Supplementary material

Progressive interstitial lung disease measured by forced vital capacity changes in combination with diffusion capacity of the lungs for carbon monoxide changes over 12-month periods

A decline in forced vital capacity (FVC) of ≥10%, or a decline in FVC of 5–10% along with a decline in diffusion capacity of the lungs for carbon monoxide (DL_{CO}) of 15%, is a proposed definition of progressive fibrosis in patients with interstitial lung disease (ILD), and is predictive of mortality in patients with systemic sclerosis (SSc)-ILD.[8, 31] We therefore also assessed the prevalence of this combined endpoint.

Materials and methods

Patients were divided into five progressive ILD subgroups based on absolute change in FVC and DL_{CO} (% predicted) during the initial 12±3-month period: significant progression (FVC decline of >10%, or FVC decline of 5–10% with DL_{CO} decline of ≥15%); moderate progression (FVC decline of 5–10% with DL_{CO} decline of <15%); stable ILD (FVC decline or improvement of <5%); moderate improvement (FVC improvement of 5–10% with DL_{CO} improvement of <15%); and significant improvement (FVC improvement of >10%, or FVC improvement of 5–10% with DL_{CO} improvement of ≥15%).

Further changes in lung function were evaluated in patients with available data over a mean follow-up of 5 years, using the definitions of progressive ILD described above.

Results

Among the 826 eligible patients with pulmonary function data over the initial 12±3-month period, 113 (14%) had significant ILD progression, 106 (13%) had moderate progression, 408 (49%) were stable, 189 (23%) had moderate improvement, and 10 (1%) had significant improvement (Table S1).

In multivariable logistic regression analyses, higher FVC (odds ratio (OR) 1.03; 95% confidence interval (CI) 1.02–1.04), shorter disease duration (OR 0.97; 95% CI 0.97–0.98), higher erythrocyte sedimentation rate (OR 1.02; 95% CI 1.01–1.02), and presence of reflux/dysphagia symptoms (OR 1.71; 95% CI 1.03–2.84; Figure S1B) were predictive for significant progressive ILD at 12±3 months. Older age, male sex, antibody profile and SSc subtype were not predictive. Further ILD progression over the 5-year follow-up (among patients who had experienced progression during the initial 12±3-month period)

was predicted by higher FVC (OR 1.02; 95% CI 1.00–1.04) and shorter disease duration (OR 1.00; 95% CI 1.00–1.02; Figure S1D). The only factor significantly predictive for cumulative progression over 5 years was higher baseline FVC (OR 1.01, 95% CI 1.00–1.02, *p*=0.01).

There were no significant differences in mortality rate between patients with significant ILD progression (14/113 [12%]), moderate progression (15/106 [14%]), or stable ILD (36/408 [9%]) after 12±3 months.

SUPPLEMENTARY TABLE S1: Overall baseline demographics and clinical characteristics of all patients with SSc-ILD and those with three serial FVC measurements (who were included in the analyses) or without three serial measurements (who were not included).

	Included (n=826)	**Not included (n=1433)**	**Overall (N=2259)**
Age, years (SD)	56 (13.1)	57 (13.4)	57 (13.3)
Male, n (%)	150 (18)	238 (17)	388 (17)
Disease characteristics			
Disease duration, years (SD)	9.7 (8.3)	9.9 (8.3)	9.9 (8.3)
Disease duration <3 years, n (%)	175 (21)	294 (21)	469 (21)
Diffuse cutaneous SSc, n (%)	365 (44)	599 (43)	964 (44)
Limited cutaneous SSc, n (%)	367 (44)	668 (48)	1035 (47)
Anti-topoisomerase I Ab, n (%)	421 (51)	700 (52)	1121 (53)
Anti-centromere Ab, n (%)	141 (17)	237 (18)	378 (18)
Anti-RNA polymerase III Ab, n (SD)	23 (3)	34 (5)	57 (5)
Follow-up period, years, mean (SD)	5.4 (2.0)	1.8 (2.2)	2.5 (2.3)
Lung characteristics			
FVC% predicted, mean (SD)	87 (21.1)	86 (22.0)	86 (21.7)
DL_{CO}% predicted, mean (SD)	59 (18.3)	59 (20.3)	59 (19.6)
NYHA class, n (%)			
1	363 (44)	527 (38)	890 (41)
2	317 (38)	578 (42)	895 (41)
3	103 (13)	236 (17)	339 (16)
4	14 (2)	31 (2)	45 (2)
Other characteristics			
mRSS, mean (SD)	10 (8.1)	10 (8.9)	10 (8.6)
Reflux/dysphagia symptoms, n (%)	547 (66)	905 (64)	1452 (65)
Digital ulcers, n (%)	266 (32)	410 (29)	676 (30)
Tendon friction rubs, n (%)	73 (9)	114 (8)	187 (9)
Synovitis, n (%)	117 (14)	224 (16)	341 (15)
Muscle weakness, n (%)	182 (22)	289 (20)	465 (21)
Scleroderma renal crisis, n (%)	11 (1)	24 (2)	90 (2)
ESR, mean (SD)	26 (20.6)	26 (20.5)	26 (20.5)
Elevated CRP, n (%)	217 (26)	417 (31)	634 (30)
Immunosuppressant use, n (%)	89 (11)	220 (15)	309 (14)

