




# Progressive lung fibrosis and mortality can occur in early systemic sclerosis patients without pulmonary abnormalities at baseline assessment

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## Abstract

**Objectives** In systemic sclerosis, baseline extent of radiological involvement is an important outcome predictor and baseline absence of radiological involvement suggests a more favourable prognosis. As current predictive models are based on cohorts with variable disease duration, we aim to assess disease dynamics in early disease.

**Methods** Patients were included from the prospective longitudinal Belgian Systemic Sclerosis Cohort. We included patients with a disease duration  $\leq 36$  months at baseline with available baseline thoracic high-resolution computed tomography (HRCT) images and longitudinal pulmonary function test (PFT) results until 42 months of follow-up.

**Results** Fifty-two patients were included; 50% were male and 44% suffered from diffuse cutaneous systemic sclerosis. A total of 46% carried anti-topoisomerase 1 antibodies. The mean disease duration at baseline visit was 11 months. At baseline visit, 40.4% (21/52) patients had HRCT abnormalities. Patients with abnormal HRCT findings more frequently suffered from diffuse cutaneous systemic sclerosis ( $p < 0.05$ ) and less frequently carried anti-centromere antibodies ( $p < 0.05$ ). Patients without CT abnormalities at baseline had a shorter disease duration ( $9 \pm 7$  months versus  $14 \pm 12$  months). After 42 months, 8/52 patients, including 3 patients with normal HRCT findings at baseline, died due to SSc-related manifestations. Progression of lung fibrosis occurred in 16 patients at month 42, including 7 patients with normal CT at baseline. No clear predictors of progression could be identified.

**Conclusion** In early SSc patients, the disease dynamics differ from the large published cohorts. Progressive lung fibrosis and mortality can also occur in patients without radiological abnormalities at baseline.

## Key Points

- Disease dynamics in early SSc differ from more established SSc.
- In early SSc, progressive pulmonary fibrosis can occur in patients without CT abnormalities at baseline.
- In early SSc, more stringent pulmonary follow-up is warranted both in lcSSc and dcSSc.

**Keywords** High-resolution computed tomography · Interstitial lung disease · Mortality · Pulmonary fibrosis · Systemic sclerosis

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## Introduction

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease characterised by vasculopathy, autoimmunity and fibrosis. Interstitial lung disease (ILD) is the leading cause of death, accounting for 35% of SSc-related mortality [1, 2]. Timely detection and therapeutic management of ILD are essential but challenging due to the highly variable clinical course, ranging between the extremes of improvement and fast decline [3]. The identification and validation of clinical tools that identify SSc patients at risk of mortality or progressive ILD are essential to allow for prognostic stratification and individualised treatment.

The majority of published papers on predictive models for progressive disease use cohorts of SSc patients with evident ILD. The extent of ILD varies between the different studies, ranging from limited ILD [4] to more extensive and established disease as is the case in the reports derived from the SSc-ILD interventional trials [5]. It is generally thought that the extent of SSc-ILD, as assessed by thoracic high-resolution computed tomography (HRCT), predicts disease course and mortality [6] and that patients without radiological abnormalities at baseline do not appear to progress over time [7]. The reports vary with regard to clinical characteristics and disease duration and the number of published papers reporting on early cohorts with long-term follow-up data is very limited [8].

We hypothesised that the dynamics of ILD progression could be distinct in the early phase of the disease. The objectives of the current study were to describe the prevalence of progressive disease over a period of 42 months of follow-up in a cohort of SSc patients in the early disease phase and to evaluate the disease characteristics of patients at risk of progressive disease.

## Material and methods

### Study cohort

In our centre, all adult SSc patients (> 18-year-olds) that fulfil the 2013 American College of Rheumatology/EULAR classification criteria [9] are prospectively followed up in the multi-centre longitudinal cohort (Belgian Systemic Sclerosis Cohort) [10]. We retrospectively addressed this cohort and selected all patients that had a disease duration of less than or equal to 36 months at baseline visit and for whom 42-month follow-up data were available. Disease onset was defined as the time of (self-reported) occurrence of the first non-Raynaud SSc-associated symptom. Patients were assessed at predefined time points: baseline visit, 6 months (M), and yearly

thereafter at M18-30-42. Patients with available baseline thoracic HRCT and pulmonary function tests (PFT) at baseline and follow-up visits were included. Repeat HRCT scans were only performed upon clinical indication.

