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Clinical science

Systemic sclerosis-associated interstitial lung disease in the EUSTAR database: analysis by region

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Abstract

Objectives: The prevalence and characteristics of SSc-associated interstitial lung disease (SSc-ILD) vary between geographical regions worldwide. The objectives of this study were to explore the differences in terms of prevalence, phenotype, treatment and prognosis in patients with SSc-ILD from predetermined geographical regions in the EUSTAR database.

Material and methods: Patients were clustered into seven geographical regions. Clinical characteristics and survival of patients with SSc-ILD were compared among these pre-determined regions.

Results: For baseline analyses, 9260 SSc patients were included, with 6732 for survival analyses. The prevalence of SSc-ILD in the overall population was 50.2%, ranging from 44.0% in 'Western Europe and Nordic countries' to 67.5% in 'Eastern European, Russia and Baltic countries'. In all regions, anti-topoisomerase antibodies were associated with SSc-ILD. Management also significantly differed; mycophenolate mofetil was prescribed at baseline in 31.6% of patients with SSc-ILD in 'America (North and South)' and 31.7% in 'Middle East' but only 4.3% in 'Asia and Oceania' ($P < 0.0001$). Patients from 'America (North and South)' and 'Middle East' had the highest survival rate at the end of follow-up (85.8% and 85.2%, respectively).

Conclusions: Our study highlights key differences among regions in terms of clinical presentation and prognosis of SSc-ILD. This work also demonstrates that the management of SSc-ILD is highly variable among the different regions considered, suggesting that efforts are still needed for the standardization of medical practice in the treatment of this disease.

Keywords: interstitial lung disease, lung fibrosis, scleroderma, SSc, autoantibodies

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Rheumatology key messages

- This worldwide study of >9000 patients reveals key differences in phenotype and prognosis of SSc-ILD.
- The management of SSc-ILD is highly variable among the seven regions considered.
- Efforts are still needed for the standardization of medical practice in the treatment of SSc-ILD.

Introduction

SSc is a chronic autoimmune disease characterized by vascular dysfunction and fibrosis of the skin and internal organs [1]. Autoimmunity in SSc includes the positivity for antinuclear antibodies with different mutually exclusive specificity, such as anti-centromere, or anti-topoisomerase (also called anti-Scl70) antibodies [2]. SSc is the rheumatic disease with the highest individual mortality; interstitial lung disease (ILD) is among the leading SSc-related causes of death [1, 3]. The prevalence of SSc-ILD and the extent of lung damage vary according to the different national registries and databases, suggesting that geographical variations may exist regarding SSc-ILD phenotypes [4, 5]. Moreover, variations in the management of SSc-ILD among different regions may also influence prognosis.

Among risk markers, autoantibodies may have a reproducible prognostic value and could be useful to stratify patients in practice or research evaluating SSc-ILD [6]. American registries have shown that patients with anti-topoisomerase antibodies had more severe pulmonary decline than patients with other specificities [7]. Nonetheless, in the SENSCIS study, a large worldwide randomized controlled trial evaluating the efficacy of nintedanib in SSc-ILD, the predictive value of anti-topoisomerase antibodies was not demonstrated [6]. This result may suggest that the predictive value of autoantibodies may, therefore, vary across geographical regions [8].

Heterogeneity in SSc is of utmost importance and is a challenge for clinical practice and trial design. As SSc is a rare disorder, international studies are needed to obtain a sufficient sample size. To date, there is no study comparing the prevalence and clinical presentation of SSc-ILD among different regions worldwide within the same database. The European Scleroderma Trials and Research (EUSTAR) group database is a multicentric international SSc database that offers the unique opportunity of exploring SSc-ILD at a worldwide scale, notably as patients from Asia and America are now included in this European initiative [9, 10]. Therefore, the objectives of this study were to explore the prevalence, clinical phenotype, management and prognosis of patients with SSc-ILD in different predetermined geographical regions based on the prospective EUSTAR database.

