical assessments, the extent of restriction, impaired gas exchange recorded in pulmonary function testing (PFT), and histologic and radiographic criteria. The pattern and distribution of radiographic abnormalities observed on HRCT can accurately predict pathologic findings, and scoring systems for HRCT can improve the prognostic yield in some conditions, especially those with SSc alone. In particular, more extensive pulmonary fibrosis on HRCT corresponds to a lower survival rate among patients with SSc-ILD [6]. Because of the largely irreversible and potentially progressive nature of ILD, it is important that diagnostic tests are performed early, so that treatment can be initiated with minimal delay. HRCT helps early diagnosis and treatment of SSC-ILD patients. Lung function can better predict the prognosis of patients with SSc. Chest HRCT can accurately display pulmonary lesions and evaluate the progress or improvement of pulmonary lesions. Early disease, although often asymptomatic, may be rapidly progressive, and a plateau in disease severity typically occurs at 3 to 5 years after onset. Furthermore, pulmonary symptoms and functional status may not correlate with pulmonary physiology [7]. Therefore, in the present study, we investigated the clinical characteristics, treatment effects, and prognostic risk factors of patients with SSc-ILD. Evaluation of disease progression and prognosis of patients with Systemic Sclerosis based on changes of HRCT, in order to provide more effective management plan for these patients.

Materials and methods

Patient selection and definitions

This retrospective observational cohort study was conducted between January 2012 and June 2019. The records of 320 patients (both inpatients and outpatients) with SSc who were treated in the First Affiliated Hospital of Guangxi Medical University were retrospectively examined. A total of 169 of these patients also had ILD. SSc was diagnosed using the 1980 criteria of the American Rheumatism Association (ARA), and the 2013 classification criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) [8]. According to the European Consensus Statement, high-resolution computed tomography (HRCT) of the chest has been identified as the main diagnostic tool for SSc-ILD, supplemented by pulmonary function testing (PFT) for screening and diagnosis [9, 10]. Patients with acute infections, tumors or other malignant diseases, or other connective tissue diseases (CTDs) were excluded. Patients with ILD not caused by SSc (such as idiopathic disease, or disease caused by exposure to drugs, coal dust, or asbestos), were also excluded. All included patients received glucocorticoids and/or immunosuppressants for at least 12 months. Only 71 patients who completed the follow-up HRCT exam at our hospital were included in the analysis of prognostic factors.

Data collection

Demographics, baseline clinical features, laboratory results, and treatment regimens were collected for analysis. These data, including age, disease duration (defined as the time from the first symptom of non-Raynaud's phenomenon to presentation), SSc subtype, autoantibody status, and presence of concomitant autoimmune diseases, were obtained from each patient at the first visit. A pulmonary arterial systolic pressure (PASP) above 40 mmHg, determined by Doppler echocardiography, was defined as pulmonary hypertension (PH) [9].

Modified Rodnan skin score (MRSS)

The skin thickness of individual patients was measured using the MRSS. For these measurements, a physician performed palpation to determine the skin thickness of 17 body sites, and rated each site as 0 (mRSS = 0 is "normal skin" where the examiner appreciates fine wrinkles but no skin thickness is present), 1 (mRSS = 1 is defined as definite but "mild" skin thickness where the examiner can easily make skin folds between 2 fingers; fine wrinkles are acceptable), 2 (mRSS = 2 is defined as "moderate" skin thickness with difficulty in making skin folds and no wrinkles), or 3 (mRSS = 3 is defined as "severe" skin thickness with inability to make skin folds between 2 examining fingers), leading to a total skin score of 0-51 [10].

HRCT scans

HRCT was performed routinely on each participant to evaluate ILD, and each patient was

assigned a score indicating the severity of ILD by two independent radiologists. The degree of ILD was determined as the amount of ground-glass opacity (GG), pulmonary fibrosis (PF), or honeycomb cysts (HC). All of the lung volume was visible, and the extent of GG, PF, and HC of each lung lobe (right upper, right middle, right lower, left upper, and left lower) was scored as 0 (absent), 1 (1-25%), 2 (26-50%), 3 (51-75%), or 4 (76-100%). The total scores (t-GG, t-PF, and t-HC) were computed by the summation of all of the scores from all 5 lung lobes, and ranged from 0 to 20. The t-GG, t-PF, and t-HC scores were also aggregated to produce a t-ILD score that ranged from 0 to 60 [11]. Follow-up HRCT examinations were taken after a 12-month post-treatment period and patients were classified as having deterioration or stable disease/improvement (see below).

