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ORIGINAL RESEARCH

Characteristics and disease course of untreated patients with interstitial lung disease associated with systemic sclerosis in a real-life two-centre cohort

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ABSTRACT

Background Interstitial lung disease (ILD) is the leading cause of death in systemic sclerosis (SSc). According to expert statements, not all SSc-ILD patients require pharmacological therapy.

Objectives To describe disease characteristics and disease course in untreated SSc-ILD patients in two well characterised SSc-ILD cohorts.

Methods Patients were classified as treated if they had received a potential ILD-modifying drug. ILD progression in untreated patients was defined as (1) decline in forced vital capacity (FVC) from baseline of ≥10% or (2) decline in FVC of 5%–9% associated with a decline in diffusing capacity for carbon monoxide (DLCO)≥15% over 12±3 months or (3) start of any ILD-modifying treatment or (4) increase in the ILD extent during follow-up. Multivariable logistic regression was performed to identify factors associated with non-prescription of ILD-modifying treatment at baseline. Prognostic factors for progression in untreated patients were tested by multivariate Cox regression.

Results Of 386 SSc-ILD included patients, 287 (74%) were untreated at baseline. Anticentromere antibodies (OR: 6.75 (2.16–21.14), p=0.001), limited extent of ILD (OR: 2.39 (1.19–4.82), p=0.015), longer disease duration (OR: 1.04 (1.00–1.08), p=0.038) and a higher DLCO (OR: 1.02 (1.01–1.04), p=0.005) were independently associated with no ILD-modifying treatment at baseline. Among 234 untreated patients, the 3 year cumulative incidence of progression was 39.9% (32.9–46.2). Diffuse cutaneous SSc and extensive lung fibrosis independently predicted ILD progression in untreated patients.

Conclusion As about 40% of untreated patients show ILD progression after 3 years and effective and safe therapies for SSc-ILD are available, our results support a change in clinical practice in selecting patients for treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ According to experts, some patients with systemic sclerosis-interstitial lung disease (SSc-ILD) may have a stable course and not require pharmacological treatment.

⇒ However, the characteristics of these patients and whether they actually have a stable course in practice is not known.

WHAT THIS STUDY ADDS

⇒ This study describes for the first time the characteristics of untreated SSc-ILD patients in real practice.

⇒ Despite their milder phenotype, almost 40% of these patients progressed over 3 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By demonstrating the high proportion of progressors among untreated SSc-ILD patients, our results argue in favour of a change in clinical practice when selecting patients for treatment.

INTRODUCTION

Systemic sclerosis (SSc) is an orphan connective tissue disease characterised by alterations of the microvasculature, disturbances of the immune system and deposition of collagen and other matrix substances in the skin and internal organs.[1 2] Among connective tissue diseases, SSc is the most severe, with a 3.5-fold excess mortality as compared with the general population, and there has been no improvement in survival over time.[3]

Interstitial lung disease (ILD) is common in SSc and is the leading cause of SSc-related deaths.[4–6] The prevalence of ILD among SSc patients is highly variable from study to study, ranging from 19% to 90% depending on the cohort studied and diagnostic modalities.[4 7–9] A population-based study points to a prevalence of ILD of about 50% in SSc patients.[4]

The course of SSc-ILD is characterised by great variability, ranging from longstanding

stable disease to rapidly progressive disease that can lead to respiratory failure and death. The proportion of patients who develop progressive SSc-ILD and the associated risk factors are not well known. In the European Scleroderma Trials and Research (EUSTAR) cohort, around 30% of SSc-ILD patients developed progressive ILD over 1 year of follow-up, cumulating at 67% over 5 years.[10] The strongest predictive factors for worsening of forced vital capacity (FVC) were male sex, higher modified Rodnan skin score and reflux/dysphagia symptoms. However, the combination of these factors does not completely predict which patients will progress.

In the last 2 years, major advances in the treatment of SSc-ILD have been achieved through the development of therapies with a high level of evidence.[11–14] In line with these findings, expert statements have recently been published to guide treatment decisions in SSc-ILD.[15–17] Notably, they all consider that some patients with limited, non-progressive ILD may not require pharmacological therapy.

However, knowledge about the characteristics and course of the disease in SSc-ILD patients, who are not treated according to current clinical practice is sparse. To address this question and to overcome intercentre variability and missing data in registries, it is important to study well-defined, unselected, prospective cohorts. Therefore, we assessed the characteristics and disease course of untreated SSc-ILD patients in prospective cohorts of two expert centres.