Abbreviations: Ab, antibody; CRP, C-reactive protein; DL_{CO}, diffusion capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; mRSS, modified Rodnan skin score; NYHA, New York Heart Association; SD, standard deviation; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

SUPPLEMENTARY TABLE S2 Overall baseline demographic and clinical characteristics of patients with SSc-ILD and characteristics stratified by ILD progression (defined by FVC and DL_{CO}) over the 12±3-month observation period

	Total (N=826)	**Significant progression (n=113)**	**Moderate progression (n=106)**	**Stable (n=408)**	**Moderate improvement (n=189)**
Progression criteria, ΔFVC (ΔDL_{CO})		<−10, or −10 to −5 (≤−15)	−10 to −5 (>−15)	>−5 to <5	5 to 10 (<15)
Age, years (SD)	56 (13.1)	59 (13.4)	55 (12.1)	55 (13.5)	58 (12.1)
Male, n (%)	150 (18)	18 (16)	17 (16)	81 (20)	34 (18.0)
Disease characteristics at baseline					
Disease duration, years (SD)	9.7 (8.3)	9.2 (7.6)	9.6 (8.4)	10.2 (8.3)	9.0 (8.6)
Disease duration <3 years, n (%)	175 (21)	27 (24)	27 (26)	70 (17)	50 (26.5)
Diffuse cutaneous SSc, n (%)	365 (44)	51 (45)	45 (43)	186 (46)	78 (41.3)
Limited cutaneous SSc, n (%)	367 (44)	58 (51)	43 (41)	180 (44)	81 (42.9)
Anti-topoisomerase I Ab, n (%)	421 (51)	48 (43)	55 (54)	222 (54)	93 (49.2)
Anti-centromere Ab, n (%)	141 (17)	19 (17)	20 (19)	60 (15)	40 (21.2)
Anti-RNA polymerase III Ab, n (%)	23 (3)	3 (3)	3 (3)	10 (3)	9.0 (8.6)
Total observation period, years (SD)	5.4 (2.0)	5.5 (2.1)	5.5 (2.1)	5.4 (2.0)	50 (26.5)
Lung characteristics					
FVC% predicted, mean (SD)	87 (21.1)	96 (23.1)	89 (21.4)	85 (20.6)	85.1 (19.5)
DL_{CO}% predicted, mean (SD)	59 (18.3)	62 (17.8)	58 (16.5)	58 (19.5)	59.0 (16.8)
ΔFVC% predicted,* mean (SD)	–0.1 (10.2)	–17 (8.0)	–7 (1.4)	0.3 (2.5)	11.0 (7.3)
ΔDL_{CO}% predicted,* mean (SD)	–0.7 (12.2)	–7 (17.2)	1 (10.0)	–0.4 (11.3)	2.4 (1.7)
Pulmonary hypertension, n (%)	162 (20)	21 (25)	16 (15)	6 (21)	30 (16)
NYHA class, n (%)					
1	363 (44)	53 (47)	46 (43)	175 (43)	89 (47)
2	317 (38)	44 (39)	41 (39)	154 (38)	77 (41)
3	103 (13)	12 (11)	14 (13)	52 (13)	24 (13)
4	14 (2)	3 (3)	1 (1)	8 (2)	2 (1)
Other characteristics					
mRSS, mean (SD)	10 (8.1)	11 (8.0)	9 (8.3)	10 (7.6)	9.9 (8.9)