### Clinical data

Demographic and clinical data included age, gender, smoking status (defined binary as ever/never smoker), disease duration, disease subset (limited cutaneous systemic sclerosis (lcSSc) or diffuse cutaneous systemic sclerosis (dcSSc)) and the presence of SSc antibodies (anti-topoisomerase 1 antibodies (ATA) or anti-centromere antibodies (ACA)). Capillaroscopy images were classified as normal, early, active or late scleroderma pattern, as described by Cutolo et al. [11].

### Assessment of interstitial lung disease

At each visit, pulmonary function tests (spirometry and diffusion capacity of the lung for carbon monoxide (DLCO)) were performed. HRCT images were available for all patients at baseline visit. Progressive ILD was defined as present if any of the following was fulfilled: a relative decrease of forced vital capacity (FVC) predicted  $\geq 15\%$ , or the combination of a relative decrease both in FVC predicted  $\geq 10\%$  and DLCO  $\geq 15\%$ .

HRCT images were analysed and scored by 2 trained radiologists (JV and NL) until consensus was reached. The radiological extent of ILD/fibrosis was evaluated and categorised as follows: 0% (absent), 1–20% (limited) or >20% (extensive). Four groups of interstitial changes were discerned: 1, ground glass opacities (GGO) without reticular changes; 2, GGO with fine reticulations; 3, definite fibrotic changes (defined as thickened reticulations and/or traction bronchiectasis); and 4, honeycombing.

### Statistical analysis

Summary statistics were generated for baseline characteristics. Group comparisons were performed using two-sample *t* tests (Mann-Whitney U test when data were not normally distributed) or independent-samples Kruskal-Wallis test for continuous data and Fisher's exact or chi-square test as appropriate for categorical data. Tests were adjusted using the Bonferroni correction. The Kaplan-Meier curve estimate was used to generate survival curves and the log-rank test was used to compare survival between groups. Binary logistic regression analysis was performed to ascertain factors affecting the likelihood to have progressive pulmonary fibrosis.

## Results

### Baseline characteristics

A total of 52 patients were included in the study. Patient characteristics are presented in Table 1. In total, 50% of the patients were male and 44% suffered from diffuse cutaneous systemic sclerosis. Forty-six percent carried anti-topoisomerase 1 antibodies. The mean disease duration at baseline visit was 11 months. Fifty-six percent of the patients were ever-smokers. The mean FVC and DLCO were 99% and 65%, respectively (respective standard deviations (SD) 22.421 and 21.397). Capillaroscopy images were available for 49 patients. In 57% of patients, an active SSc pattern was observed (3 patients with missing baseline capillaroscopy).

### HRCT findings at baseline

At baseline visit, 40.4% (21/52) patients had abnormalities on HRCT (Table 1). Patients with abnormal HRCT findings more frequently suffered from diffuse cutaneous systemic sclerosis ( $p < 0.05$ ) and less frequently carried anti-centromere antibodies ( $p < 0.05$ ). We observed a statistically significant difference in disease duration between patients with ( $14 \pm 12$  months, mean and SD) or without ( $9 \pm 7$  months, mean and SD) CT abnormalities. No differences were observed between ever and never-smokers. We noted no differences between patients with limited (1–20%) and extensive (>20%) HRCT abnormalities (Table 2).