METHODS

Study design

Post-hoc analyses on prospectively collected patient data from the Zurich and Oslo SSc cohorts were conducted. All registered patients granted their informed consent to be included in the cohorts. The Regional Committee of Health and Medical Research Ethics in South-East Norway (no. 2016/119) and the Cantonal Ethic Committee of Zurich (BASEC no. 2016-01515 and no. 2018-02165) approved the study. This study complied with the Declaration of Helsinki.

Patient population and characteristics

At the Department of Rheumatology of the University Hospital of Zurich and Oslo University Hospital, all patients with a diagnosis of SSc are prospectively included in the local EUSTAR database and in the Norwegian Systemic Connective Tissue Disease and Vasculitis Registry (NOSVAR), respectively.[18] SSc patients are followed up (at least) once a year and data are recorded in the local databases. We queried the Zurich and Oslo database at the end of April 2021, providing information on patients≥18 years old, enrolled since 2010 and who fulfilled the 2013 classification criteria for SSc by the American College of Rheumatology/European League Against Rheumatism. Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed (appendix I). Inclusion criteria were (1) diagnosis of ILD on high-resolution CT (HRCT) assessed by expert radiologists in both centres and (2) available data for therapy at baseline. The baseline visit corresponded to enrolment in the registry. Lung fibrosis was defined as ground glass opacities, traction bronchiectasis or reticulation or honeycombing on HRCT. We classified the SSc-ILD patients as 'treated' if they had a history of ILD modifying treatment or if they were currently undergoing ILD modifying treatment (ie, cyclophosphamide, mycophenolate mofetil, nintedanib, tocilizumab, rituximab, hematopoietic cell transplantation and lung transplantation),[19 20] otherwise as *untreated*. The following characteristics were recorded: age, sex, cutaneous subset of SSc,[21] disease duration defined from onset of the first non-Raynaud sign/symptom, smoking status, reflux/dysphagia assessed by medical history according to EUSTAR standards,[22] dyspnoea New York Heart Association (NYHA) functional class, auto-antibodies, C-reactive protein (CRP) levels, 6 min walking test (including distance, assessment of O_2 saturation, oxygen desaturation defined as a fall in peripheral capillary oxygen saturation. (Spo_2)≥5% at the 6 min walking test), FVC, diffusing capacity for carbon monoxide (DLCO), pulmonary hypertension defined by echocardiography (elevation of systolic pulmonary artery pressure of more than 45 mm Hg) or right heart catheterisation, corticosteroid use and dose. In case of increased risk of pulmonary arterial hypertension according to DETECT score,[23] a right heart catheterisation was performed. Precapillary pulmonary hypertension was defined by a mean pulmonary arterial pressure≥25 mm Hg at rest and a pulmonary artery wedge pressure≤15 mm Hg by right heart catheterisation (as it was the definition used at the time of data collection). Pulmonary function tests (PFTs) with FVC and DLCO were performed according to American Thoracic Society-European Respiratory Society (ATS-ERS) guidelines.[4 24] The extent of ILD (≥ or <20%) was collected. In the Oslo cohort, HRCT lung images were analysed semiquantitatively as previously described.[4 24] In the Zurich cohort, the extent of pulmonary fibrosis was assessed according to the limited/extensive staging system proposed by Goh *et al*.[25] The longitudinal study included patients with at least one follow-up visit. In the untreated patients, ILD progression was defined by the functional criteria[25 26] (FVC decline from baseline of ≥10% or an FVC decline of 5%–9% in association with a DLCO decline of ≥15% over 12±3 months), and/or decision to start of any ILD-modifying treatment due to progression or severity of the disease and/or increase in the extent of ILD (from <20% to >20%) during the follow-up. As it has been shown that there can be a slower lung function decline over longer time-periods,[10] we also assessed ILD progression defined as FVC decline from baseline of ≥10% or an FVC decline of 5%–9% in association with a DLCO decline of ≥15% over the entire follow-up, and/or decision to start of any ILD-modifying treatment and/or increase in the extent of ILD (from