Patients and methods

Patient population and characteristics

Patients aged ≥18 years enrolled since January 2009 in the EUSTAR database and fulfilling the ACR/EULAR classification criteria were included [11, 12]. The local ethics committee of each EUSTAR centre (complete list provided in the supplementary data available at *Rheumatology* online) specifically approved this cohort study, which complies with the Declaration of Helsinki. Informed written consent was provided by all participants. The data set was extracted from the database on 1 December 2020. Patients were classified as having diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc according to LeRoy classification [13]. The structure of the EUSTAR database, the nature of collected data and definitions of clinical variables have been described previously [14, 15]. Disease duration since SSc onset was defined based on the first non-Raynaud's phenomenon (RP) symptom. The first visit recorded in EUSTAR was considered as the baseline visit. For longitudinal analyses, only patients with a baseline visit and at least one follow-up visit including survival status were included. Overall mortality during follow-up was considered for survival analyses since the detailed cause of death and ILD-specific mortality were not available in the EUSTAR database. All appropriate items within the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were applied [16, 17].

SSc-ILD definition

ILD was attested by the presence of signs of ILD on high-resolution CT (HRCT) and/or X-rays, or when a date for a diagnosis of ILD was notified by the evaluator any time during the study. Pulmonary function tests (PFT) were conducted in the different centres in accordance with European Respiratory Society guidelines [18, 19]. Extent of lung fibrosis on HRCT was not included due to missing data and the absence of centralized assessment of HRCT.

Predefined geographical regions

EUSTAR inclusion centres were located within 36 different countries that were clustered into seven predefined geographical regions: 'Southern Europe', 'Western Europe and Nordic countries', 'Eastern Europe, Russia and Baltic countries', 'Central Europe', 'Middle East', 'America (North and South)' and 'Asia and Oceania'. These regions were defined prior to any analyses. The definition of these regions was adapted from a previous study evaluating the risks of rheumatic diseases in first- and second-generation immigrants in Europe, and updated based on more recent data [20, 21].

Statistical analysis

Quantitative variables are presented as mean (S.D.) and qualitative variables as N (%). Univariable associations of baseline qualitative characteristics with SSc-ILD, and overall differences between regions for qualitative parameters, were assessed using the Pearson χ^2 test. Quantitative parameters were compared using the Mann–Whitney *U* test. Multiple pairwise comparisons between regions were adjusted using Bonferroni correction. Survival analyses were conducted using the log-rank test, and censored 20 years after SSc onset; no specific adjustment for multiple testing was performed for these analyses. As antibody status may predict the course of SSc-ILD and associated survival, we stratified survival analysis based on antibody status. Only patients with known antibody status

were included in this survival analysis. As this was an observational explorative study, no power or sample size calculations were performed. A *P*-value of $P < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics Version 24.

Results

Patient population

Within the EUSTAR database, 9260 patients fulfilled inclusion criteria and had data regarding ILD status. Among them, 6732 patients had at least one follow-up visit (Fig. 1 and Supplementary Table S1, available at *Rheumatology* online). In comparison with patients without data regarding SSc-ILD status ($n = 1289$), patients with data had more severe disease, most notably when considering baseline dcSSc prevalence (30.1% *vs* 24.4% in patients with data regarding ILD in comparison with patients without) (Supplementary Table S2, available at *Rheumatology* online). Among patients with data regarding ILD status, 4648 patients had SSc-ILD (50.2%) (Supplementary Table S3, available at *Rheumatology* online).

ILD prevalence and associated characteristics in the seven predetermined geographical regions

The numbers of patients with SSc-ILD in all regions and countries are detailed in Table 1. The region with the lowest prevalence of SSc-ILD was 'Western Europe and Nordic countries' (prevalence of 44.0%) and the highest prevalence of SSc-ILD was in the region 'Eastern Europe, Russia and Baltic countries' (prevalence of 67.5%) (Table 1 and Supplementary Table S3, available at *Rheumatology* online).

The distribution of all considered parameters showed significant overall variation among the seven geographical regions (Table 2). In terms of demographic characteristics, patients from 'Asia and Oceania' had the youngest mean age [51.1 years old (15.1)]. The prevalence of males was highly variable, ranging from 28.1% in 'Western Europe and Nordic countries' to 12.0% in 'America (North and South)' ($P < 0.0001$).