Pulmonary function testing

Some patients underwent PFT. The results were classified as: (i) diffusion dysfunction, in which the carbon monoxide diffusion capacity (DLCO) was lower than the normal value of PFT in our hospital (DLCO < 80% predicted); (ii) restrictive ventilation dysfunction, in which the forced vital capacity (FVC) accounted for the estimated value below 80% and the forced expiratory capacity in 1 second (FEV1)/FVC (FEV1/FVC) was above 70%; (iii) obstructive ventilation dysfunction, in which FEV1 accounted for the estimated value below 80%, the FEV1/FVC was below 70%, the maximal voluntary ventilation was below 70%, and the forced expiratory flow (25-75%) was below 80%; and (iv) mixed ventilation dysfunction, in which the conditions of restrictive and obstructive ventilation dysfunction were both present.

Grouping

Patients were placed into several groups for comparisons. First, based on the presence of ILD in the chest HRCT images, patients were classified into SSc-ILD or SSc-non-ILD groups. Second, SSc-ILD patients were classified into a limited cutaneous disease (lcSSc-ILD) group if skin thickening was confined to distal extremities (below the elbows and knees) and above the clavicles or to a diffuse cutaneous disease (dcSSc-ILD) group if skin thickening involved the proximal extremities and the torso. Third, HRCT score (calculated as described above) was used to estimate the extent and/or degree of lung involvement. SSc-ILD patients were considered to have deteriorative SSc-ILD if the HRCT score changes less than 4%. Patients were considered to have non-deteriorative SSc-ILD if they improved (HRCT score less than -4%) or of they had stable status (the change of HRCT score: 4% to -4%) [1].

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are reported as means ± standard deviations (SDs). Normally distributed data were compared using Student's t-test and one-way ANOVA. Non-normal data are reported as medians (interquartile ranges) and compared using the Mann-Whitney U-test. Categorical variables are reported as numbers and percentages, and compared using the chi-square test. Variables with significance in the univariate analysis were entered into a multivariate logistic regression analysis. A *P*-value below 0.05 was considered statistically significant.

Results

Baseline clinical and demographic characteristics

We retrospectively examined 320 SSc patients. There were 131 (40.9%) males and 189 (59.1%) females, the age range was 13 to 81 years (average: 50.02±11.74 years), and the median course of disease (duration since the initial diagnosis) was 7.5 months. One hundred and sixty-nine patients were complicated with ILD (69 males and 100 females), and their average age was 51.30±10.86 years. The common clinical manifestations of patients with SSc-ILD were Raynaud's phenomenon (80.0%), exertional dyspnea (34.2%), joint swelling and pain (34.3%), fingertip ulcer (31.1%), cough (26.8%), and chest tightness and pain (16.3%). A total of 94.5% of these patients were positive for antinuclear antibodies (ANA). All patients were treated with immunosuppressants and/or glucocorticoids for at least 12 months. Twelve SSc-ILD patients received glucocorticoids (5 to 40 mg qd) alone, 28 received immunosuppressants alone, and 280 received both glucocorticoids and immunosuppressants. Among them, 127 patients received cyclophosphamide (CYC)

Table 1. Baseline demographic and clinical characteristics of SSc patients with and without ILD†