Table 1 Characteristics of the patients according to treatment status

	All patients (n=386)	Untreated (n=287)	Treated (n=99)	P value	N available data (%)
Age (years)	56.8±14.4	57.5±14.7	54.9±13.6	0.117	385
Male sex	82 (21.5%)	50 (17.7%)	32 (32.3%)	0.004	381
Disease duration (years)	4.6 (1.5–12.4)	5.1 (1.9–14.5)	2.6 (1.1–5.9)	<0.001	351
Ever smoker	99 (27.3%)	74 (27.3%)	25 (27.2%)	1.000	363
Diffuse cutaneous form	120 (31.5%)	69 (24.5%)	51 (51.5%)	<0.001	381
Anticentromere antibodies positive	103 (28.1%)	99 (36.3%)	4 (4.3%)	<0.001	367
Anti-Scl70 antibodies positive	127 (34.1%)	84 (30.5%)	43 (44.3%)	0.019	372
Active reflux and/or dysphagia	190 (54.9%)	138 (54.8%)	52 (55.3%)	1.000	346
Extent of lung fibrosis≥20%	66 (17.7%)	29 (10.6%)	37 (37.8%)	<0.001	372
Dyspnoea NYHA>2	40 (12.1%)	24 (9.8%)	16 (18.6%)	0.050	331
FVC (% predicted)	92.3±20.7	96.0±19.0	81.6±21.7	<0.001	375
DLCO (% predicted)	66.0±20.4	68.9±19.7	57.7±20.4	<0.001	358
6 min walking distance (m)	499.1±126.9	508.5±121.2	474.4±138.4	0.045	315
Desaturation after 6 min walking test	36 (22.5%)	12 (12.4%)	24 (38.1%)	<0.001	160
Precapillary pulmonary hypertension on RHC or echocardiography*	50 (14.8%)	34 (13.8%)	16 (17.8%)	0.360	337
CRP>5 mg/L	48 (24.0%)	26 (20.0%)	22 (31.4%)	0.103	200
Corticosteroids	85 (22.4%)	49 (17.3%)	36 (37.5%)	<0.001	379
Corticosteroids dose (prednison equivalent) mg	7.5 (5.0–10.0)	7.5 (5.0–10.0)	10 (5.0–10.0)	0.470	85

Data are mean (SD) or n (%) or median (IQR) according to the distribution of the variable.
Parameters were collected according to EUSTAR standards.[22]
*Pulmonary hypertension on echocardiography was defined as elevation of systolic pulmonary artery pressure of more than 45 mm Hg.
.DLCO, carbon monoxide diffusing capacity of the lung, oxygen desaturation defined as a fall in Spo_2≥5% at the 6 min walking test; EUSTAR, European Scleroderma Trials and Research; FVC, forced vital capacity; HRCT, high-resolution CT; NYHA, New York Heart Association; RHC, right hearth catheterisation; SSc, systemic sclerosis.

<20% to >20%) during the follow-up. Progression-free survival was defined as the time from the first visit until ILD progression and/or death.

Statistical analysis

The data collected were described using the number and the percentage (%) for categorical variables. Mean and SD or median (IQR) were used for quantitative variables according to their distribution. In the cross-sectional analysis, comparison of characteristics of treated and non-treated patients was performed by χ^2 test and Student's t-test or the Wilcoxon test, according to the distribution of the variable. In the untreated group, ILD progression was estimated using the Kaplan-Meier method.

A multivariate logistic regression analysis controlling for confounding factors was performed to determine factors associated with no-prescription of an ILD-modifying treatment at baseline with calculation of OR estimates and 95% CI. Sensitivity subanalyses included a comparison of patients with follow-up and without follow-up, as well as comparison of untreated ILD-patients before and after 2016, the year of publication of the SLS II trial.[27] Candidate prognostic factors for progression in untreated patients were tested by univariable and multivariable Cox proportional hazards regression model (with HR). Covariates associated with prescription of treatment and progression of ILD were selected according to expert opinion and evidence from literature: age, sex, cutaneous form, antibody status, smoking status, disease duration, active reflux/dysphagia, dyspnoea NYHA functional class, extent of lung fibrosis on HRCT, FVC and DLCO.[16] As CRP levels and desaturation at 6 min walking test were not collected in the Oslo database, these parameters were not included in the multivariable analysis. The different variables were tested for collinearity. A high collinearity was identified between FVC and DLCO. Thus, only one of these variables was used in the multivariable models. As multivariable model of non-prescription including DLCO had better AUC than the model with FVC and as only DLCO was significant in univariable analysis of progression, only DLCO was included in multivariable models.

To account for missing observations, the data for multivariate models (logistic and Cox regression) were analysed using multiple imputations by chained equations, with 10 imputations obtained after 10 iterations.[28 29] All tests were two-sided at a 0.05 significance level. Statistical

analyses were carried out using R Project for Statistical Computing, V.4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/).