Regarding disease characteristics at baseline (Table 2), patients from 'Asia and Oceania' had a shorter disease duration since first non-RP symptom [6.0 years (7.0)], and mean disease duration significantly differed from that of patients from all other regions ($P < 0.0001$) except for 'Eastern Europe, Russia and Baltic countries' and 'Western Europe and Nordic countries'. The prevalence of dcSSc was highest in 'America (North and South)' (53.1%) and lowest in 'Southern Europe' (40%) ($P < 0.0001$). Other major phenotypic differences concerned muscle weakness, ranging from 4.4% ('Asia and Oceania') to 38.8% ('Eastern Europe, Russia and Baltic countries'), or joint synovitis, ranging from 8.7% ('Asia and Oceania') to 28.1% ('Middle East').

The prevalence of autoantibodies also reflected this phenotypic heterogeneity. When considering the entire population ($n = 4648$ patients with SSc-ILD) regardless of the geographical location of the centre, the overall prevalence of anti-topoisomerase antibodies was 50.6%. This prevalence ranged from 26.9% in 'America North and South' to 63.0% in 'Middle East' ($P < 0.0001$) (Table 2). Nonetheless, in all regions, the presence of anti-topoisomerase antibodies was significantly more frequent in patients with SSc-ILD in comparison with patients without (Supplementary Table S3, available at *Rheumatology* online). Similarly, although the prevalence of anti-centromere antibodies was highly variable (from 12.3% in 'Asia and Oceania' to 26.6% in 'Southern Europe') (Table 2), they corresponded with lower risk of ILD in all regions (Supplementary Table S3, available at *Rheumatology* online).

In terms of PFTs, the region with the lowest mean forced vital capacity (FVC) percent predicted (%pred) at baseline was 'America (North and South)' [73.2 (21.8)], whereas the mean baseline FVC was highest in 'Southern Europe' [90.8 (21.7)] ($P < 0.0001$). In all regions, baseline FVC (%pred) was significantly lower in patients with SSc-ILD than in patients without (Supplementary Table S3, available at *Rheumatology* online). Mean diffusing capacity of the lungs for carbon

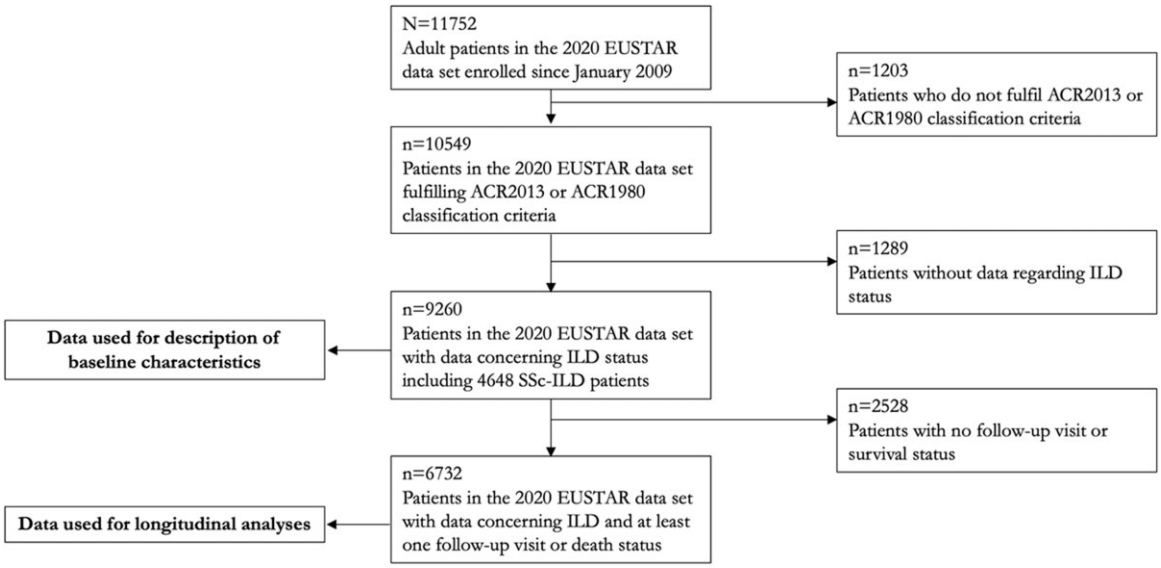

Figure 1. Flow chart. ILD: interstitial lung disease; SSc-ILD: SSc-associated interstitial lung disease

