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Systemic sclerosis

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ABSTRACT

Objectives: Interstitial lung disease (ILD) carries significant morbidity and mortality risk in systemic sclerosis (SSc). We aimed to estimate the incidence of new-onset SSc-ILD and the associated risk factors, as well as its impact on the prognosis.
Methods: Patients classified as having SSc, with the absence of ILD signs on high-resolution computed tomography (HRCT) at baseline and having at least 1 follow-up visit with available HRCT data, were selected. SSc-ILD incidence was calculated as a rate per 100 person-years. Predictors of new-onset ILD and risk factors for ILD progression and mortality were chosen according to the literature and expert opinion. Risk factors for new-onset ILD, as well as its prognostic impact on ILD progression and mortality, were tested by generalised logistic estimating equation and Cox regression models, respectively.
Results: Among 5331 patients with SSc with negative baseline HRCT, the incidence of new-onset ILD was 3.83 cases per 100 person-years. Notably, there was a continuous detection of new ILD onset up to 10 years from baseline. Risk factors for new-onset ILD included New York Heart Association stage ≥2, muscle weakness, high inflammatory markers, and SSc-specific autoantibodies, but not disease duration. Despite a lower risk of ILD progression compared with prevalent ILD diagnosed at baseline, incident ILD still carried an increased risk for mortality, which was almost double when compared with ILD-negative cases.
Conclusions: Patients with SSc should be considered for regular screening following a negative baseline HRCT, in particular when carrying high-risk features for new ILD onset, given its incidence and prognostic implications.

INTRODUCTION

Interstitial lung disease (ILD) is among the most important factors influencing the clinical course of systemic sclerosis (SSc), in terms of quality of life, morbidity, and mortality [1].

The epidemiology of ILD in SSc varies depending on the different methodologies used to detect it. Although ILD overall affects from 2.3 to 19 per 100,000 persons in the general population [2,3], its frequency is higher in patients with SSc, ranging from 13.9 to 88.1 per 100 cases [4–9]. When considering representative population-based studies, the lifetime prevalence of SSc-ILD turns out to be approximately 50% [10].

With the availability of effective treatments [11,12], consensus statements [13] and guidelines for the management of SSc-ILD have been published [14–16]. Accordingly, patients with SSc-ILD have been well characterised, and risk factors associated with the presence of SSc-ILD have been identified. These include anti-topoisomerase I (ATA) positivity, diffuse cutaneous SSc (dcSSc), oesophagal involvement, male sex, African-American ethnicity, lower % predicted forced vital capacity (FVC), and lower % predicted diffusing capacity of the lungs for carbon monoxide (DLCO) [17–21].

As most SSc-ILD studies are cross-sectional or consider baseline SSc-ILD cases in a longitudinal observation, less is known about the incidence of SSc-ILD following a negative baseline high-resolution computed tomography (HRCT) [22,23]. Single-centre and national cohort analysis revealed incidence rates of new-onset SSc-ILD between 2.0 and 4.4 per 100 patients-years [7,24,25]. However, different definitions of baseline negative patients have been applied (ie, negative HRCT but also negative chest X-ray, no symptoms, or low suspicion of ILD). In these studies, certain risk factors for new onset of SSc-ILD were proposed, including baseline pulmonary function tests (PFTs), autoantibody status, haemoglobin concentrations, age at onset of Raynaud's phenomenon (RP) [22], and rapid progression of skin fibrosis [23].

Later onset of ILD, not detectable at first presentation, might suggest a milder phenotype and better outcome. However, data

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Limited studies estimated the incidence of interstitial lung disease (ILD) in systemic sclerosis.
- The optimal combination of risk factors for accurately predicting ILD in patients with systemic sclerosis (SSc) has not yet been identified.
- The impact of new-onset, incident ILD, in comparison with prevalent ILD diagnosed at baseline, is unknown in terms of risk of progression and mortality.

WHAT THIS STUDY ADDS

- There is a continuous incidence of new-onset ILD cases in SSc, stable up to 10 years from baseline.
- We have identified factors associated with new ILD onset following a negative baseline high-resolution computed tomography, including age, dyspnoea, autoantibody profile, diffusion capacity of the lung for carbon oxide and increased inflammatory markers.
- New-onset incident ILD has a lower risk of functional progression than prevalent ILD, but determines a higher mortality burden in comparison with patients without ILD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- The prognostic implication of new-onset incident ILD should support continuous screening for ILD in patients with SSc following a negative baseline.
- Risk factors have been identified to further support the screening and the rescreening of patients at higher risk.

to prove this hypothesis are lacking. This uncertainty might have also led to a lack of consensus about rescreening initially negative cases [13–16,26]. In addition, it is unclear whether the incidence of new-onset ILD is decreasing over the disease course. This is of high practical importance, as rescreening for new-onset ILD might be adapted in patients with longer disease duration, if the incidence of new-onset ILD is decreasing over time. Identifying patients at risk of new-onset ILD might further help to stratify patients for more or fewer screenings. Notably, the findings of reduced survival, even in patients with mild lung fibrosis and normal FVC [10], might argue for a relevant disease burden in patients with new-onset ILD, after a negative baseline screening.

We therefore aimed to (1) estimate the annual incidence of new-onset SSc-ILD in baseline HRCT-negative patients in the large European Scleroderma Trials And Research (EUSTAR) cohort, (2) identify risk factors for new SSc-ILD onset, and (3) evaluate the impact of new-onset SSc-ILD on ILD progression and mortality.

METHODS

Patient population and characteristics

Patients with SSc classified according to the 2013 ACR/EULAR criteria [27] from the EUSTAR group database were eligible for this study if they showed available data for ILD on HRCT at baseline, as defined by the local expert radiologist evaluation and as reported in the database, and at least 1 follow-up visit with available HRCT data. The dataset extraction took place in June 2022 (data from September 2003 to February 2022 were available). The framework of the EUSTAR database, the structure of the presented data, and definitions of clinical variables, including ILD and disease duration (from the first non-RP sign or symptom), have been previously provided [17]. Patients with pulmonary hypertension, defined as mean pulmonary artery pressure >20 mmHg on right heart catheterisation, were excluded, as well as those with unknown ILD status on HRCT and inconsistent cases. Presence of overlapping rheumatic conditions, such as rheumatoid arthritis or idiopathic inflammatory myopathies, did not represent an exclusion criterion.