RESULTS

The combined cohort included 386 SSc-ILD patients and 1570 visits (Flow-chart in online supplemental figure 1). Of these 386 patients, 299 (78.5%) were females, mean age was 56.8±14.4 years, median disease duration 4.6 years, 120 (31.5%) had diffuse cutaneous SSc and 127/372 (34.1%) were positive for anti-Scl70 antibodies. Other disease characteristics are presented in table 1. The two cohorts had similar characteristics, with the exception of a higher frequency of anti-Scl70 antibodies and of treated patients in the Zurich ILD cohort (online supplemental table 1).

Of the 386 patients, 99 were treated at baseline with the following treatments (cyclophosphamide n=20, mycophenolate mofetil alone n=28, nintedanib n=1, tocilizumab alone n=25, tocilizumab+mycophenolate mofetil n=1, rituximab alone n=14, rituximab+mycophenolate mofetil n=9, hematopoietic cell transplantation n=0 and lung transplantation and mycophenolate mofetil n=1), 287 (74%) were untreated at baseline.

Untreated patients in both cohorts had similar characteristics regarding lung involvement, except for a lower DLCO in the Oslo cohort (online supplemental table 2).

Overall, untreated patients had less severe disease than treated SSc-ILD patients (table 1).

We next aimed at identifying independent parameters characterising the phenotype of untreated patients at baseline. In multivariable logistic regression, anticentromere antibodies (OR: 6.75 (2.16–21.14), p=0.001), a limited extent of ILD (OR: 2.39 (1.19–4.82), p=0.015), a higher DLCO (OR: 1.02 (1.01–1.04), p=0.005) and a longer disease duration (OR: 1.04 (1.00–1.08), p=0.038) were associated with no treatment of ILD at baseline (table 2). Untreated patients were also less frequently treated with corticosteroids (OR: 0.45 (0.24–0.82), p=0.010). The AUC of the model was 0.829. The multivariable logistic regression model with FVC is presented in online supplemental table 3 (AUC: 0.822).

Due to emergence of mycophenolate mofetil as a less toxic alternative to cyclophosphamide for treating SSc-ILD from 2016, we also analysed the repartition of the patients in our cohort before and after 2016.[27] Out of the 386 patients, 240/301 (79%) untreated patients were included before 2016 and 47/85 (55%) after 2016. Characteristics of the untreated patients included before and after 2016 were not significantly different (online supplemental table 4).

For the longitudinal analysis, 234/287 (81.5%) untreated patients had at least-one follow-up visit with a median number of 5 visits per patient, including the baseline visit. During follow-up, 94% of patients had an FVC measurement at each visit, with a median of 5 FVC measurements per patient, and 86% of patients had a DLCO measurement at each visit, with a median of 4 DLCO measurements per patient. The characteristics of the patients with and without follow-up were not significantly different except for a younger age of the patients with a follow-up (online supplemental table 5). The median follow-up was 4.2 years (min–max: 0.3–12.9).

Table 2 Factors associated with non-prescription of a ILD treatment in multivariable analysis

Variable	OR (95% CI)	P value
Male sex	0.60 (0.31 to 1.15)	0.12
Age	1.00 (0.98 to 1.02)	0.82
Disease duration	1.04 (1.00 to 1.08)	0.038
Ever smoker	0.94 (0.47 to 1.86)	0.86
Limited cutaneous SSc	1.72 (0.96 to 3.08)	0.071
Anticentromere antibodies	6.75 (2.16 to 21.14)	0.001
Anti-Scl70 antibodies	0.97 (0.54 to 1.74)	0.91
Active reflux and/or dysphagia	0.90 (0.50 to 1.62)	0.72
Extent of lung fibrosis<20%	2.39 (1.19 to 4.82)	0.015
Dyspnoea NYHA>2	1.19 (0.45 to 3.11)	0.73
DLCO predicted	1.02 (1.01 to 1.04)	0.005
Corticosteroids	0.45 (0.24 to 0.82)	0.010

.DLCO, carbon monoxide diffusing capacity of the lung; ILD, interstitial lung disease; NYHA, New York Heart Association; SSc, systemic sclerosis.

In all, 120 patients (51.3%) experienced progression during the follow-up. The 1 and 3 year cumulative incidence (95% CI) of progression defined by the functional criteria (ie, FVC decline from baseline of ≥10% or an FVC decline of 5%–9% in association with a DLCO decline of ≥15% over 12±3 months), and/or decision to start of any ILD-modifying treatment and/or increase in the extent of ILD during the follow-up were 19.7% (14.3–24.6) and 39.9% (32.9–46.2) (figure 1). The median time to progression was 4.6 years (3.5–6.1). There were no significant differences between the centres in the incidence of progression (3 year cumulative incidence of progression 41.6% (32.3–49.6) in Oslo and 37.4% (26.3–46.9) in Zurich (p=0.99)). There was no significant difference in 3 year cumulative incidence of progression between patients included before and after 2016 (40.6% (33.4–47.1) vs 28.4% (3.3–46.9), p=0.36). When considering only the functional criteria, 117 patients met the progression criteria, the 1 and 3 year cumulative incidence of progression were 8% (4.4–11.4) and 26.1% (19.9–31.9) (figure 2). In univariable analysis, among the untreated patients lung progressors were more often of diffuse cutaneous subtype, had higher dyspnoea NYHA class, more frequently extensive ILD and lower DLCO and FVC at baseline as compared with non-progressors (table 3).

