




ORIGINAL RESEARCH

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

Moritz Scheidegger,¹ Marouane Boubaya,² Alexandru Garaiman,¹ Imon Barua,³ Mike Becker,¹ Hilde Jenssen Bjørkekjær,⁴ Cosimo Bruni,^{1,5} Rucsandra Dobrota ,¹ Håvard Fretheim,³ Suzana Jordan,¹ Oyvind Midtvedt,³ Carina Mihai,¹ Anna-Maria Hoffmann-Vold,^{1,3} Oliver Distler ,¹ Muriel Elhai ¹

To cite: Scheidegger M, Boubaya M, Garaiman A, *et al.* Characteristics and disease course of untreated patients with interstitial lung disease associated with systemic sclerosis in a real-life two-centre cohort. *RMD Open* 2024;**10**:e003658. doi:10.1136/rmdopen-2023-003658

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2023-003658>).

Received 29 August 2023
Accepted 21 December 2023



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Muriel Elhai;
Muriel.Elhai@usz.ch

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 $\geq 10\%$ or (2) decline in FVC of 5%–9% associated with a decline in diffusing capacity for carbon monoxide (DLCO) $\geq 15\%$ 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.

INTRODUCTION

Systemic sclerosis (SSc) is an orphan connective tissue disease characterised by alterations of the microvasculature, disturbances of the

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.

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 O₂ saturation, oxygen desaturation defined as a fall in peripheral capillary oxygen saturation. (SpO₂) $\geq 5\%$ 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 (\geq 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 $\geq 10\%$ or an FVC decline of 5%–9% in association with a DLCO decline of $\geq 15\%$ over 12 \pm 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 $\geq 10\%$ or an FVC decline of 5%–9% in association with a DLCO decline of $\geq 15\%$ 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 (prednisone 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 SpO₂≥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 heart 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, anti-centromere 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

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.

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).

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)

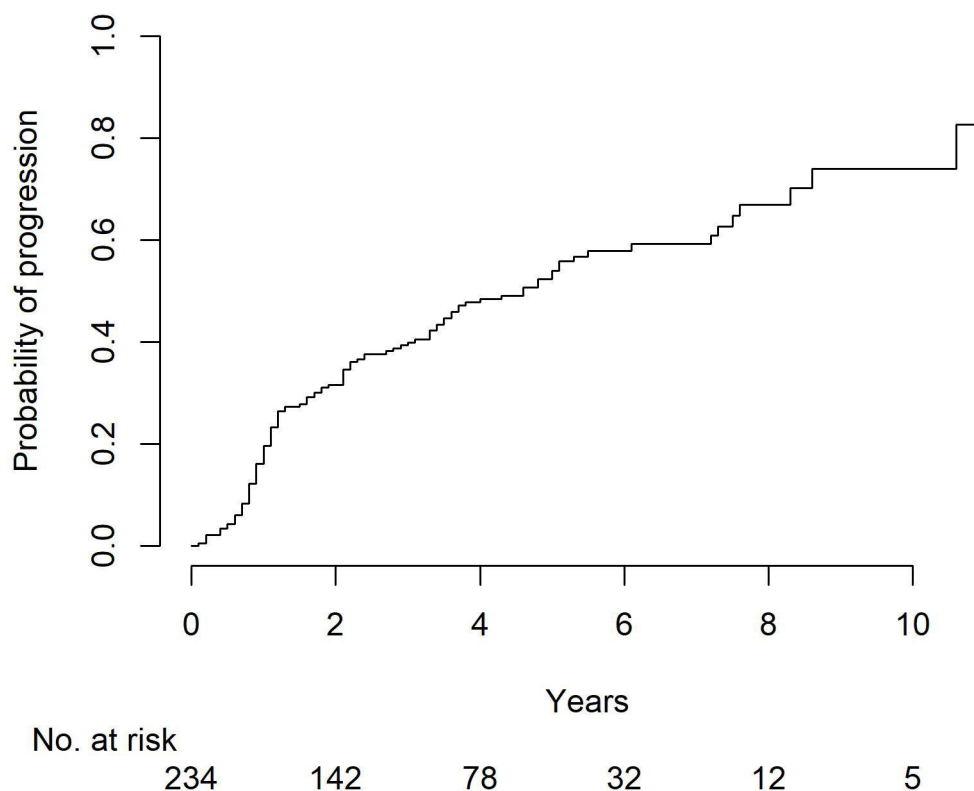


Figure 1 Time to lung fibrosis progression in untreated patients. Kaplan-Meier curve for cumulative lung fibrosis progression in untreated systemic sclerosis patients from the combined cohort. Lung fibrosis progression was defined by FVC decline from baseline of $\geq 10\%$ or FVC decline of 5% – 9% in association with a DLCO decline of $\geq 15\%$ 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