At baseline, no patients showed signs of honeycombing. Five patients (24%) had ground glass opacities, and 4 (19%) showed ground glass opacities with tiny, fine reticulations (Table 2). Twelve patients (57%) showed clear fibrotic

changes at baseline visit. No statistically significant differences were observed between patients with different types of HRCT abnormalities. However, numerically, patients with only GGO opacities appeared to have a shorter disease duration (median 5 months; percentile (P)25–75, 1.5–8.5 months) than patients with fibrotic changes (median 13 months; P25–75, 5–33 months). One patient with definite fibrotic changes had a disease duration of only 1 month. We did not observe differences in the type of HRCT abnormalities between ever and never-smokers. Patients with definite fibrotic alterations more often had extensive involvement (8/12, 67%). Capillaroscopy patterns were evenly distributed in patients with or without HRCT abnormalities.

### Mortality and progressive pulmonary fibrosis at 42 months

After 42 months of follow-up, 3/31 patients without and 5/21 patients with HRCT abnormalities died due to SSc-related manifestations (Table 3). Death was caused by SSc-associated pulmonary arterial hypertension ( $n = 4$ ), by infectious complications of ILD ( $n = 1$ ) and digital ulcers ( $n = 2$ , bacteraemia of the deep venous access) and by gastrointestinal failure with malnutrition ( $n = 1$ ). No statistical difference in mortality rate was observed between patients with or without HRCT abnormalities at baseline (hazard ratio (HR) log-rank 2.621 (95% confidence interval (CI) 0.6524–11.21). Likewise, no difference in mortality was observed between patients with limited and extensive radiological involvement (log-rank (Mantel-Cox) test chi-square 2.32,  $p$  value ns). SSc-related death occurred in patients with all types of interstitial lung changes (2/5 patients with ground glass opacities, 1 out of 4 patients with GGO with fine reticulations and 2/12

**Table 1** Baseline characteristics. *SD*, standard deviation; *ATA*, anti-topoisomerase 1 antibody; *ACA*, anti-centromere antibody; *PFT*, pulmonary function test; *lcSSc*, limited cutaneous systemic sclerosis; *dcSSc*,

diffuse cutaneous systemic sclerosis; *FVC*, forced vital capacity; *DLCO*, diffusion capacity of lung for carbon monoxide; *CT*: computed tomography

	Total ( $n = 52$ )	No CT abnormalities ( $n = 31$ )	CT abnormalities ( $n = 21$ )	$p$ value
Age in years (mean, SD)	54 (13.416)	53 (13.592)	55 (13.439)	ns
Gender male/female ( $n$ , %)	26/26 (50/50%)	15/16 (48/52%)	11/10 (52/48%)	ns
Disease duration in months (mean, SD)	11 (9.693)	9 (6.785)	14 (12.393)	$p < 0.05$
Disease subset lcSSc/dcSSc ( $n$ , %)	29/23 (56/44%)	22/9 (71/29%)	7/14 (33/67%)	$p < 0.05$
ATA positive	24 (46%)	11 (35%)	13 (62%)	ns
ACA positive	16 (31%)	15 (48%)	1 (5%)	$p < 0.05$
Smoking status never/ever smoker ( $n$ , %)	23/29 (44.56%)	14/17 (45/55%)	9/12 (43/57%)	ns
PFT in % predicted—FVC (mean, SD)	99 (22.421)	107 (20.683)	88 (20.195)	ns
PFT in % predicted—DLCO (mean, SD)	65 (21.397)	72 (21.257)	55 (17.913)	ns
Capillaroscopy pattern ( $n = 49$ ) ( $n$ , %)				
Normal	3 (6%)	2	1	ns
Early	12 (25%)	5	7	ns
Active	28 (57%)	19	9	ns
Late	6 (12%)	3	3	ns

**Table 2** Radiological assessment of HRCT abnormalities at baseline. *P*, percentile; *ATA*, anti-topoisomerase 1 antibody; *ACA*, anti-centromere antibody; *PFT*, pulmonary function test; *CT*, computed tomography; *lcSSc*, limited cutaneous systemic sclerosis; *dcSSc*, diffuse cutaneous systemic sclerosis; *FVC*, forced vital capacity; *DLCO*, diffusion capacity of lung for carbon monoxide; *GGO*, ground glass opacities