The first visit with available HRCT data recorded was considered as the baseline visit. Based on the baseline ILD status, patients were divided into 2 groups: those with ILD on baseline HRCT (prevalent ILD group) and those without ILD on baseline HRCT. Based on follow-up HRCTs, patients without ILD on baseline HRCT were further classified into patients with new onset of ILD on HRCT at follow-up (incident ILD group) and patients who remained ILD negative (ILD-negative group).

Primary outcome

The primary outcome of this post hoc analysis of prospectively collected data was the estimation of the crude incidence of SSc-ILD. The incidence was calculated by dividing the number of patients with SSc who developed ILD according to HRCT during follow-up by the number of patients with SSc without ILD at baseline. The incidence rate was presented as a rate per 100 person-years (dividing the number of incidental ILD cases by the total number of person-years accumulated by the cohorts of ILD-negative patients), starting from the baseline visit and from disease onset (corresponding to the date of the first non-RP sign or symptom).

Secondary outcomes

In addition, we tested the risk factor for new onset of SSc-ILD, both for 1-year and long-term (ever) incidence. Secondly, we tested the impact of incident SSc-ILD compared with prevalent SSc-ILD on progression at 12±3 months intervals. The following 3 different definitions of progression were applied: (1) absolute FVC decline ≥5% predicted [28], (2) absolute FVC decline ≥5% predicted or absolute DLCO decline ≥10% predicted [29], and (3) relative FVC decline ≥10% predicted or 5% to 9% with relative DLCO decline ≥15% predicted [30]. Finally, we tested the association of new-onset SSc-ILD with mortality, compared with prevalent or negative ILD.

Statistical methods

Categorical variables were reported as number (%) and continuous variables as mean with SD or median with IQR, depending on distribution. Poisson rate CI were calculated for measuring the 95% CI for each incidence rate.

Multivariable, logistic, generalised estimating equation models, using backward selection, with odds ratio (OR) and 95% CI, were applied to identify risk factors for 1-year SSc-ILD incidence, as well as for ILD progression. Generalised estimating equation modelling accounts and balances for multiple observations of the same patient, and the adjusting factors refer to the start of each observation (ie, each yearly interval).

Cox regression models, using backward selection, were used to estimate adjusted hazard ratio (HR) and 95% CI of incident ILD ever and for mortality. In these longitudinal analyses, risk factors and adjusting covariates from the baseline visit were included.

All prediction models included adjusting confounders, based on previous preliminary data and expert opinion [22,23,31,32]. Common adjusting factors to all models belonged to demographics (age, sex, disease duration, and smoking), clinical (cutaneous subtype, arthritis ever, muscle weakness, oesophageal symptoms, digital ulcers, digital pitting scars, dyspnoea—defined as New York Heart Association [NYHA] stage ≥2), functional (DLCO%, FVC%), and laboratory features. The latter included SSc-specific autoantibodies (including ATA, anticentromere [ACA], anti-RNA polymerase III [ARA], and anti-PM/Scl antibodies), increased inflammatory markers (defined as C-reactive protein or erythrocyte sedimentation rate above the upper level of normality according to local laboratory).

For both ILD onset analyses, body mass index, ethnicity, modified Rodnan's skin score, tendon friction rubs, and haemoglobin level represented additional covariates. All ILD progression models included as predictor of interest the categorisation of patients with ILD into incident vs prevalent. The mortality analysis also included ILD status (in terms of incident, prevalent, or negative), the abovementioned adjusting factors, as well as further mortality risk factors such as left ventricle ejection fraction, pericardial effusion, diastolic dysfunction and estimated systolic pulmonary artery pressure, measured through echocardiography.

Additionally, the number of HRCTs during follow-up, the average time between HRCTs and the exposure to immunosuppressants (including corticosteroids above 10 mg/d, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, rituximab, and tocilizumab) during the observation were also included in the long-term incidence model.

To account for the variation in time of onset of ILD during follow-up, the number of visits and the follow-up duration, sensitivity analyses for ILD incidence as outcome were performed and restricted to 1) patients with at least 3 visits within 5 years from baseline, and 2) patients with disease duration ≤5 years.

Finally, hypothesising a major role for ATA for ILD incidence, we implemented the final steps of both ILD onset prediction models by adding interaction terms between ATA and the other predictors to confirm their predictive role among the ATA status strata. To quantify this, marginal estimates effects were computed.

The survival analysis included patients with at least 6 months of follow-up after the first visit with an HRCT reporting the presence of ILD (for prevalent and incident cases). For ILD-negative patients, a minimum of 6 months follow-up from the first HRCT available was required. In addition to the Cox regression model, a Kaplan-Meier analysis was performed to compare survival among groups.

All statistical analyses were performed with SAS 9.4 M7. Missing data on the predictors and confounders were handled with an imputation algorithm (Random Forest) [33], when at least 51% information was present. The variables considered for imputation, with the prevalence of missing data, are presented in the supplementary annex S1. Given the high percentage of missingness, exposure to immunosuppressants was not imputed and tested only as an exploratory evaluation.

RESULTS

Baseline demographics

Within the EUSTAR database, 11,601 patients fulfilled inclusion criteria (Fig 1). Among them, we identified 6270 (54.5%) patients with prevalent ILD at baseline. Among 5331 ILD-negative patients at baseline, new ILD onset occurred in 1075 (20.2%) cases over a median 3.8 (1.6-7.3) years follow-up, with a median time to ILD detection of 3.23 (95% CI: 1.39-6.74) years from the baseline visit.