Table 1. Geographical regions, country selection and SSc-ILD patients from the EUSTAR database

Geographical region *n* (%)[a]	Countries	Patients with SSc-ILD, *n* (%)[b]	ILD prevalence in SSc patients in this region, (%)[c]
Southern Europe, *n* = 1416 (30.5), patients with ILD	Italy	1110 (78.4)	48.6
	Spain	209 (14.8)	
	Portugal	29 (2.0)	
	Greece	66 (4.7)	
	Malta	2 (0.1)	
Western Europe and Nordic countries, *n* = 1693 (36.4), patients with ILD	Germany	673 (39.8)	44.0
	France	329 (19.4)	
	Switzerland	296 (17.5)	
	United Kingdom	128 (7.6)	
	Belgium	110 (6.5)	
	Netherlands	108 (6.4)	
	Norway	21 (1.2)	
	Denmark	15 (0.9)	
	Ireland	10 (0.6)	
	Austria	3 (0.2)	
Eastern Europe, Russia and Baltic countries, *n* = 388 (8.3), patients with ILD	Romania	267 (68.8)	67.5
	Russia	93 (24.0)	
	Lithuania	17 (4.4)	
	Republic of Moldova	6 (1.5)	
	Estonia	5 (1.3)	
Central Europe, *n* = 482 (10.4), patients with ILD	Poland	177 (36.7)	64.1
	Hungary	153 (31.7)	
	Croatia	73 (15.1)	
	Czech Republic	46 (9.5)	
	Serbia	33 (6.8)	
Middle East, *n* = 284 (6.1), patients with ILD	Turkey	122 (43.0)	58.3
	Israel	116 (40.8)	
	Egypt	26 (9.2)	
	Iran	20 (7.0)	
America (North and South), *n* = 175 (3.8), patients with ILD	USA	62 (35.4)	52.1
	Brazil	41 (23.4)	
	Dominican Republic	36 (20.6)	
	Argentina	36 (20.6)	
Asia and Oceania, *n* = 210 (4.5), patients with ILD	China	132 (62.9)	60.9
	Japan	51 (24.3)	
	New Zealand	27 (12.9)	

[a] Represents the % among all SSc-ILD patients included at baseline (*n* = 4648).
[b] Represents the % of SSc-ILD patients from the country within the region considered.
[c] Represents the % of SSc patients with SSc-ILD among the SSc patients from the region considered (detailed in Supplementary Table S3, available at *Rheumatology* online).
ILD: interstitial lung disease; SSc: systemic sclerosis; SSc-ILD: systemic-sclerosis-associated interstitial lung disease.

monoxide (%pred) was severely impaired in all regions with the lowest mean value in 'Eastern Europe, Russia and Baltic countries' [56.0 (18.0)].

Immunomodulatory therapies in the seven predetermined geographical regions

Management at baseline was also significantly different depending on the region. Immunomodulatory therapies were prescribed at baseline in 61.0% of the patients when considering the entire population (*n* = 4648 patients with SSc-ILD), with large variations (from 18.6% in 'Asia and Oceania' to 79.9% in 'Middle East'). In all regions, mycophenolate mofetil (MMF) was more frequently prescribed in patients with SSc-ILD than in patients without, except in 'Asia and Oceania' (Supplementary Table S3, available at *Rheumatology* online). 'Middle East' and 'America (North and South)' had the highest rates of MMF use (31.7% and 31.6%, respectively). This baseline prescription of MMF in 'America (North and South)' and 'Middle East' was significantly greater in comparison with each region taken separately ($P < 0.01$ after Bonferroni correction) except for 'Southern Europe', where the prevalence was numerically lower (24.9%) but without reaching statistical significance after Bonferroni correction ($P > 1.000$). The lowest rate of MMF use at baseline was in 'Asia and Oceania' (4.3%).