Variable	Total (n = 320)	SSc-non-ILD (n = 151)	SSc-ILD (n = 169)	*P*	Univariate analysis OR (95% CI)
Gender					
Male	131 (40.9%)	62 (41.1%)	69 (40.9%)	0.967	0.990 (0.634, 1.548)
Female	189 (59.1%)	89 (58.9%)	100 (59.2%)		
Age, years	50.02±11.74	48.58±12.52	51.30±10.86	0.039	
Duration of disease, months	7.5 (4.0, 21.75)	6.5 (3.0, 13.75)	9.5 (4.0, 24.75)	0.016	
MRSS	21.59±6.85	21.61±7.38	21.57±6.37	0.961	
Raynaud's phenomenon	252 (79.2%)	113 (75.3%)	139 (82.7%)	0.104	0.637 (0.369, 1.100)
Exertional dyspnea	109 (34.2%)	35 (23.2%)	74 (44.0%)	< 0.001	2.609 (1.606, 4.240)
Arthritis	108 (34.3%)	49 (32.5%)	59 (36.0%)	0.510	1.170 (0.734, 1.865)
Fingertip ulcer	99 (31.1%)	45 (45.5%)	54 (54.5%)	0.680	1.105 (0.687, 1.779)
Cough	85 (26.8%)	27 (17.9%)	58 (34.9%)	0.001	2.466 (1.460, 4.167)
Chest tightness and pain	22 (16.3%)	6 (9.4%)	16 (22.5%)	0.039	2.812 (1.026, 7.707)
Dysphagia	33 (10.6%)	12 (8.1%)	21 (12.9%)	0.166	1.688 (0.800, 3.564)
PH	50 (15.6%)	17 (11.2%)	33 (19.5%)	0.046	1.792 (1.012, 3.497)
ESR, mm/h	28 (16.00, 45.25)	21 (12.00, 40.00)	31 (18.00, 52.00)	0.001	
CRP, mg/L	7.95 (3.78, 18.83)	6.30 (2.84, 12.52)	10.15 (5.18, 24.13)	< 0.001	
Anti-Scl-70 antibody	227/317* (71.6%)	99 (65.6%)	128 (77.1%)	0.023	1.769 (1.080, 2.899)
ANA	275/291* (94.5%)	130 (94.9%)	145 (94.2%)	0.784	0.868 (0.314, 2.395)
Nucleolar pattern	106/201* (52.7%)	51 (52.6%)	55 (52.9%)	0.965	0.993 (0.571, 1.726)
Speckled pattern	72/201* (35.8%)	35 (36.1%)	37 (35.6%)	0.940	1.088 (0.609, 1.943)
Homogeneous pattern	73/201* (36.3%)	29 (29.9%)	44 (42.3%)	0.068	1.833 (0.998, 3.294)
PFT dysfunction					
Diffusion	39/84* (46.4%)	15 (35.7%)	24 (57.1%)	0.049	2.400 (1.002, 5.778)
Restrictive ventilation	15/84* (17.9%)	4 (9.5%)	11 (26.2%)	0.046	3.371 (1.001, 11.635)
Mixed ventilation	10/83* (12.0%)	2 (4.9%)	8 (19.0%)	0.100	4.588 (0.911, 23.099)

†Data are presented as n (%) or median (IQR). *Total includes patients with missing data. SSc, systemic sclerosis; ILD, interstitial lung disease; MRSS, modified Rodnan skin score; PH, pulmonary hypertension; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; ANA, antinuclear antibody; PFT, pulmonary function test.

pulse therapy (1 g every 2 to 4 weeks), 38 received mycophenolate mofetil (750 mg bid), 45 received azathioprine (100 mg qd), 2 received cyclosporine (50 mg tid), 118 received methotrexate (10 to 15 mg weekly), 7 received leflunomide (10 to 20 mg qd), 71 received thalidomide (50 to 75 mg qd), 55 received tripterygium glycosides (50 mg tid), and 28 received hydroxychloroquine (200 mg bid). Some patients received a combination of immunosuppressants. The drug delivery methods and dosages of the immunosuppressants during the whole treatment period were individualized according to each patient's condition.