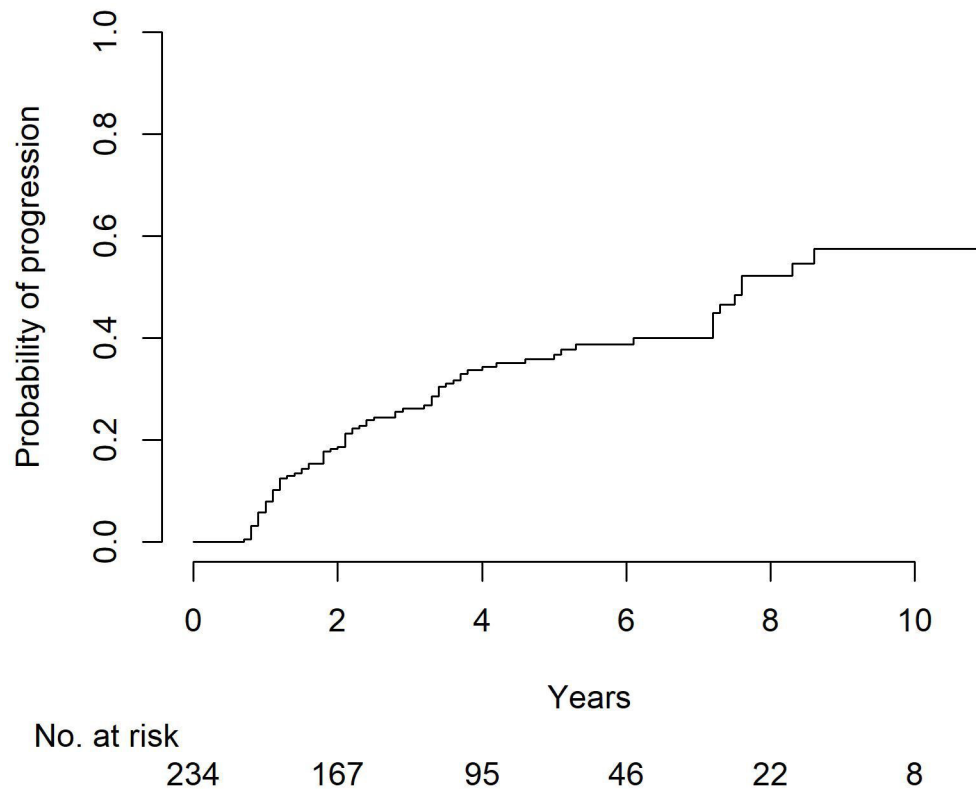


Figure 2 Time to lung fibrosis progression in untreated patients according to functional criteria. Kaplan-Meier curve for cumulative lung fibrosis progression in untreated systemic sclerosis patients from the combined cohort. Lung fibrosis progression was defined by FVC decline from baseline of $\geq 10\%$ or FVC decline of 5%–9% in association with a DLCO decline of $\geq 15\%$ 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, anti-centromere 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-Sci70 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 $\geq 10\%$ or an FVC decline of 5%–9% in association with a DLCO decline of $\geq 15\%$ over 12 \pm 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-Sci70 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 $\geq 10\%$ or an FVC decline of 5%–9% in association with a DLCO decline of $\geq 15\%$ over 12 \pm 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.

Author affiliations

¹Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

²Department of Clinical Research, CHU Avicenne, APHP, Bobigny, France

³Department of Rheumatology, Oslo University Hospital, Oslo, Norway

⁴Department of Rheumatology, Hospital of Southern Norway, Kristiansand, Norway

⁵Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence - University Hospital Careggi, Florence, Italy

Twitter Cosimo Bruni @CosimoBruni and Muriel Elhai @MurielElhai

Contributors ME, MS and OD designed the study, analysed and interpreted the results. MS, AG, IB, MB, HJB, CB, RD, HF, SJ, ØM, CM, A-MH-V and ME collected the data. MB did the statistical analysis. ME and MS wrote the first draft of the manuscript. All authors critically reviewed the manuscript. ME is the guarantor for this manuscript.

Funding This project was supported by the EULAR research funding voucher (ID Q222RSV13).