Similar results were obtained in the sensitivity analysis, including 3358 patients with at least 3 visits with available

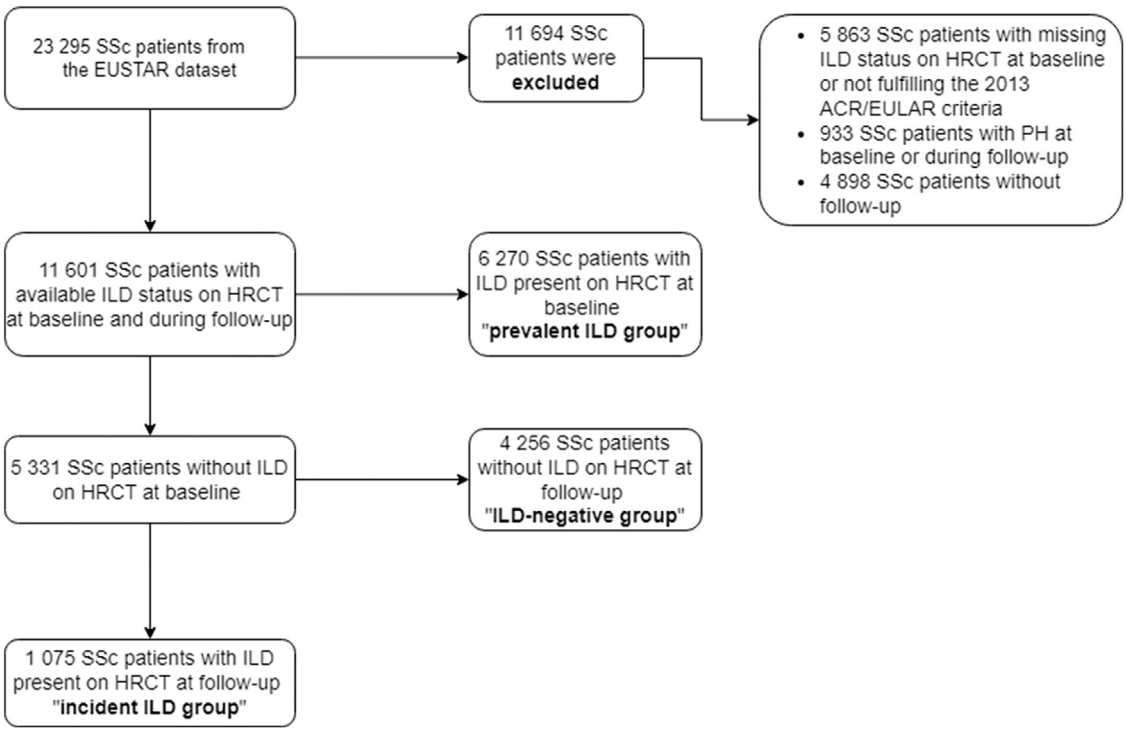

Figure 1. Flow chart of the study population. ACR/EULAR, American College of Rheumatology/European Alliance of Associations for Rheumatology; EUSTAR, European Scleroderma Trials And Research; PH, pulmonary hypertension; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

HRCTs within 5 years from baseline. Among them, 2727 (81.2%) were ILD negative at baseline, and 631 (18.8%) developed ILD during follow-up. Interestingly, we noted a numerically shorter time to new ILD detection, at a median of 2.25 (1.23-3.75) years after baseline.

In the second sensitivity analysis focusing on patients with disease duration ≤5 years, 576/2674 (21.5%) patients developed ILD after a median 3.1 (1.3-6.4) years of follow-up (Supplementary Table S1). Time to ILD onset was comparable with the whole population, with a median time to ILD onset of 3.05 (1.60-7.36) years.

In comparison with the prevalent ILD group, the incident ILD group was characterised by shorter disease duration, lower prevalence of peripheral vascular manifestations, arthritis, and smoking exposure at baseline (Table). Similarly, compared with patients who remained ILD-negative during follow-up, patients with incident ILD were younger at baseline, more frequently men, with dcSSc subset, ATA positivity, and increased inflammatory markers, but less frequently smokers. Moreover, patients with incident ILD already had a higher dyspnoea NYHA class at baseline, as well as lower FVC% and DLCO% (Table).

Except for age and NYHA functional class, the sensitivity analyses confirmed the baseline differences between incident ILD and ILD-negative cases (Supplementary Table S1).

Incidence rate of new-onset ILD

The overall ILD incidence rate was 3.83 (95% CI, 3.12-4.63) per 100 person-years. There was a continuous detection of new onset of ILD for up to 10 years from baseline (range of incidence rates 2.40-5.14 per 100 person-years; Fig 2, left panel). Interestingly, when the incidence rate was quantified from disease onset, we confirmed the persistent incidence of new cases up to 15 years, with an overall ILD incidence rate of 1.66 (95% CI, 1.19-2.25) per 100 person-years (Fig 2, right panel). Similar rates and ranges over time were confirmed in the 2 sensitivity analyses (Supplementary Figs S1-S2).

Predictors of 1-year incidence of SSc-ILD

Given the annual follow-up of patients with SSc and the potential design of a 1-year preventive clinical trial, we focused our ILD incidence analysis on patients having at least a 1-year observation period. This resulted in the analysis of 13,339 yearly follow-ups from 4067 baseline negative patients, with 482 new ILD onset detected. In multivariable analysis, male sex (OR, 1.42; 95% CI, 1.10-1.84), older age (OR, 1.01; 95% CI, 1.00-1.02), dyspnoea NYHA stage ≥2 (OR, 1.38; 95% CI, 1.13-1.67), ATA (OR, 2.10; 95% CI, 1.60-2.76) and increased inflammatory markers (OR, 1.31; 95% CI, 1.03-1.67) were associated