Baseline demographic and clinical characteristics of the SSc-ILD and SSc-non-ILD groups

Our comparison of SSc patients with and without ILD (**Table 1**) indicated many significant differences ($P < 0.05$ for all). The SSc-ILD group was older, had a longer course of disease (6.5, range: 3.0-13.75 vs. 9.5 years, range: 4.0-24.75); higher prevalence of cough (OR: 2.466, 95% CI: 1.460-4.167), chest tightness and pain (OR: 2.812, 95% CI: 1.026-7.707), exertional dyspnea (OR: 2.609, 95% CI: 1.606-4.240), and pulmonary hypertension (OR: 1.792, 95% CI: 1.012-3.497); higher levels of erythrocyte sedimentation rate (ESR) (21, range: 12.00-40.00 vs. 31 mm/h, range: 18.00-52.00), and C-reactive protein (CRP) (6.30, range: 2.84-12.52 vs. 10.15 mg/L, range: 5.18-24.13); and a higher prevalence of anti-Scl-70 antibody positivity (OR: 1.769, 95% CI: 1.080-2.899). The two groups had no significant differences in immunological markers (immunoglobulin G [IgG], IgA, IgM, complement 3 [C3], and C4), MRSS, positivity for ANA, and prevalence of nucleolar ANA patterns. The results of PFT demonstrated that some SSc patients without ILD also had diffusion dys-

Table 2. Baseline demographic and clinical characteristics of SSC-LID patients with dcSSc-ILD and lcSSc-ILD†

Variable	Total SSc-ILD (n = 169)	lcSSC-ILD (n = 69)	dsSSc-ILD (n = 100)	*P*	Univariate analysis OR (95% CI)
Gender					
Male	69 (40.8%)	19 (27.5%)	50 (50.0%)	0.003	0.380 (0.197, 0.734)
Female	100 (59.2%)	50 (72.5%)	50 (50.0%)		
Age, years	51.30±10.86	51.72±11.66	51.00±10.33	0.671	
Duration of disease, months	9.50 (4.00, 24.75)	12 (5, 38.5)	8 (4, 24)	0.483	
MRSS	21.57±6.37	15.83±4.43	25.53±4.07	< 0.001	
Smoking	35 (20.7%)	11 (15.9%)	24 (24.0%)	0.204	1.665 (0.755, 3.673)
Raynaud's phenomenon	139 (82.7%)	54 (79.4%)	85 (85.0%)	0.347	1.469 (0.657, 3.284)
Exertional dyspnea	74 (44.0%)	27 (39.7%)	47 (47.0%)	0.350	1.347 (0.721, 2.515)
Arthritis	59 (36.0%)	21 (31.3%)	38 (39.2%)	0.304	1.411 (0.731, 2.724)
Fingertip ulcer	54 (32.1%)	17 (25.0%)	37 (37.0%)	0.102	1.762 (0.890, 3.487)
Cough	58 (34.9%)	21 (30.9%)	37 (37.8%)	0.361	1.358 (0.704, 2.618)
Chest tightness and pain	16/71* (22.5%)	8 (20.5%)	8 (25.0%)	0.653	1.292 (0.423, 3.941)
Dysphagia	21 (12.9%)	6 (9.0%)	15 (15.6%)	0.211	1.883 (0.690, 5.135)
PH	33 (19.5%)	17 (24.6%)	16 (16.0%)	0.164	0.553 (0.247, 1.240)
ESR, mm/h	31 (18, 52)	34 (19,53)	30 (18, 51.75)	0.410	
CRP, mg/L	10.15 (5.18, 24.13)	9.1 (5.15, 16.76)	10.9 (5.1, 29.5)	0.406	
Anti-Scl-70 antibody	128/166* (77.1%)	52 (75.4%)	76 (78.4%)	0.652	1.183 (0.570, 2.456)
ANA	145/154* (94.2%)	59 (96.7%)	86 (92.5%)	0.272	0.416 (0.084, 2.075)
Nucleolar pattern	55/104* (52.9%)	22 (46.8%)	33 (57.9%)	0.260	1.562 (0.718, 3.401)
Speckled pattern	37/104* (35.6%)	20 (42.6%)	17 (29.8%)	0.177	0.574 (0.255, 1.290)
Homogeneous pattern	44/104* (42.3%)	19 (40.4%)	25 (43.9%)	0.724	1.151 (0.526, 2.519)
HRCT score	8 (4.5, 12)	6 (4, 10)	8 (5, 14)	0.141	
PFT dysfunction					
Diffusion	24/42* (50.0%)	6/13 (46.2%)	18/29 (62.1%)	0.335	1.909 (0.508, 7.172)
Restrictive	11/42* (26.2%)	4/13 (30.8%)	7/29 (24.1%)	0.651	0.716 (0.167, 3.061)
Mixed ventilation	8/42* (19.0%)	1/13 (7.7%)	7/29 (24.1%)	0.210	3.818 (0.419, 34.812)