	1–20% CT extent ( <i>n</i> = 10)	> 20% CT extent ( <i>n</i> = 11)	<i>p</i> value	Type of CT abnormalities ( <i>n</i> = 21)		<i>p</i> value
				GGO ( <i>n</i> = 5)	GGO with fine reticulations ( <i>n</i> = 4)	
Age in years (median, P25–75)	48 (43–67)	61 (43–69)	ns	59 (50–69)	50 (40–63)	53 (41–68)
Gender male/female	5/5	6/5	ns	4/1	2/2	5/7
Disease duration (median, P25–75)	7.5 (4–28)	13 (8–31)	ns	5 (1.5–8.5)	20 (8.5–33)	13 (5–33)
Disease subset lcSSc/dcSSc	3/7	4/7	ns	2/3	1/3	4/8
ATA positive	5	8	ns	4	3	6
ACA positive	0	1	ns	0	0	1
Smoking status never/ever smoker	5/5	4/7	ns	2/3	2/3	5/7
PFT in % predicted (median, P25–75)-FVC	97 (88–111)	87 (72–86)	<i>p</i> < 0.05	104 (68–121)	100 (80–112)	80 (72–87)
PFT in % predicted (median, P25–75)-DLCO	67 (55–74)	41 (30–61)	<i>p</i> < 0.05	48 (41–71)	68 (46–73)	55 (31–75)
Extent of CT abnormalities 1–20% > 20%				3/2	3/1	4/8
Capillaroscopy pattern ( <i>n</i> = 20) ( <i>n</i> , %)	Normal 0	1	ns	1	0	0
	Early 3	4	ns	0	1	6
	Active 4	5	ns	3	1	5
	late 2	1	ns	1	1	1

**Table 3** Mortality and progressive pulmonary fibrosis at 42 months. CT, computed tomography; M, months; GGO, ground glass opacities

	SSc-related death at M42 ( <i>n</i> = 8)	Progressive pulmonary fibrosis at M42 ( <i>n</i> = 16)
No CT abnormalities ( <i>n</i> = 31)	3 (10%)	7 (23%)
CT abnormalities ( <i>n</i> = 21)	5 (24%)	9 (43%)
1–20% CT extent ( <i>n</i> = 10)	3 (30%)	4 (40%)
> 20% CT extent ( <i>n</i> = 11)	2 (18%)	5 (46%)
Type of CT abnormalities		
GGO ( <i>n</i> = 5)	2	2
GGO with fine reticulations ( <i>n</i> = 4)	1	2
Definite fibrotic changes ( <i>n</i> = 12)	2	5
Capillaroscopy pattern ( <i>n</i> = 49) ( <i>n</i> , %)		
Normal	1	0
Early	2	4
Active	3	8
Late	0	3

patients with definite fibrotic changes) and in all types of baseline capillaroscopy patterns. Kaplan-Meier survival curves are depicted in Fig. 1.

Progression of lung fibrosis occurred in 16 patients at month 42 (3 patients with missing PFT data, 16/41, 39%), including 7 patients without CT abnormalities at baseline. A logistic regression was performed to ascertain the effects of age, gender, disease duration, disease subtype, antibody status, presence or absence and extent of HRCT abnormalities at baseline and baseline capillaroscopy pattern on the likelihood that participants have progressive pulmonary fibrosis. The logistic regression model showed an adequate fit (Hosmer and Lemeshow  $p = 0.874$ ). The model explained 55.9% (Nagelkerke  $R^2$ ) of the variance in progressive pulmonary fibrosis and correctly classified 84.2% of cases. In this model, only increasing age was associated with an increased likelihood of exhibiting progressive lung fibrosis, although only a very limited absolute effect was observed (exp(B) 1.129, 95% CI 1.019–1.252). Progression of pulmonary fibrosis occurred in both lcSSc and dcSSc patients and in patients with different types of HRCT abnormalities (2/5 patients with GGO, 2/4 patients with GGO and fine reticulations and 5/12 patients with definite fibrotic changes) and in all types of baseline capillaroscopy patterns.