Table
Baseline characteristics of patients with SSc according to the ILD status

	ILD prevalent group (n = 6270)	ILD incident group (n = 1075)	ILD-negative group (n = 4256)
Age (y), mean±SD	57±13	52±14	53±14
Sex female, n (%)	4054 (80)	873 (81)	3692 (87)
Disease duration (y), mean±SD	9±8	6±7	7±7
Caucasian, n (%)	5823 (92)	1007 (94)	4057 (95)
Smoking ever, n (%)	916 (15)	75 (7)	409 (10)
BMI, mean±SD	25±4	25±4	25±4
Diffuse cutaneous SSc, n (%)	3062 (49)	490 (46)	1023 (24)
Raynaud's phenomenon present, n (%)	5876 (94)	880 (82)	3595 (85)
Modified Rodnan skin score, median (IQR)	9 (0-51)	7 (3-13)	4 (2-10)
Digital ulcers ever, n (%)	2007 (32)	186 (17)	577 (14)
Pitting scars on fingertips, n (%)	2485 (40)	358 (33)	1184 (28)
Puffy fingers, n (%)	3249 (55)	568 (53)	2141 (50)
Telangiectasia, n (%)	717 (66)	4123 (66)	2644 (64)
Arthritis ever, n (%)	780 (12)	21 (2)	133 (3)
Tendon friction rubs, n (%)	473 (8)	75 (7)	192 (5)
Muscle weakness, n (%)	1044 (17)	168 (16)	503 (12)
Oesophagal symptoms, n (%)	4159 (66)	653 (61)	2521 (59)
Scleroderma renal crisis, n (%)	118 (2)	7 (0.7)	20 (0.5)
Dyspnoea NYHA stage ≥2, n (%)	3403 (54)	372 (35)	1258 (30)
Pericardial effusion, n (%)	365 (6)	29 (3)	113 (3)
Diastolic function abnormal, n (%)	1280 (20)	166 (15)	481 (11)
DLCO% predicted, mean±SD	61±18	70±17	75±17
FVC % predicted, mean±SD	86±21	93±18	99±18
TLC% predicted, mean±SD	84±20	93±19	101±17
Systolic PAP on ECHO (mmHg), mean±SD	31±9	30±6	29±7
ACA, n (%)	1187 (19)	312 (29)	2495 (59)
ATA, n (%)	3297 (53)	521 (48)	770 (18)
ARA, n (%)	206 (3)	29 (3)	170 (3)
PM/Scl, n (%)	125 (2)	13 (1)	40 (1)
None of above or other, n (%)	1455 (23)	200 (19)	807 (19)
Increased inflammatory markers, n (%)	1470 (23)	195 (18)	495 (12)
Hb (g/dL), mean±SD	12±3	12±2	12±3
Immunosuppressants ever, n (%)	1588/2058 (77)	432/ 577 (75)	593/955 (62)
Immunosuppressants ongoing, n (%)	1586/2056 (77)	375/562 (67)	593/955 (62)

ACA, anticentromere antibodies; ARA, anti-RNA polymerase III antibodies; ATA, anti-topoisomerase antibodies; BMI, body mass index; CRP, C-reactive protein; DLCO/SB, carbon monoxide diffusing capacity; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; ILD, interstitial lung disease; NYHA, New York Heart Association; PAP on ECHO, pulmonary artery pressure on echocardiogram; PM/Scl, anti-PM/Scl antibodies; SSc, systemic sclerosis; TLC, total lung capacity.

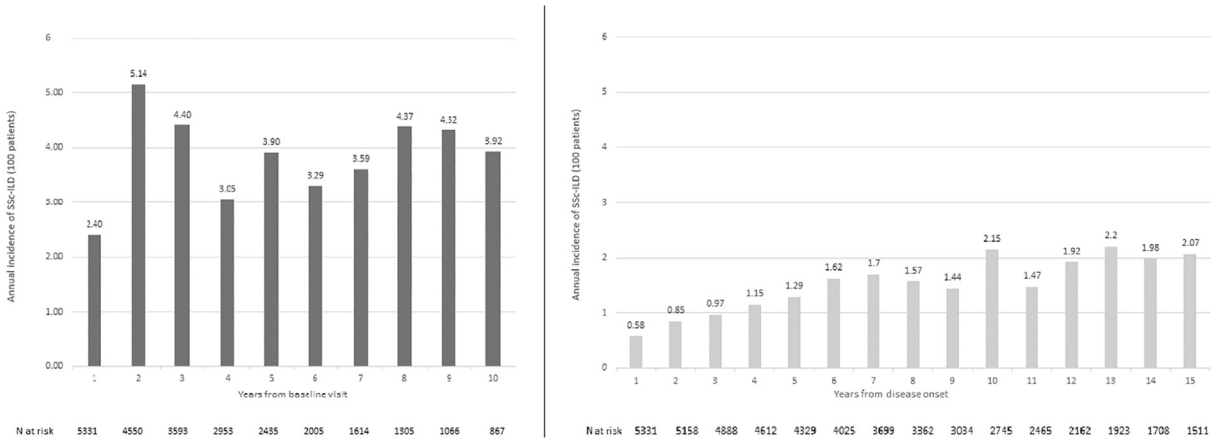

Figure 2. Annual incidence rate of new onset of ILD per 100 patients from the baseline visit (left panel) and from disease onset, defined as the date of first non-Raynaud's phenomenon sign or symptom (right panel). ILD, interstitial lung disease; SSc, systemic sclerosis.

with an increased risk of 1-year SSc-ILD incidence. Conversely, higher DLCO% (OR, 0.98; 95% CI, 0.98-0.99) and haemoglobin level (OR, 0.98; 95% CI, 0.98-0.99), arthritis ever (OR, 0.66; 95% CI, 0.50-0.87), ACA (OR, 0.40; 95% CI, 0.29-0.54), and ARA (OR, 0.52; 95% CI, 0.28-0.97) were independent protective factors of 1-year SSc-ILD incidence (Fig 3A). When exposure to immunosuppressants was forced into the 2 models, as an exploratory evaluation, this was not retained as a protective factor. When testing the interaction of ATA with the other predictors, no statistically significant result was detected, supporting a comparable role of the risk factors regardless of autoantibody specificity (data not shown).

Predictors of incidence of SSc-ILD ever

In the Cox regression analysis of the cumulative incidence over the whole observation period, new-onset SSc-ILD was independently predicted by dyspnoea NYHA stage ≥2 (HR, 1.15;

