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EUSTAR SSc-ILD Progression

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 $\geq 10\%$, 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 \pm 3-month period: significant progression (FVC decline of $>10\%$, or FVC decline of 5–10% with DL_{CO} decline of $\geq 15\%$); 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 $\geq 15\%$).

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 \pm 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 \pm 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 \pm 3-month period)

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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.

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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.

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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)	5.0 (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)

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	Total (N=826)	Significant progression (n=113)	Moderate progression (n=106)	Stable (n=408)	Moderate improvement (n=189)
Δ 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.

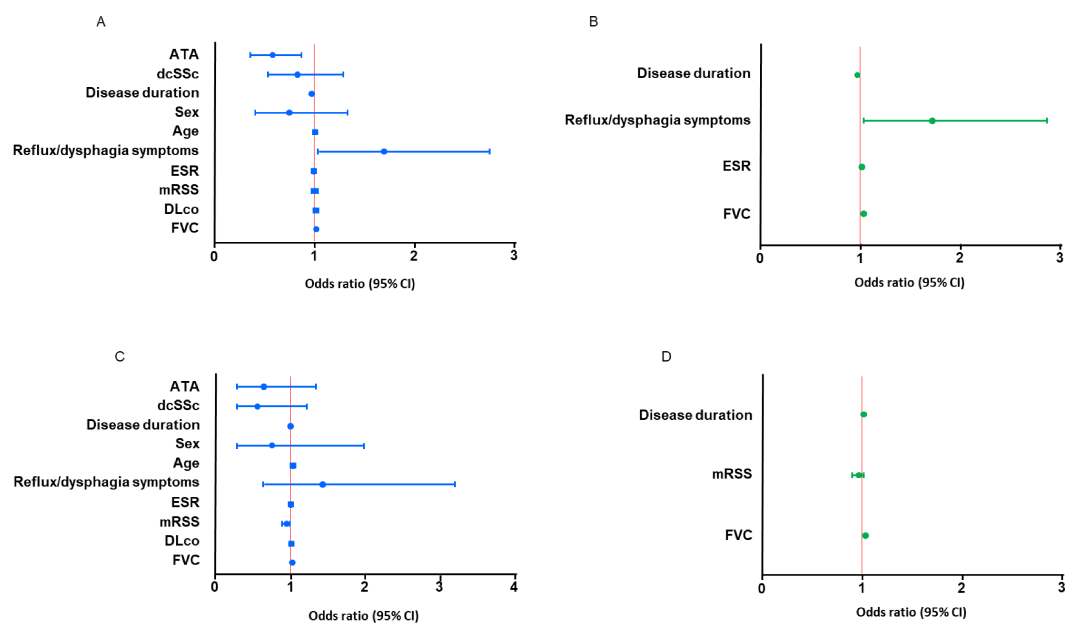
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SUPPLEMENTARY FIGURE S1 Variables predictive for progression in patients during the 12±3-month observation period in (A) univariable and (B) multivariable logistic regression; and variables predictive for further progression over the 5-year follow-up 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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Appendix:
List of EUSTAR Collaborators

Marco Matucci Cerinic	Florence (Italy)
Ulrich Walker	Basel (Switzerland)
Florenzo Iannone	Bari (Italy)
Radim Becvar	Prague (Czech Republic)
Gabriele Valentini	Naples (Italy)
Elise Siegert	Berlin (Germany)
C. Montecucco	Pavia (Italy)
Patricia E. Carreira	Madrid (Spain)
Carlo Chizzolini	Geneva (Switzerland)
Eugene J. Kucharz	Katowice (Poland)
Andrea Doria	Padova (Italy)
Pr Dominique Farge Bancel	Paris (France)
Roger Hesselstrand	Lund (Sweden)
Alexandra Balbir-Gurman	Haifa (Israel)
Raffaele Pellerito	Torino (Italy)
Cristian Caimmi	Verona (Italy)
Christopher Denton	London (United Kingdom)
Nemanja Damjanov	Belgrade (Serbia & Montenegro)
Jörg Henes	Tübingen (Germany)
Vera Ortiz-Santamaria	Granollers Barcelona (Spain)
Stefan Heitmann	Stuttgart (Germany)
Maria João Salvador	Coimbra (Portugal)
Bojana Stamenkovic	Niska Banja (Serbia and Montenegro)
Carlo Francesco Selmi	Rozzano, Milano (Italy)
Ariane Herrick	Salford (United Kingdom)
Ulf Müller-Ladner	Bad Nauheim (Germany)
Merete Engelhart	Hellerup (Denmark)
Valeria Riccieri	Roma (Italy)
Ruxandra Maria Ionescu	Bucharest (Romania)
Ana Maria Gheorghiu	Bucharest (Romania)
Cord Sunderkötter	Münster (Germany)
Jörg Distler	Erlangen (Germany)
Francesca Ingegnoli	Milano (Italy)
Luc Mouthon	Paris (France)
Vanessa Smith	Gent (Belgium)
Francesco Paolo Cantatore	Foggia (Italy)
Susanne Ullman	Copenhagen (Denmark)
Maria Rosa Pozzi	Monza (Italy)
Piotr Wiland	Wroclaw (Poland)
Marie Vanthuyne	Brussels (Belgium)
Brigitte Petra Saar	Krummel-Lorenz Frankfurt (Germany)

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Kristine Herrmann		Dresden (Germany)
Ellen De Langhe		Leuven (Belgium)
Branimir Marko Miroslav Mayer	Anic Baresic	Zagreb (Croatia)
Sule Yavuz		Altunizade-Istanbul (Turkey)
Carolina de Souza Müller		Curitiba (Brasil)
Thierry Zenone		Valence (France)
Alessandro Alessandra Vacca	Mathieu	Monserrato (CA) (Italy)
Kamal Solanki		Hamilton (New Zealand)
Edoardo Rosato		Roma (Italy)
Fahrettin Figen Yargucu	Oksel	Bornova, Izmir (Turkey)
Cristina-Mihaela Tanaseanu		Bucharest (Romania)
Rosario Foti		Catania (Italy)
Daniel E. Furst		Los Angeles (USA)
Peter Sabine Adler	Villiger	Bern (Switzerland)
Paloma García de la Peña Jorge Juan González Martín	Lefebvre	Madrid (Spain)
Ira Litinsky		Tel-Aviv (Israel)
Francesco Del Galdo		Leeds (United Kingdom)
Goda Seskute		Vilnius (Lithuania)
Lesley Ann Saketkoo		New Orleans (USA)
Eduardo Kerzberg		Buenos Aires (Argentina)
Ivan Castellví		Barcelona (Spain)
François Spertini		Lausanne (Switzerland)
Vivien M. Hsu		New Brunswick (USA)
Thierry Martin		Strasbourg (France)
Tim Schmeiser		Wuppertal-Elberfeld (Germany)
Dominik Majewski		Poznan (Poland)
Vera Bernardino		Lisboa (Portugal)
Piercarlo Sarzi Puttini		Milano (Italy)