†Data are presented as n (%) or median (IQR). *Total includes patients with missing data. SSc, systemic sclerosis; ILD, interstitial lung disease; MRSS, modified Rodnan skin score; PH, pulmonary hypertension; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; ANA, antinuclear antibody; HRCT, high-resolution computed tomography; PFT, pulmonary function test.

function and restricted ventilation dysfunction, and that diffusion dysfunction was more common. SSc-ILD patients were more likely to have diffusion ventilation dysfunction and restricted ventilation dysfunction than SSc patients without ILD.

Baseline clinical characteristics and treatment effects of the dcSSc-ILD and lcSSc-ILD groups

ILD occurred in 100 of 198 dcSSc patients and in 69 of 122 lcSSc patients (50.5% vs. 56.6%, P = 0.292). Among males, those with dcSSc were more likely to have ILD than those with lcSSc. A comparison of dcSSc-ILD and lcSSc-ILD patients indicated no significant differences in respiratory symptoms, gastrointestinal symptoms, fingertip ulcer, Raynaud's phenomenon, joint swelling and pain, presence of PH, and t-ILD score (P > 0.05 for all). ANA positivity was 95.2% in dcSSc-ILD patients and 96.7% in lcSSc-ILD patients (P > 0.05), and these two groups also had no statistically significant differences in inflammatory indicators, anti-Scl-70 antibody positivity, ANA karyotype patterns, and pulmonary function (**Table 2**).

Baseline clinical characteristics and treatment effects of the SSc-ILD non-deteriorative and deteriorative groups

The t-PF and t-ILD scores at the 12-month follow-up were significantly higher than at baseline (t-PF: 4.57±4.34 vs. 6.22±4.44, t = -5.026, P < 0.001; t-ILD: 10.91±6.27 vs. 12.69±7.04, t = -2.891, P = 0.005), but there were no signifi-

Table 3. Baseline clinical characteristics of patients with SSc-ILD who did and did not experience deterioration†

Variable	No deterioration (n = 42)	Deterioration (n = 29)	Z/X^2 value	*P*	Univariate analysis OR (95% CI)
Age, years	50.31±10.16	57.97±9.61	-3.189	0.002	
Duration of disease, months	13 (6.75, 72.00)	13 (5.00, 90.00)	-0.094	0.925	
MRSS	20.02±6.237	18.38±6.09	1.102	0.274	
Smoking	10 (23.8%)	7 (24.1%)	0.001	0.975	1.018 (0.336, 3.083)
Raynaud's phenomenon	37 (88.1%)	23 (82.1%)	0.122	0.727	0.622 (0.162, 2.384)
Exertional dyspnea	15 (35.7%)	18 (62.1%)	4.790	0.029	2.945 (1.105, 7.850)
Arthritis	14 (33.3%)	13 (48.1%)	1.514	0.218	1.857 (0.690, 5.001)
Fingertip ulcer	12 (28.6%)	7 (25.0%)	0.108	0.742	0.833 (0.281, 2.469)
Cough	17 (40.5%)	13 (44.8%)	0.133	0.715	1.195 (0.459, 3.110)
Chest tightness and pain	8 (19.5%)	7 (24.1%)	0.216	0.642	1.312 (0.416, 4.141)
Dysphagia	7 (16.7%)	4 (14.3%)	0.000	1.000	0.833 (0.220, 3.163)
PH	15 (36.6%)	10 (37.0%)	0.001	0.970	1.020 (0.372, 2.791)
ESR, mm/h	27.5 (18.0, 39.25)	42 (23.0, 59.0)	-2.455	0.014	
CRP, mg/L	9.09 (5.39, 14.78)	10.20 (4.70, 19.60)	-0.446	0.656	
Anti-Scl-70 antibody	30 (71.4%)	25 (89.3%)	3.182	0.074	3.333 (0.845, 13.144)
ANA	38/41* (92.7%)	27/27 (100%)	2.067	0.151	1.148 (0.316, 1.010)
Nucleolar pattern	20/38* (52.6%)	14/27 (51.9%)	0.004	0.951	0.969 (0.361, 2.602)
Speckled pattern	15/38* (39.5%)	7/27 (25.9%)	1.294	0.255	0.537 (0.182, 1.579)
Homogeneous pattern	17/38* (44.7%)	13/27 (48.1%)	0.074	0.786	1.147 (0.427, 3.085)
HRCT score	8 (4, 12.5)	6 (5, 10)	-0.112	0.911	