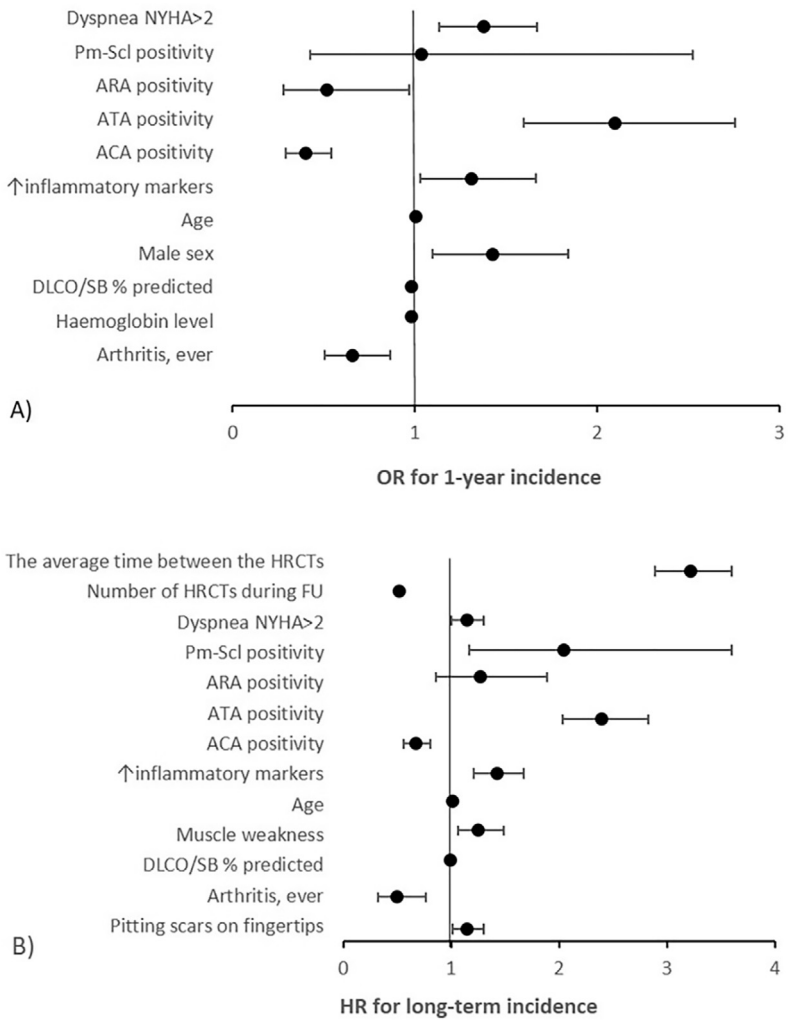

Figure 3. Multivariable prediction models of new onset of ILD for 1- (A) and long-term observation (B), respectively, applying logistic and Cox regression. ACA, anticentromere antibodies; ARA, anti-RNA polymerase III antibodies; ATA, anti-topoisomerase antibodies; DLCO/SB, carbon monoxide diffusing capacity; FU, follow-up; HR, hazard ratio; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NYHA, New York Heart Association; OR, odds ratio.

95% CI, 1.01-1.30), digital pitting scars (HR, 1.15; 95% CI, 1.01-1.31), muscle weakness (HR, 1.26; 95% CI, 1.06-1.49), age (HR, 1.01; 95% CI, 1.01-1.02), increased inflammatory markers (HR, 1.42; 95% CI, 1.21-1.67), ATA (HR, 2.40; 95% CI, 2.03-2.82) and anti-Pm/Scl antibodies (HR, 2.05; 95% CI, 1.16-3.60). A higher DLCO% (HR, 1.77; 95% CI, 1.49-2.08) was mildly associated with a reduced risk of incidence, as well as ACA (HR, 0.68; 95% CI, 0.56-0.81) and arthritis ever (HR, 0.50; 95% CI, 0.32-0.77) (Fig 3B). These results were independent of the average time between HRCTs and the number of HRCTs performed during the follow-up. Notably, the incidence of new onset of ILD was independent of disease duration. When testing the interaction of ATA with the other predictors, we observed a significant interaction between ATA and age (P = .02) and ATA and dyspnoea, NYHA stage ≥2 (P = .04). Combining the results into marginal estimates, we observed that dyspnoea NYHA stage ≥2 (HR, 1.32; 95% CI, 1.11-1.58) and age (HR, 1.02; 95% CI, 1.01-1.02) were confirmed as independent predictors of new ILD onset ever in the ATA negative population, hypothesising a more prominent role for these risk factors in this subpopulation. Conversely, in patients with ATA positive, these 2 predictors were not independently associated with the ILD onset (dyspnoea NYHA stage ≥2, HR, 0.99; 95% CI, 0.82-1.21: age, HR, 1.00; 95% CI, 0.99-1.01).

Impact of ILD on overall survival in patients with SSc

During a median of 4.1 (IQR, 2.0-7.7 years) years of follow-up, 708/9003 (7.8%) deaths were recorded. The survival rate was lower in the prevalent ILD group (88.1%), compared with both the incident ILD (92.2%) and ILD-negative (96.4%) groups (P = .0008 by Log-rank test). In the adjusted Cox regression model (Fig 4), both incident ILD (HR, 0.68; 95% CI: 0.51-0.89) and ILD-negative (HR, 0.35; 95% CI, 0.29-0.42) status showed a lower mortality risk than the prevalent ILD. Additionally, the incident ILD group had a higher risk of mortality than the ILD-negative group (HR, 1.94; 95% CI, 1.41-2.67), even after adjustment for confounders.

SSc-ILD progression in incident and prevalent groups

ILD progression was analysed in 7337 follow-ups of 2803 patients with SSc-ILD, including both incident and prevalent SSc-ILD cases for a median observation of 3.15 (1.52-6.42) years. Incident and prevalent cases were similarly observed, respectively for 3.03 (1.50-5.99) years and 3.18 (1.53-6.50) years. Overall, progression occurred in 25%, 35%, and 19% yearly follow-ups, respectively, according to the 3 abovementioned definitions. In comparison to the ILD prevalent group, the ILD incident group was associated with a decreased risk of ILD progression by definition B (*absolute FVC decline ≥5% or absolute DLCO decline ≥10% predicted*; OR, 0.85; 95% CI, 0.79-0.97; P = .02) and C (*relative FVC decline ≥10% predicted or 5-9% predicted with relative DLCO decline ≥15% predicted* − OR, 0.83; 95% CI, 0.69-0.98; P = .03), after adjustment for covariates. This association was not confirmed for definition A (*absolute FVC decline ≥5% predicted*—Fig 5).

DISCUSSION

Our EUSTAR study shows an incidence rate for new-onset SSc-ILD of 3.8 cases per 100 person-years and, to our knowledge, for the first time, a continuous detection of new onset of ILD up to 10 years from baseline visit. Additionally, we confirmed a negative impact on survival also for incident SSc-ILD compared with ILD-negative cases, in addition to the already known increased risk for prevalent ILD.