In a multivariable Cox prediction model, the diffuse cutaneous form (HR: 2.99 (1.79–4.97), p<0.0001) and extensive ILD (HR: 2.65 (1.25–5.60), p=0.016)

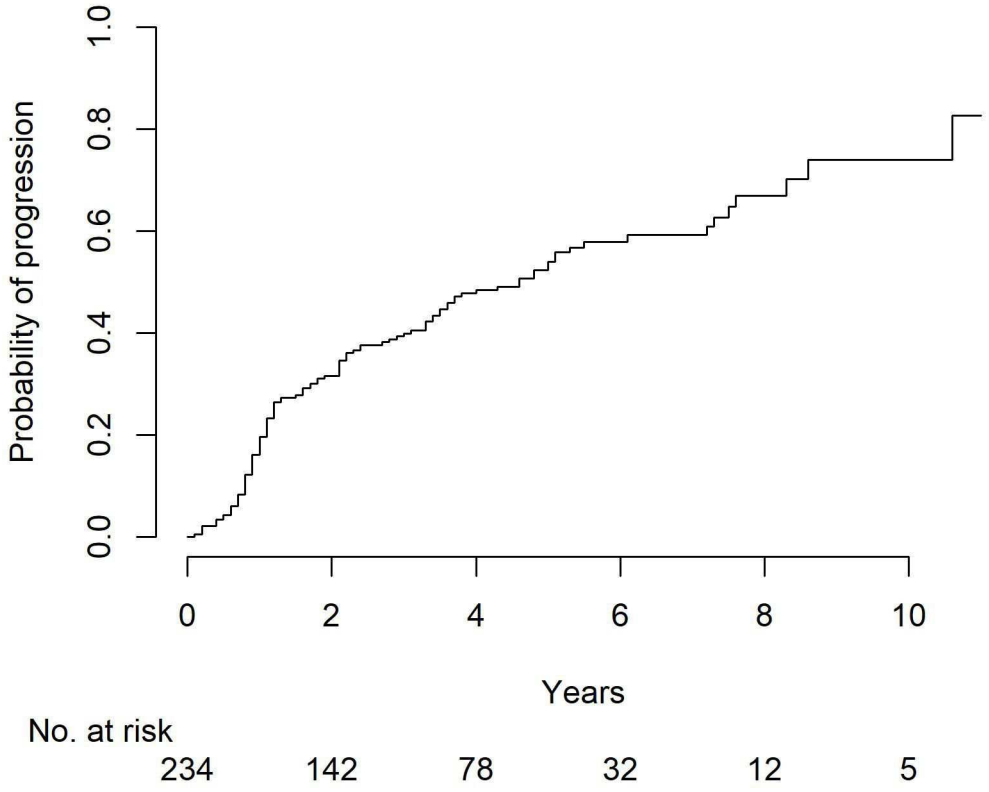

Figure 1 Time to lung fibrosis progression in untreated patients. Kaplan-Meier curve for cumulative lung fibrosis progression in untreated systemic sclerosis patients from the combined cohort. Lung fibrosis progression was defined by FVC decline from baseline of ≥10% or FVC decline of 5%–9% in association with a DLCO decline of ≥15% over 12±3 months, and/or decision to start of any ILD-modifying treatment and/or increase in the extent of ILD (from <20% to >20%) during the follow-up. The number of patients at risk is indicated below. DLCO, carbon monoxide diffusing capacity of the lung; FVC, forced vital capacity; ILD, interstitial lung disease.

independently predicted ILD progression during follow-up in untreated patients (table 4). There was a trend for lower DLCO values to predict ILD progression (HR: 0.99 (0.97–1.00), p=0.060).