†Data are presented as n (%) or median (IQR). *Total includes patients with missing data. SSc, systemic sclerosis; ILD, interstitial lung disease; MRSS, modified Rodnan skin score; PH, pulmonary hypertension; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; ANA, antinuclear antibody; HRCT, high-resolution computed tomography.

cant changes in the t-GG and t-HC scores (t-GG: 4.66±4.28 vs. 4.59±4.38, t = 0.161, P = 0.872; t-HC: 1.58±3.07 vs. 2.01±3.62, t = -1.642, P = 0.105). Post-treatment analysis of the 71 patients with SSc-ILD who completed the follow-up indicated that 19 patients improved, 18 remained stable, and 34 patients deteriorated. Among lcSSc-ILD patients, 9 improved, 9 were stable, and 21 deteriorated; among dcSSc-ILD patients, 10 improved, 9 were stable, and 13 deteriorated. Overall, patients who deteriorated were older than those who did not deteriorate (57.535±9.21 vs. 49.68±10.45 years), but these groups had no differences in disease duration, smoking, or SSc subtype.

Patients who deteriorated had a greater prevalence of exertional dyspnea (OR: 2.945, 95% CI: 1.105-7.850) and a higher level of ESR (27.5, range: 18.0-39.25 vs. 42 mm/h, range: 23.0-59.0 mm/h) than those who did not deteriorate. However, the deteriorated and non-deteriorated patients had no significant differences in disease duration, smoking status, cough, chest tightness and pain, dysphagia, fingertip ulcer, Raynaud's phenomenon, joint swelling and pain, MRSS, and blood biochemistry (ESR, CRP, complement, and autoimmune antibodies; P > 0.05 for all; **Table 3**).

Prognostic indicators based on multivariate logistic regression analysis

We performed multivariate analysis to determine the significance of differences in clinical manifestations and laboratory data in the different groups. Multivariate analysis comparing SSc-ILD with SSc-non-ILD patients indicated that course of disease (OR: 1.027, 95% CI: 1.003-1.052; P = 0.027) was the only independent risk factor for ILD. A separate multivariate analysis of prognosis showed that greater age (OR: 1.107, 95% CI: 1.018-1.205; P = 0.018) and presence of exertional dyspnea (OR: 7.517, 95% CI: 1.415-39.918; P = 0.018) were significantly associated with deterioration of SSc-ILD (**Table 4**).

Table 4. Multivariate logistic regression analysis of factors associated with ILD in SSc patients and factors associated with deteriorative disease in patients with SSc-ILD

Variable	Predictors of ILD in SSc patients			Predicators of deteriorative disease in SSc-ILD patients		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	0.965	0.878, 1.062	0.470	1.100	1.017, 1.189	0.017
Duration of disease	1.027	1.003, 1.052	0.027	1.001	0.991, 1.010	0.872
MRSS	0.946	0.868, 1.030	0.202	1.053	0.937, 1.182	0.389
Exertional dyspnea	2.900	0.218, 38.541	0.420	6.437	1.342, 30.876	0.020
Cough	10.855	0.868, 135.786	0.064	0.914	0.232, 3.601	0.898
Chest tightness and pain	11.027	0.118, 1.032	0.300	0.503	0.089, 2.842	0.437
PH	2.338	0.167, 32.797	0.528	0.576	0.158, 2.100	0.403
ESR	1.087	0.988, 1.195	0.087	1.027	0.989, 1.067	0.171
CRP	0.938	0.848, 1.038	0.087	0.987	0.958, 1.018	0.413

SSc, systemic sclerosis; ILD, interstitial lung disease; MRSS, modified Rodnan skin score; PH, pulmonary hypertension; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