ILD incidence is not a rare event

Our incidence rate data are in line with recent results from national registries (2.0-4.4 per 100 person-years) [3,4,7,24,25,34]. Compared with these cohorts, our multicentre study included larger numbers and considered HRCT as the gold standard sole method to confirm both the presence and absence of ILD. In contrast, the previous studies identified new ILD [24,25], also based on other criteria, such as chest X-ray or 'velcro-like crackles' on physical examination. The high number of patients with SSc included in the EUSTAR cohort and the long follow-up allowed us to perform sensitivity analyses, show new SSc-ILD cases up to 10 years after baseline and to determine the independence of this phenomenon with respect to disease duration.

Risk factors of incident ILD

Our study identified risk factors of incident ILD both at 1-year follow-up and overall, long-term observation, confirming predictors such as DLCO% [21,22,35], older age [21,22], ATA or ACA positivity [21,22,25], haemoglobin [10], and increased inflammatory markers [36]. Some risk factors were identified only in one of the two prediction analyses, such as ARA reducing the risk of 1-year ILD incidence and of anti-PM/Scl antibody increasing the risk of SSc-ILD onset ever. In fact, ARA has been

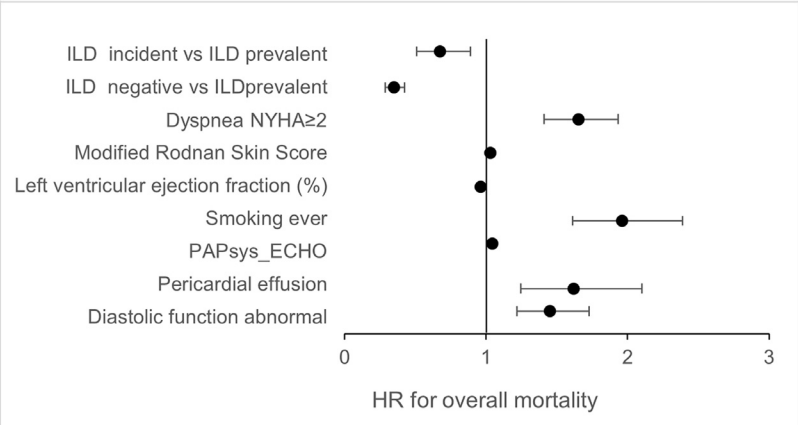

Figure 4. Prediction model of mortality in patients with SSc according to ILD status. ILD, interstitial lung disease; NYHA, New York Heart Association functional class; OR, odds ratio; PAPsys_ECHO, systolic pulmonary artery pressure estimated on echocardiogram; SSc, systemic sclerosis.

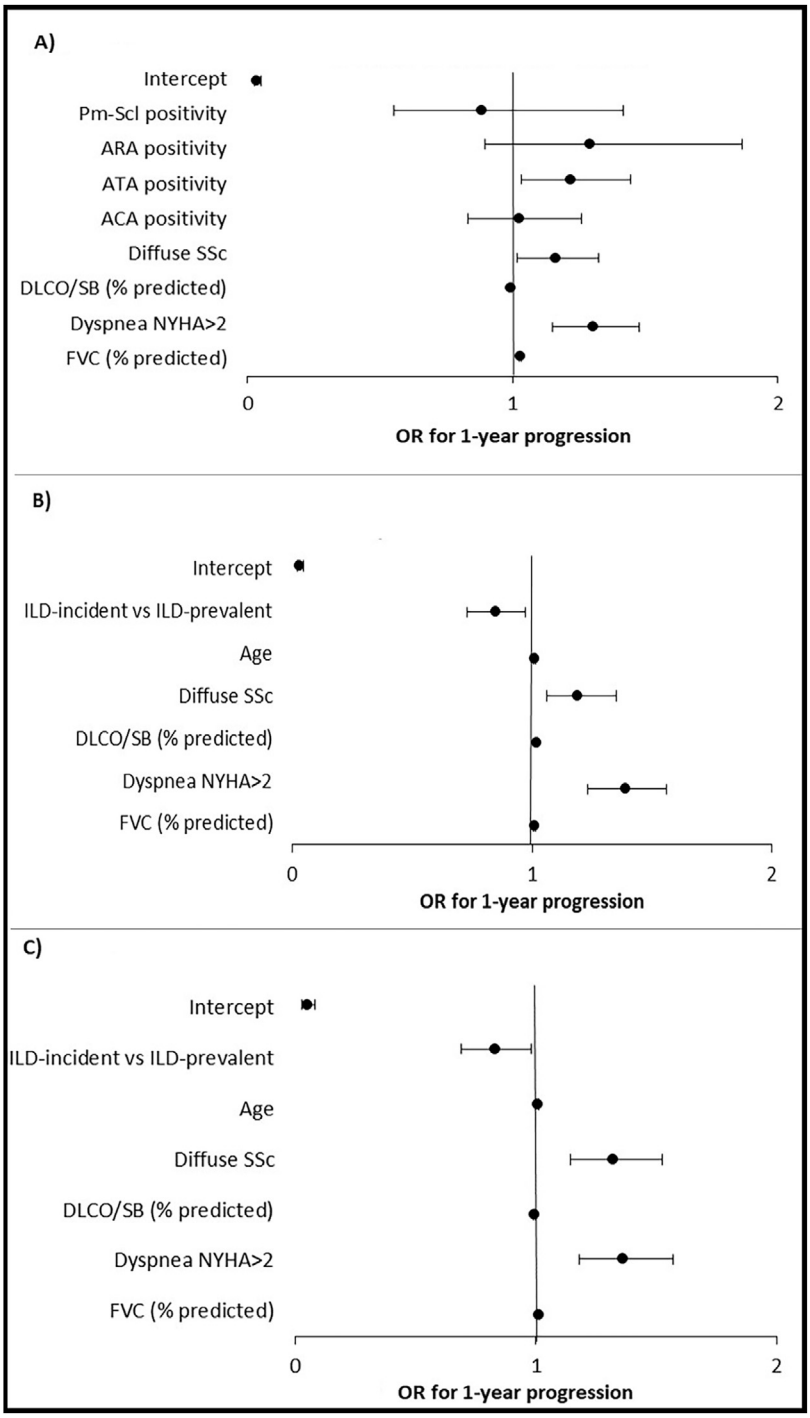

Figure 5. Prediction models of SSc-ILD progression according to definition A (*absolute FVC decline ≥5% predicted*), definition B (*absolute FVC decline ≥5% or absolute DLCO decline ≥10% predicted*), and (C) (*relative FVC decline ≥10% predicted or 5-9% predicted with relative DLCO decline ≥15% predicted*), over 12±3 mo intervals. ACA, anticentromere antibodies; ARA, anti-RNA polymerase III antibodies; ATA, anti-topoisomerase antibodies; DLCO/SB, carbon monoxide diffusing capacity; FVC, forced vital capacity; ILD, interstitial lung disease; NYHA, New York Heart Association; PM/Scl, anti-PM/Scl antibodies; SSc, systemic sclerosis; TLC, total lung capacity.