Impact of ILD on survival and overall survival in patients with SSc-ILD across the seven predetermined geographical regions

Patients with SSc-ILD had significantly lower rates of survival than patients without in all regions ($P < 0.05$), except in 'America (North and South)' and 'Middle East' ($P = 0.559$ and $P = 0.997$, respectively) (Fig. 2). This difference did not reach statistical significance in 'Eastern Europe, Russia and Baltic countries' ($P = 0.077$), although a trend was observed (Fig. 2). Similarly, patients from 'Middle East' and 'America (North and South)' had the highest survival rate at the end of the follow-up (85.2% and 85.8%, respectively) (Fig. 3). 'Asia and Oceania' had the lowest survival rate (66.2%), and survival in this region tended to be lower than in other regions [$P < 0.05$ in comparison with 'America

Table 2. Baseline characteristics of 4648 patients with SSc-ILD in the different predetermined geographical regions

	Data available (*n*/4648)	Total	Southern Europe	Western Europe and Nordic countries	Eastern Europe, Russia and Baltic countries	Central Europe	Middle East	America (North and South)	Asia and Oceania	Overall *P*-value[c]
Characteristics										
N	4648	4648	1416	1693	388	482	284	175	210	—
Age at baseline (year, mean) (S.D.)	4648	56.6 (13.3)	57.9 (13.8)	57.8 (13.0)	54.2 (11.7)	56.9 (11.7)	51.9 (12.9)	52.0 (13.5)	51.1 (15.1)	<0.0001
Male gender (%)	4648	903 (19.4)	189 (13.3)	475 (28.1)	65 (16.8)	74 (15.4)	50 (17.6)	21 (12.0)	29 (13.8)	<0.0001
HRCT available (%)	4648	4309 (92.7)	1390 (98.2)	1560 (92.1)	341 (87.9)	371 (77.0)	279 (96.2)	164 (93.7)	204 (97.1)	<0.0001
Disease duration since first non-RP symptom (year, mean) (S.D.)	3935	7.7 (8.0)	7.7 (7.9)	7.4 (8.5)	7.3 (7.8)	8.8 (7.7)	8.9 (7.4)	8.7 (7.4)	6.0 (7.0)	<0.0001
Age at first non-RP symptom (year, mean) (S.D.)	3958	48.8 (14.0)	49.9 (14.2)	50.3 (13.9)	46.6 (12.0)	48.8 (13.2)	42.6 (12.7)	43.4 (12.8)	44.7 (15.4)	<0.0001
dcSSc (%)	3857	1630 (42.2)	441 (40.0)	585 (41.3)	163 (48.8)	159 (45.8)	115 (46.9)	86 (53.1)	81 (50.6)	<0.0001
mRSS (S.D.)	4115	10.3 (8.9)	9.3 (8.3)	9.6 (8.8)	11.4 (9.4)	12.7 (8.4)	13.5 (10.1)	12.9 (10.6)	9.2 (8.5)	<0.0001
Current DU (%)	2912	522 (17.9)	118 (13.7)	218 (18.8)	58 (22.9)	39 (13.8)	58 (26.1)	23 (31.1)	8 (14.0)	<0.0001
Joint synovitis (%)	4510	667 (14.8)	182 (13.2)	213 (13.1)	95 (25.0)	64 (13.5)	76 (28.1)	19 (11.4)	18 (8.7)	<0.0001
Tendon friction rubs (%)	4462	370 (8.3)	110 (8.0)	124 (7.7)	50 (13.4)	30 (6.4)	22 (8.2)	30 (17.7)	4 (2.0)	<0.0001
Muscle weakness (%)	4501	852 (18.9)	214 (15.5)	275 (17.0)	148 (38.8)	114 (24.1)	53 (19.5)	39 (23.3)	9 (4.4)	<0.0001
Oesophageal symptoms (%)	4574	2918 (63.8)	870 (62.7)	1016 (60.1)	270 (70.31)	314 (65.3)	226 (83.1)	113 (65.7)	109 (53.4)	<0.0001
Pulmonary hypertension (%)	3337	686 (20.6)	208 (19.5)	184 (16.0)	78 (25.6)	85 (25.9)	63 (29.9)	28 (21.4)	40 (27.4)	<0.0001
ACA+ (%)[a]	4344	994 (21.4)	379 (26.6)	323 (19.1)	72 (18.6)	105 (21.8)	55 (19.3)	34 (19.4)	26 (12.3)	<0.0001
ATA+ (%)[a]	4445	2354 (50.6)	702 (40.6)	846 (50.0)	243 (62.6)	244 (50.6)	179 (63.0)	47 (26.9)	93 (44.3)	<0.0001
Anti-RNA pol III (%)[a]	3255	262 (5.6)	57 (4.0)	136 (8.0)	6 (1.5)	23 (4.8)	20 (7.0)	10 (5.7)	10 (4.8)	<0.0001
Triple negative (%)	3546	1150 (32.4)	302 (26.7)	448 (32.6)	72 (30.0)	124 (35.1)	51 (28.7)	74 (54.0)	79 (59.8)	<0.0001
DLCO %pred (S.D.)	3570	61.7 (19.8)	65.7 (20.1)	59.5 (19.8)	56.0 (18.0)	62.6 (19.5)	61.5 (16.6)	58.1 (22.2)	59.8 (16.9)	<0.0001
FVC %pred (S.D.)	3833	86.7 (21.7)	90.8 (21.7)	87.3 (21.9)	82.8 (20.6)	87.4 (20.4)	76.9 (18.8)	73.2 (21.8)	81.6 (18.3)	<0.0001
TLC %pred (S.D.)	2739	85.5 (20.1)	85.5 (20.0)	86.5 (19.9)	79.5 (19.8)	89.7 (21.5)	76.8 (17.4)	79.5 (26.7)	85.1 (17.1)	<0.0001
Immunomodulatory therapies[b]	4648	2836 (61.0)	912 (64.4)	1051 (62.1)	269 (69.3)	235 (48.8)	227 (79.9)	103 (58.9)	39 (18.6)	<0.0001
MMF (%)	4638	928 (20.0)	353 (24.9)	327 (19.4)	52 (13.4)	42 (8.7)	90 (31.7)	55 (31.6)	9 (4.3)	<0.0001
MTX (%)	4634	639 (13.8)	127 (9.0)	314 (18.6)	81 (20.9)	47 (9.8)	40 (14.1)	27 (15.5)	3 (1.4)	<0.0001
Corticosteroids (%)	4637	1780 (38.4)	670 (47.4)	587 (34.8)	176 (45.4)	149 (30.9)	124 (43.7)	51 (29.3)	23 (11.0)	<0.0001
Cyclophosphamide (%)	4638	418 (9.0)	57 (4.0)	161 (9.5)	84 (21.6)	59 (12.2)	32 (11.3)	13 (7.5)	12 (5.7)	<0.0001