Competing interests MS, MB, AG, IB, SJ, ØM: none. MB: as consultancy relationship with and/or received research funding from and/or served as speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: GSK, Amgen, Novartis and outside of this research area: Vifor. HJB: grant/research support from: Janssen. CB: speakers bureau: Eli-Lilly, consultant of: Boehringer Ingelheim, grant/research support from: Gruppo Italiano Lotta alla Scleroderma (GILS), European Scleroderma Trials and Research Group (EUSTAR), Foundation for research in Rheumatology (FOREUM), Scleroderma Clinical Trials Consortium (SCTC), Scleroderma Research Foundation (SRF). Educational grants from AbbVie and Wellcome Trust. Congress Support from: Boehringer Ingelheim. RD: speakers bureau/consultancy: Actelion, Boehringer-Ingelheim; grant/research support from: Pfizer, Actelion, Iiten-Kohaut; congress participation support: Amgen, Otsuka. HF: speakers bureau: Boehringer Ingelheim, consultant of: Bayer, grant/research support from: GSK and Actelion, CM had consultancy relationship with and/or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: Boehringer Ingelheim, Janssen, Roche. AMHV has received research funding and/or consulting fees and/or other remuneration from ARXX, Boehringer Ingelheim, Genentech, Janssen, Lilly, Medscape, Merck Sharp & Dohme, Roche. OD has/had relationships with the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: speaker fee: Bayer, Boehringer Ingelheim, Janssen, Medscape; consultancy fee: 4P-Pharma, Abbvie, Acceleron, Alcedim, Altavant Sciences, Amgen, AnaMar, Arxx, AstraZeneca, Baecon, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galapagos, Glenmark, Horizon, Inventiva, Kymera, Lupin, Miltenyi Biotec, Mitsubishi Tanabe, MSD, Novartis, Prometheus, Redxpharma, Roivant, Sanofi and Topadur; research

grants: Kymera, Mitsubishi Tanabe. OD has/had relationships with the following companies in the area of dermatomyositis in the last three calendar years: consultancy fee: Pfizer (2021). ME: congress travel support from Janssen and Astrazeneca.

Patient consent for publication Consent obtained directly from patient(s).

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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Rucsandra Dobrota <http://orcid.org/0000-0001-9819-7574>

Oliver Distler <http://orcid.org/0000-0002-0546-8310>

Muriel Elhai <http://orcid.org/0000-0001-8627-5758>

REFERENCES

- Allanore Y, Simms R, Distler O, *et al*. Systemic sclerosis. *Nat Rev Dis Primers* 2015;1:15002.
- Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. *Journal of Scleroderma and Related Disorders* 2017;2:137–52.
- Elhai M, Meune C, Avouac J, *et al*. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2012;51:1017–26.
- Hoffmann-Vold A-M, Fretheim H, Halse A-K, *et al*. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. *Am J Respir Crit Care Med* 2019;200:1258–66.
- Elhai M, Meune C, Boubaya M, *et al*. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* 2017;76:1897–905.
- Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis. *Annals of the Rheumatic Diseases* 1972;66:940–4.
- Schurawitzki H, Stiglbauer R, Graninger W, *et al*. Interstitial lung disease in Progressive systemic sclerosis: high-resolution CT versus radiography. *Radiology* 1990;176:755–9.
- Vonk MC, Broers B, Heijdra YF, *et al*. Systemic sclerosis and its pulmonary complications in the Netherlands: an Epidemiological study. *Ann Rheum Dis* 2009;68:961–5.
- Solomon JJ, Olson AL, Fischer A, *et al*. Scleroderma lung disease. *Eur Respir Rev* 2013;22:6–19.
- Hoffmann-Vold A-M, Allanore Y, Alves M, *et al*. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis* 2021;80:219–27.
- Distler O, Gahlemann M, Maher TM. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019;381:1596–7.
- Khanna D, Lin CJF, Furst DE, *et al*. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020;8:963–74.
- Khanna D, Denton CP, Jhreis A, *et al*. Safety and efficacy of subcutaneous Tocilizumab in adults with systemic sclerosis