previously associated with the hazard of clinically significant pulmonary fibrosis that peaked in the first 3 years, whereas this hazard was increased after the first decade in patients with anti-PM/Scl-positive SSc [37]. Interestingly, arthritis ever was associated with lower ILD incidence: this might be related to the coexistence in the model of increased inflammatory biomarkers (potentially representing an active musculoskeletal disease status), as well as to the disease-modifying drugs these patients might have received for the very same complication, for which we cannot exclude a potential protective effect.

Once validated, the prediction models derived from our data would define the patient phenotype at higher risk of incident ILD. Practically, this would represent the phenotype of patients who could benefit from a more intensive observation and rescreening, In fact, our analysis also indirectly supports the rescreening for ILD in patients with an initially negative HRCT, as we observed patients undergoing more frequent HRCTs were detected with new-onset ILD almost 1 year earlier. This is an advance in the *window of opportunity* for the treatment of SSc-ILD, to possibly start treating earlier, as well as the basis for an enrichment cohort for preventive trials, in which pharmacologic and nonpharmacologic interventions might be tested.

Progression and prognosis of incident vs prevalent ILD

Early progression of ILD based on PFTs is associated with an increased risk of mortality in both clinical trials [38] and observational studies [10,30], which highlights the importance of

early detection and treatment of SSc-ILD. In our cohort, we could detect a variable incidence of ILD functional progression in line with previous EUSTAR data [28]. Importantly, we observed a significantly lower risk of progression in patients with incident ILD, compared with prevalent ILD, within a comparable follow-up observation. This might be partially explained by the lower ILD extent on HRCT [39] and previous immunosuppressive treatment for organ involvement [25]. Regarding prognosis, our results indicate an increased mortality risk even for incident SSc-ILD, despite mild functional impairment at baseline compared with prevalent ILD cases. Although this difference might also be explained by a milder ILD extent [40], we could not confirm this due to the high amount of missing data in the visual quantification of ILD extent in the EUSTAR database. Additionally, we hypothesise that the new detection of incident ILD could be associated with a prompt initiation of immunosuppressive therapy, which would be theoretically less delayed compared with prevalent ILD cases, in which the baseline detection of ILD determines the impossibility to date its onset.

Limitations of our analysis

Limitations of our study are derived from its observational nature, including decentralised reading of HRCT images. Additionally, our population presented with long disease duration [21]. However, this possible bias was neutralised by the sensitivity analysis, showing comparable incidence rates in cases with disease duration <5 years. In addition, not all patients with ILD-negative baseline underwent a follow-up HRCT, which might determine a selection bias and overestimate the incidence rate of SSc-ILD, as only more severe cases could have been referred to additional HRCTs. To control for this selection bias, we performed a subanalysis focusing on patients followed up more tightly, which did not show a meaningfully higher incidence. However, HRCT represents the current gold standard for the detection of SSc-ILD and, therefore, has face validity supporting our decision. Despite a possible slight overestimation, the data still show that ILD has an impact on survival, making its application very relevant. Another potential limitation was using the exposure to immunosuppressant as a composite group, without specification of the compound, intermittent exposure, or total duration of treatment. This decision was based on the different availability of medications across centres, as well as on the large time span of the patients recorded in the EUSTAR registry, going over almost 20 years, which determines profound changes in availability and prescriptions. Additionally, data about exposure to immunosuppressants were present in less than half of the study population and not balanced within the groups, also determining a certain risk of bias. Although Hoa et al [25] showed the protective role of mycophenolate mofetil on SSc-ILD development, larger size, prospective studies, using dedicated matching methods to balance risk factors, are needed to evaluate the potential role of immunosuppressive drugs and other categories of medications on the primary prevention of SSc-ILD. It is also important to point out that our progression analysis was limited to definitions based on PFTs deterioration [28–30], and did not include the recent complex definition of progressive pulmonary fibrosis [29,41,42], due to the lack of detailed information on the worsening of clinical symptoms and radiological progression in the EUSTAR dataset. However, not all these multidomains definitions have been specifically validated for SSc-ILD [29].

In conclusion, our study showed that new-onset ILD can appear at any time after SSc diagnosis, with stable numerical incidence during the disease course, after a negative baseline HRCT. We have identified a clinical phenotype of patients with SSc at risk of developing new ILD, which would be a candidate for an intensified screening approach following a negative baseline HRCT, which could be feasible using noninvasive and validated screening tools [43], as well as a hypothetical target population for preventive medicine approaches. In fact, even though incident ILD might represent a milder phenotype of pulmonary involvement, at lower risk of functional progression in comparison to SSc-ILD detected at the first presentation, it still has a relevant impact on patient survival.