### Follow-up HRCT findings in patients with progressive pulmonary fibrosis without HRCT abnormalities at baseline

Seven out of 31 (23%) patients without HRCT abnormalities at baseline showed progression of pulmonary fibrosis at month 42. Three patients suffered from lcSSc, 2 from dcSSc. Three carried ATA antibodies. In all 5 patients, the extent of radiological involvement at follow-up was limited. In 4/5 patients, clear reticular changes were observed, with

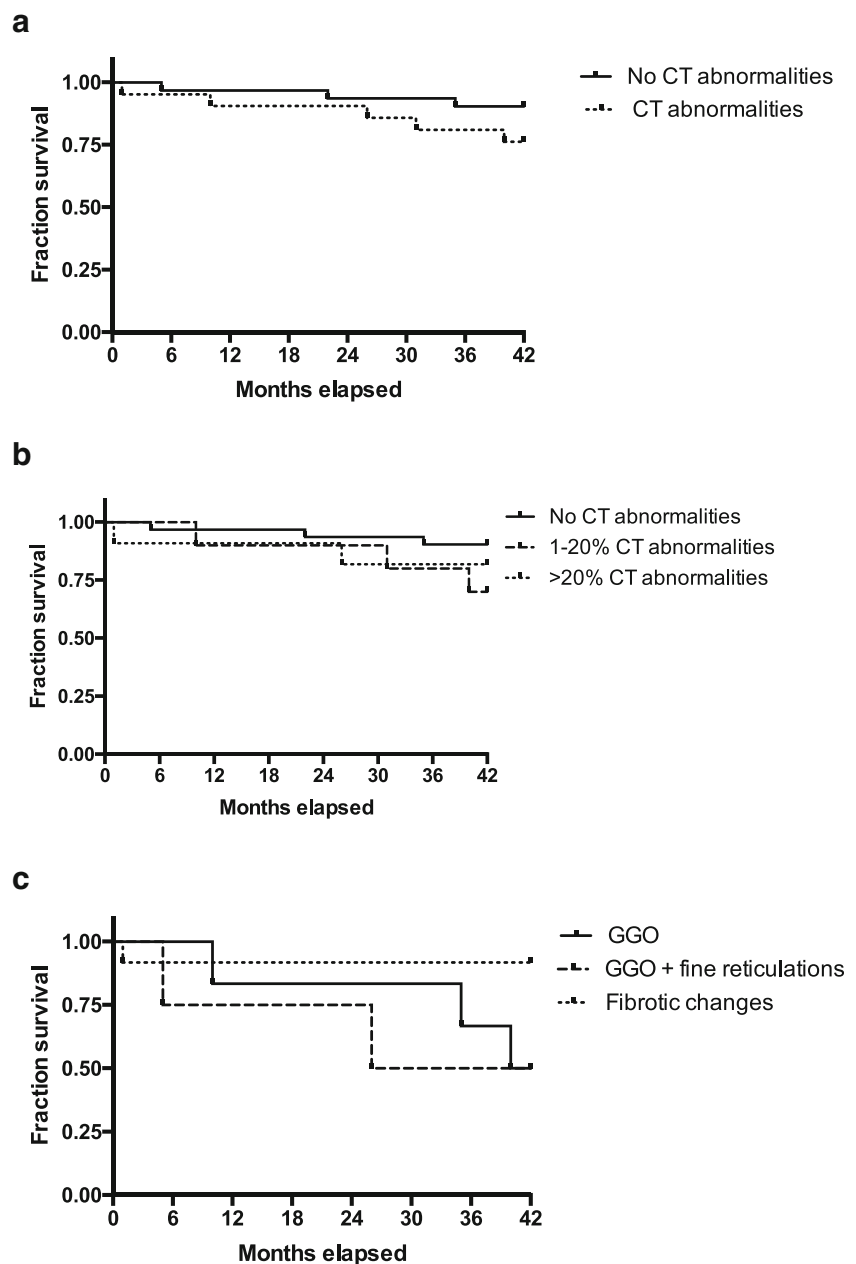
definite fibrotic alterations (bronchiectasis) in 2/5, both carrying ATA antibodies.