As it has been shown that there can be a slow lung function decline over longer time-periods,[10] we also assessed progression defined by the functional criteria over the entire follow-up and/or decision to start of any ILD-modifying treatment and/or increase in the extent of ILD during the follow-up. Using this definition of progression, 144 patients (61.5%) experienced progression during the follow-up. The 1 year and 3 year cumulative incidence of progression were 21.7% (16.2–26.8) and 45.9% (38.3–52.6) (online supplemental figure 2). The multivariable Cox prediction model also identified the diffuse cutaneous subtype and an extensive ILD as predictors for progression as well as an older age (online supplemental table 6). A total of 57 deaths occurred during follow-up among the 287 untreated patients. Most patients (41/57) had already experienced ILD progression prior to death, and 16 died without previous ILD progression. In a multivariable Cox prediction model, the diffuse cutaneous form (HR: 2.82 (1.75–4.55), p<0.0001) and extensive ILD (HR: 2.47 (1.40–4.37), p=0.002) independently predicted progression-free survival during follow-up in untreated patients (online supplemental table 7).

DISCUSSION

To the best of our knowledge, this is the first study to specifically characterise the phenotype of untreated patients with SSc-ILD and to study them in terms of progression. Three quarters of patients in our combined cohort from two centres with expertise in the management of SSc-ILD patients did not receive treatment at baseline. These results are consistent with previously unselected cohorts. In the multicentre EUSTAR cohort, 63% of SSc-ILD patients for whom treatment information was available (n=244) were not treated at inclusion.[10] Similarly, in two US cohorts, approximately two-thirds of patients with SSc-ILD were untreated.[30 31] In another cohort of mild SSc-ILD, approximately 90% of patients were not treated.[32] One may argue that this finding is related to the historical nature of our cohort, at a time when evidence-based therapies were not yet available. Indeed, we saw a lower number of untreated patients after mycophenolate mofetil became available. However, when considering patients included after 2016 (n=85), the proportion of untreated SSc-ILD patients remains high (55% of the cohort). In addition, two studies also

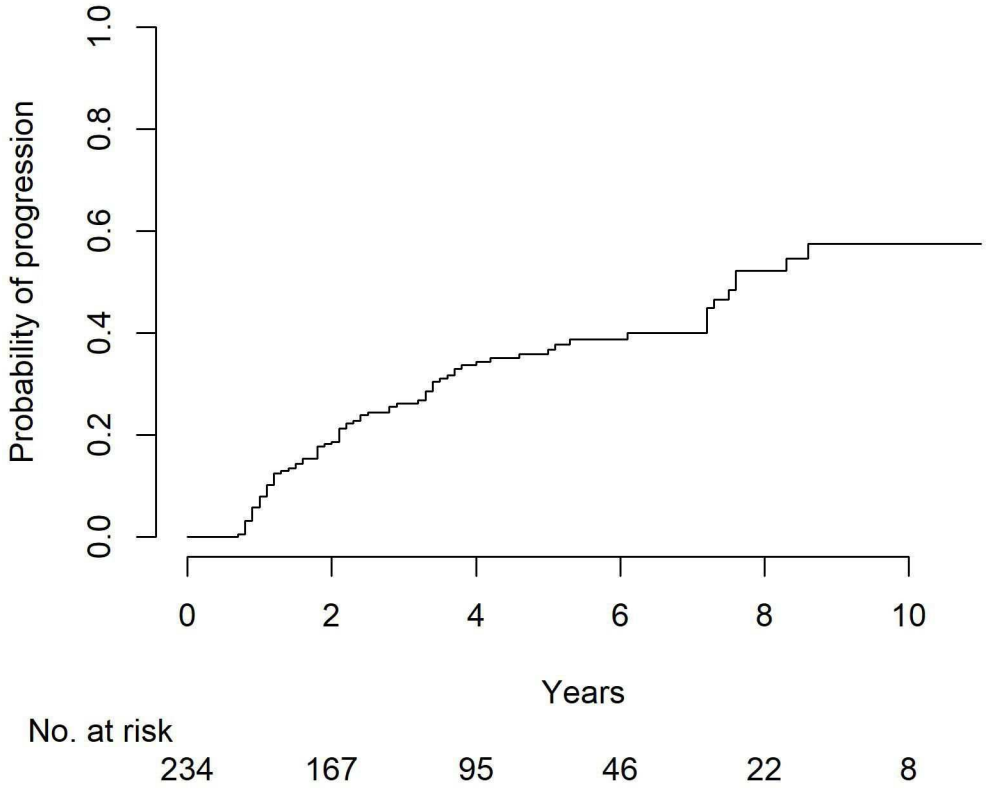

Figure 2 Time to lung fibrosis progression in untreated patients according to functional criteria. Kaplan-Meier curve for cumulative lung fibrosis progression in untreated systemic sclerosis patients from the combined cohort. Lung fibrosis progression was defined by FVC decline from baseline of ≥10% or FVC decline of 5%–9% in association with a DLCO decline of ≥15% over 12±3 months. The number of patients at risk is indicated below. DLCO, carbon monoxide diffusing capacity of the lung; FVC, forced vital capacity.