Discussion

The prevalence of SSc is 7.2 to 33.9 per 100,000 in Europe and 13.5 to 44.3 per 100,000 in North America, and the 10-year survival rate is 65 to 73% in Europe and 54 to 82% in North America [12]. ILD occurs in up to approximately 56% of patients with SSc in East Asia [13]. The diagnostic onset of ILD generally appears during early-stage SSc (after 3 to 4 years), and ILD is one of the main complications and the leading cause of death from SSc [2]. The 5-year survival rate of SSc patients without ILD is 83% but is only 69% when SSc is complicated with ILD [14]. Early detection of pulmonary dysfunction and chest HRCT imaging are key to the diagnosis and treatment of SSc patients, and chest HRCT is the most effective method for diagnosis of SSc-ILD [15].

Previous studies showed that SSc was more common in females, the average age of onset was 50.1±13.5 years, and that 35% to 80% of patients had ILD [12, 13, 15, 16]. Thus, the age, predominance of females, and incidence of ILD (52.8%) in our patients were consistent with previous studies. The incidence of ILD was also similar in dsSSc and lcSSc patients. However, male dcSSc patients were more likely to have ILD than lcSSc, and the incidence of ILD in male patients with dcSSc was greater than in those with lcSSc. Consistently, a previous study by Chowaniec [17] found that the incidence of SSc-ILD was greater in males with dsSSc.

Our results also indicated that, compared with SSc-non-ILD patients, SSc-ILD patients were older and had a longer disease duration; had a higher prevalence of cough; and had higher levels of ESR and CRP. These results are also similar to those of previous studies [12, 13, 16-18]. We suggest that onset of SSc at a later age and prolonged disease duration might be responsible for the development of ILD, during which cough and dyspnea occur. It is possible that SSc patients who develop ILD have stronger inflammatory responses than those who do not develop ILD. Generally, ILD occurs during the early course of SSc, in which case it requires close monitoring [17]. The early inflammatory response in SSc-ILD is relatively strong, but there is typically a good response to immunosuppressive treatments, and these improve patient prognosis. Furthermore, our study also confirmed that the incidence of PH was greater in SSc-ILD patients. PH is often concomitant with ILD in SSc patients, and is also associated with a decreased survival rate [19], indicating that SSc patients with ILD should be closely monitored for PH.

A previous study of South Africans with SSc demonstrated that the most common ANA pattern was speckled, and that a speckled ANA pattern was more common in those with ILD and independently associated with ILD. This previous study found no significant differences in homogeneous and nucleolar ANA patterns in SSc patients with or without ILD [20]. However, our patients with SSc-ILD were more likely to have a homogenous ANA pattern (although without statistical significance). It is possible that the different ANA karyotype results in our study and the previous study of South Africans

are attributable to differences in race or ethnicity. Patients with SSc typically have several autoantibodies, some of which are SSc-specific and associated with certain clinical features. Numerous studies have found that anti-Scl-70 positivity was associated with dcSSc and ILD, but ACA positivity was associated with lcSSc and pulmonary arterial hypertension (PAH), and was protective for ILD [15, 18, 21, 22]. However, other studies suggested no correlation in anti-Scl-70 antibody positivity with dcSSc or ILD, or in ACA positivity with lcSSc or PAH [23]. Our study showed that anti-Scl-70 antibody positivity was more prevalent in patients with SSc-ILD than SSc-non-ILD, and supported the finding that anti-Scl-70 antibody positivity correlated with the occurrence of ILD in SSc. The ACA positivity rates in these two groups were too low for a meaningful comparison.

In addition to our HRCT findings, PFT is a sensitive indicator for the detection of early ILD and the evaluation of prognosis. Diffusion dysfunction occurs during early-stage SSc-ILD, and FVC decreases as disease progresses (namely restricted ventilation dysfunction). Recent research demonstrated that a decline in FVC and DLCO over 2 years was a better predictor of mortality than baseline FVC and DLCO [20]. These findings suggest that short-term changes in surrogate measures of SSc-ILD progression may be associated with long-term outcome [24]. Our results suggest that DLCO diffusion dysfunction and restricted ventilation dysfunction also occur in SSc patients without HRCT lesions, indicating early lung function impairment, mainly diffuse dysfunction. In our SSc patients, diffusion dysfunction and restricted ventilation dysfunction were significantly more common in those with than without our ILD.