	Total (N=826)	Significant progression (n=113)	Moderate progression (n=106)	Stable (n=408)	Moderate improvement (n=189)
∆mRSS, mean (SD)*	–0.4 (4.6)	0.5 (4.2)	–0.4 (3.2)	–0.4 (4.6)	–1.2 (5.3)
Reflux/dysphagia symptoms, n (%)	547 (66)	87 (77)	68 (64)	268 (66)	118 (62.4)
Digital ulcers, n (%)	266 (32)	43 (38)	28 (26)	144 (35)	60 (32)
Tendon friction rubs, n (%)	73 (9)	8 (7)	8 (8)	36 (9)	20 (11)
Synovitis, n (%)	117 (14)	18 (16)	13 (12)	62 (15)	23 (12)
Muscle weakness, n (%)	182 (22)	29 (26)	24 (23)	83 (20)	47 (25)
Scleroderma renal crisis, n (%)	11 (1)	4 (4)	3 (3)	6 (2)	1 (0.5)
ESR, mean (SD)	26 (20.6)	29 (23.8)	25 (21.9)	26 (19.0)	25.9 (20.8)
Elevated CRP, n (%)	217 (26)	38 (34)	32 (30)	102 (25)	47 (25)
Immunosuppressant use, n ($)	88 (11)	8 (7)	9 (9)	50 (12)	21 (11)

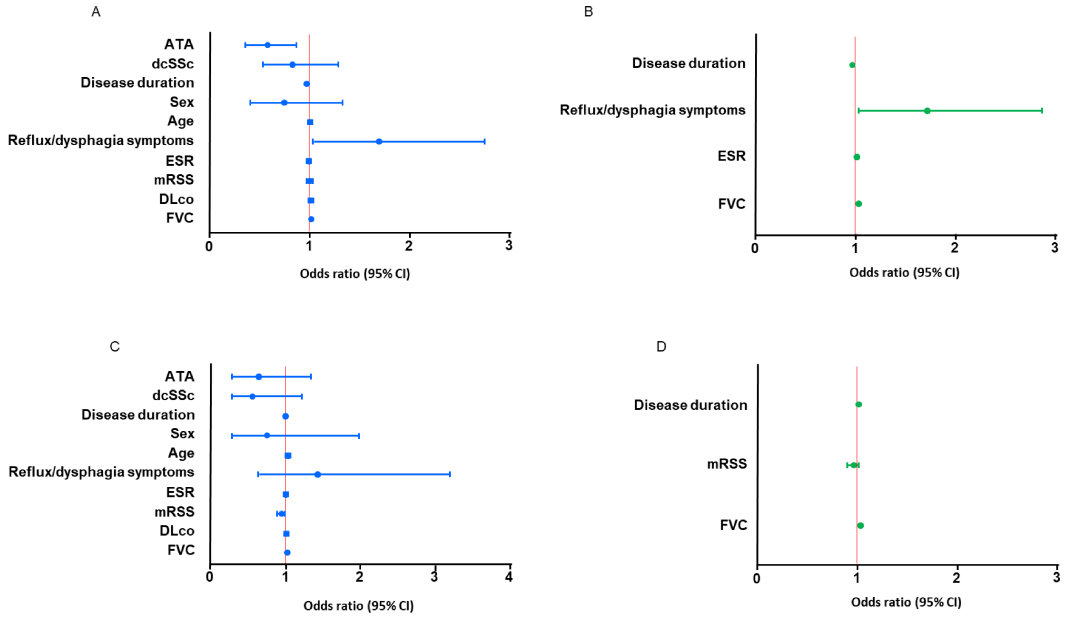
*Change from baseline to 12 months.

Significant progression (FVC decline of >10%, or FVC decline of 5–10% with DL_{CO} decline of ≥15%); moderate progression (FVC decline of 5–10% with DL_{CO} decline of <15%); stable ILD (FVC decline or improvement of <5%); moderate improvement (FVC improvement of 5–10% with DL_{CO} improvement of <15%).

Abbreviations: Ab, antibody; CRP, C-reactive protein; DL_{CO}, diffusion capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; mRSS, modified Rodnan skin score; NYHA, New York Heart Association; SD, standard deviation; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

SUPPLEMENTARY FIGURE S1 Variables predictive for progression in patients during the 12±3-month observation period in (A) univariable and (B) multivariable logistic regression; and variables predictive for further progression over the 5-year follow-up in patients with progression during the 12±3-month observation period in (C) univariable and (D) multivariable logistic regression.

Significant progression was defined as FVC decline of >10%, or FVC decline of 5–10% with DL_{CO} decline of ≥15%.



Abbreviations: ATA, anti-topoisomerase A antibody; CI, confidence interval; dcSSc, diffuse cutaneous systemic sclerosis; DL_{CO}, diffusion capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; mRSS, modified Rodnan skin score.

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