included contemporary patients and showed a similar prevalence of untreated patients.[10 31] Here, we were able to characterise the untreated patients in a real-life context. Untreated patients were more often female, had a longer disease duration, a more frequent limited cutaneous form and anticentromere antibodies. They had more frequently limited ILD and better performance on PFTs and the 6 min walking test. These data are consistent with published recommendations and consensus guidance documents.[15–17] It is interesting to note that the characteristics of untreated patients were similar between those included before 2016 and after 2016, indicating that the main drivers of treatment initiation had not significantly changed.

It should be noted that in our cohort, untreated patients had preserved FVC (whereas DLCO had already decreased), suggesting that FVC was used in clinical practice to guide treatment prescription. This is in agreement with a recently published review, which showed that FVC was the most commonly used measure in practice to assess lung function in SSc-ILD.[33] However, nowadays, it is no longer used as a major parameter to guide the prescription of ILD therapy, since FVC could be preserved in patients with already moderate or advanced lung disease.[34] Similarly, it has been shown that FVC does not outperform other measures of lung function to assess the severity of ILD.[33]

Although we have seen evidence that a lower DLCO is also a good predictor of ILD progression and previous literature suggests that DLCO may be more sensitive than FVC,[32 33 35–37] the use of DLCO as an outcome measure for ILD is limited in practice in SSc due to the possible low specificity in the presence of associated pulmonary hypertension.

Our findings have important implications for clinical practice. Frequently, physicians wait for disease progression to initiate ILD treatment, mostly using FVC as a decision-making tool. The aim is to avoid overtreatment of stable patients, in the belief that patients with longer disease duration, limited cutaneous form, anticentromere antibodies, no meaningful dyspnoea, limited extent of lung fibrosis and preserved FVC are unlikely to progress. However, in our cohort of untreated patients frequently presenting with these mild disease characteristics, the cumulative 3 year incidence of progression was 39.9%, with no significant difference between historical and contemporary subgroups. Data on disease progression in this subgroup of FVC-preserved SSc-ILD patients are still scarce. A study from the Canadian Scleroderma Research group involving 116 SSc-ILD patients with preserved FVC found a rate of progression of almost 25% over 2 years in untreated patients,[32] which is consistent with our findings.

Table 3 Factors predicting progression of SSc-ILD in untreated patients in Cox univariable analysis

Variable	HR (95%CI)	P value
Male sex	1.02 (0.64 to 1.64)	0.93
Age	1.00 (0.99 to 1.02)	0.72
Disease duration	0.99 (0.98 to 1.01)	0.50
Ever smoker	0.98 (0.65 to 1.47)	0.91
Diffuse cutaneous SSc	2.26 (1.55 to 3.3)	<0.0001
Anticentromere antibodies	0.71 (0.48 to 1.06)	0.096
Anti-Scl70 antibodies	0.92 (0.62 to 1.37)	0.69
Active reflux and/or dysphagia	0.86 (0.59 to 1.27)	0.46
Extent of lung fibrosis>20%	3.49 (2.13 to 5.71)	<0.0001
Dyspnoea NYHA>2	2.65 (1.52 to 4.61)	0.0006
FVC predicted	0.99 (0.98 to 1.00)	0.015
DLCO predicted	0.98 (0.96 to 0.99)	<0.0001
Corticosteroids	1.25 (0.78 to 2.00)	0.36

ILD progression was defined by an FVC decline from baseline of ≥10% or an FVC decline of 5%–9% in association with a DLCO decline of ≥15% over 12±3 months, and/or decision to start of any ILD-modifying treatment and/or increase in the extent of ILD (from <20% to >20%) during the follow-up.
DLCO, carbon monoxide diffusing capacity of the lung; FVC, forced vital capacity; ILD, interstitial lung disease; NYHA, New York Heart Association; SSc, systemic sclerosis.