Numerous studies showed that the risk factors for ILD in SSc patients are course of disease, male sex, cough, exertional dyspnea, dcSSc, African-American status, older age at onset, anti-scl-70 antibody positivity, speckled ANA pattern, and elevated biomarkers (such as serum IL-6, CXCL4, KL-6 and IL-33) [15, 16, 21, 25, 26]. Our study showed that ILD in SSc correlated with exertional dyspnea, high baseline levels of ESR and CRP, PH, and anti-Scl70 antibody positivity, in agreement with the above studies. However, course of disease was the only risk factor for SSc-ILD, indicating that prolonged disease duration was associated with an increased risk of ILD in SSc, especially after 4 to 5 years [17]. This is consistent with Li's research that patients with SSc-ILD were older, with increased complications and diagnostic procedures at baseline [27]. Guler et al. [28] demonstrated that a recent change in FVC predicted future change in FVC within shorter follow-up intervals. These findings provide important information on the course of disease in patients with SSc-ILD.

Glucocorticoids and immunosuppressants remain the main treatments for SSc-ILD, and several studies suggested that CYC is one of the evidence-based drugs with proven effectiveness. The efficacy of CYC is usually assessed as an improvement of pulmonary function [29], but only rarely as an improvement based on HRCT. Our research showed that after 12 months of active immunosuppressive therapy, HRCT evaluation indicated that 40.8% SSc-ILD patients were still undergoing disease progression, indicating the need for future clinical trials that seek to optimize the treatment of SSc-ILD. Cappelli et al. [15] concluded that despite advances in treatment, such as immunosuppressants (CYC, mycophenolate mofetil, received azathioprine) and biologic agents, it remains difficult to significantly slow the progression of SSc-ILD. Sumida et al. [30] found no significant differences in age, course of disease, sex, type of auto-antibodies, and skin sclerosis score when comparing good responders and poor responders with SSc-ILD who were ever treated with intravenous cyclophosphamide in combination with prednisolone. Other studies showed that the risk factors for deterioration of SSc after immunosuppressive treatment were advanced age, African ancestry, short 6-min walking distance, arthritis, HRCT lesions of more than 20%, and co-occurrence of ILD [28, 31, 32]. Our study showed that SSc-ILD patients who deteriorated (based on HRCT) after treatment were older at disease onset and were more likely to have exertional dyspnea and elevated ESR. This suggests that poor treatment efficacy occurred in SSc-ILD patients who were older, and had exertional dyspnea and active inflammation, resulting in a poor prognosis.

In conclusion, our study showed that the incidence of ILD in SSc patients was 52.8%, and that ILD in SSc correlated with prolonged disease duration, presence of cough and PH,

active inflammation, anti-Scl70 antibody positivity, and diffusion dysfunction and restricted ventilation dysfunction in PFT. After immunosuppressive therapy, only 26.8% of SSc-ILD patients improved, and disease progression occurred in 47.9% patients. Older age at disease onset and exertional dyspnea were associated with deterioration of SSc-ILD. Thus, the development of more advanced therapies that inhibit inflammation and fibrosis appears to be a key to improving the treatment of patients with SSc-ILD.

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Disclosure of conflict of interest

None.

Abbreviations

ILD, interstitial lung disease; SSc, systemic sclerosis; HRCT, high-resolution computed tomography; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; PFT, pulmonary function testing; HRQoL, health-related quality of life; ARA, American Rheumatism Association; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; CTDs, connective tissue diseases; PASP, pulmonary arterial systolic pressure; MRSS, modified Rodnan skin score; GGO, ground-glass opacity; PF, pulmonary fibrosis; HC, honeycomb cysts; DLCO, carbon monoxide diffusion capacity; FVC, forced vital capacity; FEV1, forced expiratory capacity in 1 second; CYC, Cyclophosphamide; ANA, antinuclear antibodies; Ig, Immunoglobulin; C3, Complement 3; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension.

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