Competing interests

LP has received research grant from the Swiss National Research Foundation/Scholars at risk. ME has received for the last 3 years grant/research support from Pfizer, Novartis Foundation for Bio-Medical Research, Iten Kohaut foundation, Kurt und Senta Herrmann foundation, Foundation for research in Rheumatology (FOREUM), University Zurich, Walter and Gertrud Siegenthaler Foundation and Theodor und Ida Herzog-Egli – Stiftung. Congress Support from Astrazeneca and Janssen. RD has received for the last 3 years grant/research support from Iten Kohaut, Walter und Gertrud Siegenthaler Fellowship; congress/workshop participation support: Amgen, Otsuka. CM is consultant for Janssen Cilag AG and Boehringer Ingelheim, speakers bureau for Boehringer Ingelheim, Medbase, Mepha, MED Talks Switzerland, Novartis and PlayToKnow AG, and has received travel support for congress from Boehringer Ingelheim. SM has received congress participation support from AstraZeneca. EH is on speakers bureau of Johnson & Johnson, GlaxoSmithKline, Astra Zeneca; research funding from CSL Behring, GlaxoSmithKline, Johnson & Johnson, Pfizer; consultant of Bayer, Boehringer Ingelheim, GlaxoSmithKline, Astra Zeneca; Johnson & Johnson, Sanofi Genzyme, Novartis, Grant/research support from GlaxoSmithKline, Roche-Chugai, Sanofi Genzyme, Sobi, Novartis. PEC is on speakers bureau: (last 5 years) of Janssen Lilly VivaCell Emerald Health Pharmaceuticals Gesynta Pharma Boehringer Ingelheim Abbie Sanofi Genzyme Mitsubishi Tanabe Consultant of: (last 5 years): Janssen, Lilly, VivaCell, Emerald Health Pharmaceuticals, Gesynta Pharma, Boehringer Ingelheim, AbbVie, Sanofi, Genzyme, and Mitsubishi Tanabe. IC is on speakers bureau (last 5 years) of Janssen, Kern Pharma, BMS, Roche, Boehringer Ingelheim, Sanofi Genzyme, and Gebro; is a consultant of (last 5 years) Janssen, Boehringer Ingelheim, Kern, Novartis, Innovaderm, GSK. ABG received support from AbbVie, Novartis, Boehringer Ingilheim, Pfizer, Sanofi, Astra Zeneca, Genetec, and Elli Lily, in the last 5 years. PA is on speakers bureau of Bristol Myers Squibb, Bohringer Ingelheim; received grant/research support from Bristol Myers Squibb, Bohringer Ingelheim; Roche; Novartis; CSL Behring; Janssen- Cilag: CSL Vifor, Gruppo Italiano Lotta alla Sclerodermia (GILS), European Scleroderma Trials and Research Group (EUSTAR). YA: is a consultant of AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Mylan, Janssen, Medsenic, and Prometheus; grant/research support from Alpine Immunosciences Medsenic and Corvus. GR is a consultant of Boehringer Ingelheim. Janssen; grants from Sanofi; speaker fees from AbbVie, Janssen, Boehringer Ingelheim, Galapagos, Roche, MSD, and Novartis; all outside the submitted study. KS is an Honorary Adjunct International Professor of Apollo Hospitals Educational and Research Foundation (AHERF). MCV received research grants from Boehringer Ingelheim, Ferrer, Galapagos and Janssen Pharmaceutical

Companies of Johnson & Johnson; received consulting fees from Boehringer Ingelheim and Janssen Pharmaceutical Companies of Johnson & Johnson; received speaker fees from Boehringer Ingelheim, Bristol Myers Squibb, GSK, Janssen Pharmaceutical Companies of Johnson & Johnson, MSD, Novartis, and Roche; served as a data safety monitoring board member at Corbus; and is treasurer of EUSTAR and steering committee member of the ERN ReCONNET. JdV-B is on speakers bureau of AbbVie, Janssen, Boehringer-Ingerlheim, consultant of: ABBvie, Janssen, Boehringer- Ingerlheim, grant/research support from: Janssen Cilag, Galapagos, and Roche. A-MH-V has received fees as speaker for Boehringer Ingelheim, Janssen, Medscape, Merck Sharp & Dohme, Novartis and Roche; consultant for AbbVie, ARXX, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, Janssen, Medscape, Merck Sharp & Dohme, Pliant Therapeutics, Roche and Werfen; research grant from Boehringer Ingelheim, Janssen. EULAR study group leader on the lung in rheumatic and musculoskeletal diseases, CTD-ILD ERS/EULAR convenor. MM-C is on speakers bureau of Actelion, Janssen, Inventiva, Bayer, Biogen, Boehringer CSL, Behring, Corbus, Galapagos, Mitsubishi, Samsung, Regeneron, Acceleron, MSD, Chemomab, Lilly, Pfizer, and Roche; consultant of Actelion, Astra Zeneca, Janssen, Inventiva, Bayer, Biogen, Boehringer CSL, Behring, Corbus, Argenx, Galapagos, Mitsubishi, Samsung, Regeneron, Acceleron, MSD, Chemomab, Lilly, Pfizer, and Roche. OD has/had consultancy relationships 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 3 calendar years: 4P-Pharma, AbbVie, Acceleron, Acepodia Biotech, Aera, Alcimed, Altavant, Amgen, AnaMar, Anaveon AG, Argenx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Calluna (Arxx), Cantargia AB, Catalyze Capital, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, Horizon, Janssen, Kymera, Lupin, Medscape, MSD Merck, Miltenyi Biotec, Mitsubishi Tanabe, Nkarta Inc., Novartis, Orion, Pilan, Prometheus, Quell, Redxpharma, Roivant, EMD Serono, Topadur and UCB. Patent issued "mir-29 for the treatment of systemic sclerosis" (US8247389, EP2331143). Cofounder of CITUS AG. Research grants: BI, Kymera, Mitsubishi Tanabe, UCB. CBruni received consulting fees for Boehringer Ingelheim. Research grants from Gruppo Italiano Lotta alla Sclerodermia (GILS), Scleroderma Clinical Trials Consortium (SCTC), EMDO Foundation, Novartis Foundation for medical-biological research. Congress participation support from Boehringer Ingelheim. All other authors have no conflicts of interest to disclose.

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Contributors

CBruni, LT, and OD made substantial contributions to conception and design of the study. LP, AV, RD, MOB, CM, SM, ME, SJ, EH, UM-L, ES, YA, GR, CBergmann, RB, KS, BA, IS, BS, JD, PEC, GC, EH, IC, AB-G, PA, IL, LAS, MCV, JdV-B, A-MH-V, MM-C, OD, and CBruni contributed substantially to data acquisition. All authors contributed substantially to data analysis and interpretation, drafted the article or revised it critically for important intellectual content, and approved the final manuscript for publication.

Patient consent for publication

Patients were not actively involved in this study; we thank all of them for their research contribution to the whole EUSTAR database.

Ethics approval

The EUSTAR registry protocol was reviewed and approved by the local committee of each centre. Written informed consent was obtained from all participants. The study was approved by the EUSTAR board (number CP 133) and conducted according to the Declaration of Helsinki.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Anonymised data might be available from OD at the Department of Rheumatology, University Hospital Zurich, University of Zurich, Switzerland on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.12.008.

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