Table 4 Factors predicting progression of SSc-ILD in untreated patients in Cox multivariable analysis

Variable	HR (95%CI)	P value
Male sex	0.85 (0.50 to 1.43)	0.54
Age	1.01 (0.99 to 1.03)	0.21
Disease duration	1.00 (0.98 to 1.01)	0.81
Ever smoker	0.90 (0.57 to 1.42)	0.66
Diffuse cutaneous SSc	2.99 (1.79 to 4.97)	<0.0001
Anticentromere antibodies	1.06 (0.60 to 1.86)	0.85
Anti-Scl70 antibodies	0.72 (0.45 to 1.15)	0.17
Active reflux and/or dysphagia	0.66 (0.43 to 1.01)	0.062
Extent of lung fibrosis>20%	2.65 (1.25 to 5.60)	0.016
Dyspnoea NYHA>2	1.01 (0.47 to 2.17)	0.98
DLCO predicted	0.99 (0.97 to 1.00)	0.060
Corticosteroids	1.05 (0.62 to 1.76)	0.86

ILD progression was defined by an FVC decline from baseline of ≥10% or an FVC decline of 5%–9% in association with a DLCO decline of ≥15% over 12±3 months, and/or decision to start of any ILD-modifying treatment and/or increase in the extent of ILD (from <20% to >20%) during the follow-up.
DLCO, Carbon Monoxide Diffusing Capacity of the lung; FVC, forced vital capacity; ILD, carbon monoxide diffusing capacity of the lung; NYHA, New York Heart Association; SSc, systemic sclerosis.

In idiopathic pulmonary fibrosis, it is now widely recommended to start treatment also in patients with preserved lung function before lung function declines, in order to prevent progression and improve long-term outcomes.[38–41] Data on the efficacy and safety of ILD treatment in SSc patients with mild disease are still scarce. In the study from the Canadian Scleroderma Research group, the use of immunosuppressive drugs was associated with a lower risk of progression among subjects with mild ILD at 1 year,[32] underlining the efficacy of these therapies in this subgroup and the existence of a window of opportunity for treatment in SSc-ILD.

Our results therefore argue in favour of including SSc patients with a 'milder' form of ILD in clinical trials, in order to better assess the safety and efficacy of these therapies in this subgroup of patients.

Interestingly, progression occurred earlier when functional data, increase in the extent of ILD and initiation of treatment were taken into account, compared with functional progression alone, meaning that some patients require treatment despite not yet meeting the functional criteria for progression, underlining the need to consider the disease as a whole and evaluate different criteria to assess ILD progression. The reason for prescribing treatment was not collected. One may argue that this criterion does not necessarily reflect pulmonary progression of the disease. However, all the treatments considered in our study had pulmonary fibrosis as their main indication. Moreover, all the patients included had ILD, and the choice of treatment is often guided by several parameters of disease activity and severity, including lung involvement primarily.

Our study needs to be interpreted within its limitations: first, our cohort mainly included historical patients before the publication of SLS II trial in 2016. However, sensitivity analyses restricted to patients included after 2016, despite their small size, showed a high proportion of untreated SSc patients with similar characteristics to patients included before 2016, suggesting that treatment prescription patterns have not significantly changed over time. However, this may have changed recently with more data in favour of early treatment and an increase in effective treatments available. Furthermore, in this contemporary subgroup, the proportion of untreated patients who progressed was not significantly different from patients included before 2016. Some patients included in the baseline analysis did not have a follow-up visit and were therefore not included in the longitudinal analysis, which could determine a bias. However, the characteristics of patients with and without follow-up were not significantly different, particularly with regard to lung involvement. In addition, we did not use a computer-assisted diagnostic system for quantitative analysis of patient images to determine the extent of total ILD and validate semiquantitative

finding. However, the semiquantitative visual assessment is the one proposed in the Goh criteria,[25] and our two centres are expert centres with a long-lasting experience of radiologists in ILD assessment. Finally, most of the patients were Caucasian, so our results need to be validated in other ethnic groups.

Our study has several strengths: it is the first study to assess the characteristics and outcomes of untreated patients in a large, well-phenotyped cohort from two centres in a real-life setting. The rate of ILD progression was similar in the two centres, which highlights the reliability of the results. To account for missing data, we also performed multiple imputations and multivariate analyses to ensure the validity of our results.

In conclusion, most patients with SSc-ILD, in particular with preserved FVC, were not treated according to current indications, but a large proportion of them still progressed over 4 years. With the recent development of effective and safe therapies for SSc-ILD, our results argue for a change in practice in selecting patients for treatment, and should be also considered for patients' selection in clinical trials.

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Ethics approval This study involves human participants. All registered patients granted their informed consent to be included in the cohorts. The Regional Committee of Health and Medical Research Ethics in South-East Norway (no. 2016/119) and the Cantonal Ethic Committee of Zurich (BASEC no. 2016-01515 and no. 2018-02165) approved the study. This study complied with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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