- (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016;387:2630–40.
- 14 Ebata S, Yoshizaki A, Oba K, *et al.* Safety and efficacy of Rituximab in systemic sclerosis (DESIREs): a double-blind, investigator-initiated, randomised, placebo-controlled trial. *The Lancet Rheumatology* 2021;3:e489–97.
 - 15 Rahaghi FF, Hsu VM, Kaner RJ, *et al.* Expert consensus on the management of systemic sclerosis-associated interstitial lung disease. *Respir Res* 2023;24:6.
 - 16 Hoffmann-Vold A-M, Maher TM, Philpot EE, *et al.* The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *The Lancet Rheumatology* 2020;2:e71–83.
 - 17 Hachulla E, Agard C, Allanore Y, *et al.* French recommendations for the management of systemic sclerosis. *Orphanet J Rare Dis* 2021;16(Suppl 2):322.
 - 18 Tennøe AH, Murbræch K, Andreassen JC, *et al.* Systolic dysfunction in systemic sclerosis: prevalence and Prognostic implications. *ACR Open Rheumatol* 2019;1:258–66.
 - 19 Perelas A, Silver RM, Arrossi AV, *et al.* Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med* 2020;8:304–20.
 - 20 Distler O, Volkman ER, Hoffmann-Vold AM, *et al.* Current and future perspectives on management of systemic sclerosis-associated interstitial lung disease. *Expert Rev Clin Immunol* 2019;15:1009–17.
 - 21 LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001;28:1573–6.
 - 22 Meier FMP, Frommer KW, Dinser R, *et al.* Update on the profile of the EUSTAR cohort: an analysis of the EULAR scleroderma trials and research group database. *Ann Rheum Dis* 2012;71:1355–60.
 - 23 Coghlan JG, Denton CP, Grünig E, *et al.* Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014;73:1340–9.
 - 24 Hoffmann-Vold A-M, Aaløkken TM, Lund MB, *et al.* Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. *Arthritis Rheumatol* 2015;67:2205–12.
 - 25 Goh NSL, Desai SR, Veeraraghavan S, *et al.* Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008;177:1248–54.
 - 26 Goh NS, Hoyles RK, Denton CP, *et al.* Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol* 2017;69:1670–8.
 - 27 Tashkin DP, Roth MD, Clements PJ, *et al.* Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016;4:708–19.
 - 28 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
 - 29 White IR, Royston P. Imputing missing Covariate values for the Cox model. *Stat Med* 2009;28:1982–98.
 - 30 Li Q, Wallace L, Patnaik P, *et al.* Disease frequency, patient characteristics, Comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a US cohort study. *Rheumatology* 2021;60:1915–25.
 - 31 Ramahi A, Lescoat A, Roofeh D, *et al.* Risk factors for lung function decline in systemic sclerosis-associated interstitial lung disease in a large single-center cohort. *Rheumatology (Oxford)* 2023;62:2501–9.
 - 32 Hoa S, Bernatsky S, Steele RJ, *et al.* Association between immunosuppressive therapy and course of mild interstitial lung disease in systemic sclerosis. *Rheumatology (Oxford)* 2020;59:1108–17.
 - 33 Caron M, Hoa S, Hudson M, *et al.* Pulmonary function tests as outcomes for systemic sclerosis interstitial lung disease. *Eur Respir Rev* 2018;27:148.
 - 34 Denton CP, Goh NS, Humphries SM, *et al.* Extent of fibrosis and lung function decline in patients with systemic sclerosis and interstitial lung disease: data from the SENSICIS trial. *Rheumatology (Oxford)* 2023;62:1870–6.
 - 35 König G, Luderschmidt C, Hammer C, *et al.* Lung involvement in scleroderma. *Chest* 1984;85:318–24.
 - 36 Wells AU, Hansell DM, Rubens MB, *et al.* Fibrosing Alveolitis in systemic sclerosis: indices of lung function in relation to extent of disease on computed tomography. *Arthritis Rheum* 1997;40:1229–36.
 - 37 Tashkin DP, Volkman ER, Tseng C-H, *et al.* Relationship between quantitative radiographic assessments of interstitial lung disease and physiological and clinical features of systemic sclerosis. *Ann Rheum Dis* 2016;75:374–81.
 - 38 Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018;379:797–8.
 - 39 Wells AU, Brown KK, Flaherty KR, *et al.* What's in a name? that which we call IPF, by any other name would act the same. *Eur Respir J* 2018;51:1800692.
 - 40 Behr J, Kreuter M, Hoepfer MM, *et al.* Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF Registry. *Eur Respir J* 2015;46:186–96.
 - 41 Cottin V, Hirani NA, Hotchkiss DL, *et al.* Presentation, diagnosis and clinical course of the spectrum of progressive-Fibrosing interstitial lung diseases. *Eur Respir Rev* 2018;27:150.