## Discussion

In this observational study of 52 early SSc patients, we describe the baseline HRCT findings and the evolution over 42 months of follow-up. We found that in early SSc patients, the disease dynamics differ from the large published cohorts and we demonstrate that progressive lung fibrosis and mortality can occur in patients without radiological abnormalities and normal lung function tests at baseline assessment.

Our study cohort is relevant as it includes patients with recent disease onset, with a mean disease duration of only 11 months. Furthermore, as our centre is a tertiary referral centre, our cohort is enriched for patients at risk of a more severe disease course, reflected by the high proportion of male patients (50%) and patients suffering from the diffuse subtype (44%). In this early disease cohort, 40.4% of patients had HRCT abnormalities at baseline visit. We confirm the association of diffuse cutaneous systemic sclerosis and anti-topoisomerase 1 antibodies with an increased prevalence of pulmonary fibrosis at baseline and the negative association of anti-centromere antibodies with SSc-associated ILD. We observed that patients without CT abnormalities at baseline have a shorter disease duration (mean 9 months) than patients in whom HRCT abnormalities are present (mean 14 months). This suggests that even a minimal increase in disease duration increases the frequency of observed HRCT abnormalities, indicating that the dynamics of emerging HRCT abnormalities are highly relevant early after disease onset. The finding of definite fibrosis in a patient with a disease duration as limited as 1 month is intriguing and adds to existing literature that

**Fig. 1** Kaplan-Meier survival curves. **a** No CT abnormalities at baseline (full line), CT abnormalities at baseline (dotted line). **b** Extent of CT abnormalities: no abnormalities (full line), 1–20% abnormalities (dashed line), > 20% abnormalities (dotted line). **c** Type of CT abnormalities: ground glass opacities (full line), GGO with fine reticulations (dashed line), definite fibrotic changes (dotted line). CT, computed tomography; GGO, ground glass opacities



pulmonary involvement can precede the typical clinical onset of systemic sclerosis, a phenomenon that is only sporadically observed [12].

In a study by Panopoulos, predictors of morbidity and mortality were evaluated in a single-centre inception cohort of 115 SSc patients with a disease duration of less than 12 months that were prospectively followed for 3 years [8]. In this cohort, consisting of 47% dcSSc patients with a high number of ATA-positive patients (58%), pulmonary fibrosis was present in 32% of patients and was an independent predictor of mortality. This highlights the importance of timely diagnosis and treatment of incident pulmonary fibrosis in early SSc.

In our cohort, 8/52 patients (15%) died as a consequence of SSc-related manifestations. No statistical difference in mortality rate was observed between patients with or without HRCT abnormalities at baseline. However, it should be noted that the cause of death was ILD-related in a minority of cases (and evenly distributed across groups) and due to other SSc-related causes of death (renal crisis, PAH) in the majority. A EUSTAR analysis of early SSc patients presenting within 12 months of disease onset showed that approximately half of all incident organ manifestations became evident within the first 2 years, again highlighting the importance of vigilance in early disease [13]. From our data, we conclude that in early disease, the absence of CT abnormalities should not be considered an

unequivocal favourable prognostic finding as early dynamic changes in the context of SSc are real and clinically relevant.

In our cohort, progression of lung fibrosis occurred in 39% of patients. No clear predictive factors could be identified, other than a very modest effect of increasing age. It is noteworthy that the presence or absence of HRCT abnormalities at baseline did not significantly add to the model. We observed progressive pulmonary fibrosis in as many as 7/31 (23%) of patients without HRCT abnormalities at baseline. The majority of these patients (5/7) had normal PFT at baseline. These findings align with the mortality data and strengthen the message that a more careful and systematic approach is warranted in patients with early disease when attempting prognostic stratification. When accepting that the disease dynamics in early disease are inherently different, caution and critical appraisal of the existing literature on prognostic stratification are warranted. As published data on early SSc cohorts are limited, previously published findings may not be valid for patients with early disease. Hoffmann-Vold et al. evaluated annual fibrosis progression rate in a large cohort of SSc patients and demonstrated that over a mean follow-up of 3.1 years, none of the patients without fibrosis at baseline had progressive fibrosis [7], which might be in contrast to our data. The high-risk nature of our cohort, resulting from selection bias inherently associated with the nature of our centre (university referral centre), could partially explain this discrepancy, reflected by a higher proportion of dcSSc patients (44% versus 29%), a higher proportion of ATA-positive patients (46% versus 17%) and a higher proportion of male patients (50% versus 21%), all associated with progressive pulmonary fibrosis in the reported univariate analysis by Hoffmann-Vold. Furthermore, the mean disease duration in their entire cohort was 4.2 years. The authors did evaluate the annual fibrosis progression rate (defined as the difference in the extent of fibrosis between the baseline and follow-up HRCTs divided by the actual follow-up period in years) in relation to disease duration and found that the group with <3 years of disease duration had a significantly higher annual rate of fibrosis progression compared with patients with a longer disease duration, confirming the clinical significance of this early phase in disease development.

Our findings, indicating that rapid negative evolution can occur early in the disease course, agree with the work of Man et al. [3]. In this work, the authors define subsets of individual SSc patients following distinct trajectories of FVC evolution over time and assessed the association of clinical variables with the different trajectory groups. The patient population consisted of 254 patients, 20% male, 48% dcSSc, with a median disease duration of 1.6 years. They show that the course over a 12-year period was highly variable and that the group that was characterised by a fast decline in FVC was associated with male sex, a short disease duration (< 2 years) and

presence of ATA. Based on our data, one could argue that, in the case of normal baseline HRCT findings in a high-risk patient (early disease, male gender, dcSSc subtype, ATA antibodies), a routine repeat HRCT should be scheduled after 1 year and that—maybe—at this time point, the prognostic value of absent radiological abnormalities is more valid.

Furthermore, in our cohort, progressive pulmonary fibrosis and mortality also occurred in lcSSc patients without baseline abnormalities. A recent publication by the EUSTAR group studied 8013 lcSSc and 4786 dcSSc patients and demonstrated that in 35% of lcSSc patients, ILD was present on imaging at baseline [14]. As many as 32% of lcSSc patients had progressive ILD after 36 months of follow-up (defined as FVC-10% compared with baseline). Pulmonary progression was similar in lcSSc and dcSSc patients, arguing that with regard to pulmonary involvement, caution is warranted in all SSc patients.

The strengths of our work are the patient population with early disease, enriched for high-risk patients and with standardised follow-up at predefined time points registering a complete set of baseline HRCT images, pulmonary function tests and corresponding clinical findings. Furthermore, our definition of progressive pulmonary fibrosis is very stringent.

Some limitations should however be discussed. First, the monocentric nature and the limited number of patients, precluding firm conclusions. The second is the retrospective nature of patient selection. We selected patients with complete 42-month follow-up data, acknowledging the fact that patients that were lost to follow-up were not included. Furthermore, due to the retrospective nature, we cannot adequately control factors that affect mortality and pulmonary fibrosis progression such as standard of care (that was heterogeneous in our cohort), timing of treatment initiation and cessation and comorbidities. Third, a clear limitation is selection bias. As we operate in a tertiary referral centre and only included patients with early disease, we are likely to have selected patients with higher initial disease kinetic, as reflected by higher proportion of males, ATA positivity and dcSSc. Finally, our population is a homogeneous Caucasian population. Continued research, addressing larger cohorts such as the complete Belgian Systemic Sclerosis Cohort or the EUSTAR database, are needed to validate our findings.

In conclusion, we demonstrate that mortality and progressive pulmonary fibrosis, defined by worsening of PFT, can occur in patients with early systemic sclerosis that present with normal HRCT imaging at baseline visit. We provide further evidence that the early phase of SSc is characterised by a rapid initial disease kinetic, especially in high-risk patients. We plead for a more careful approach, carefully considering repeated HRCT imaging, in patients with early disease when attempting prognostic stratification, as previously published findings may not all be valid for patients with early disease.

## Compliance with ethical standards

**Disclosures** None.

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