[a] % calculated based on the entire population and not on available data, as some identifications were not performed if a specificity was already identified.
[b] Immunomodulatory therapies are one or more among 'abatacept, Enbrel, golimumab, Humira, infliximab, Janus kinase inhibitor, rituximab, TNF-alpha antagonist, tocilizumab, other biologic therapy, azathioprine, ciclosporin A, cyclophosphamide, D-penicillamine, chloroquine/hydroxychloroquine, imatinib, leflunomide, MTX, MMF, prednisone, sulfasalazine'.
[c] *P*-values given here are the *P*-value from overall test before *post hoc* pairwise comparisons; a *P*-value <0.05 reflects a significantly overall inhomogeneous repartition of the considered parameter among the different regions. Main relevant pairwise comparisons with *P*-value adjusted for multiple comparisons are provided in the text of the manuscript. anti-RNA pol III: anti-RNA polymerase III antibodies; ATA: anti-topoisomerase antibodies; dcSSc: diffuse cutaneous SSc; DLCO: diffusing capacity of the lung for carbon monoxide; DU: digital ulcers; FVC: forced vital capacity; HRCT: high-resolution CT; ILD: interstitial lung disease; mRSS: modified Rodnan Skin Score; RNA: ribonucleic acid; SSc-ILD: SSc associated interstitial lung disease; TLC: total lung capacity.

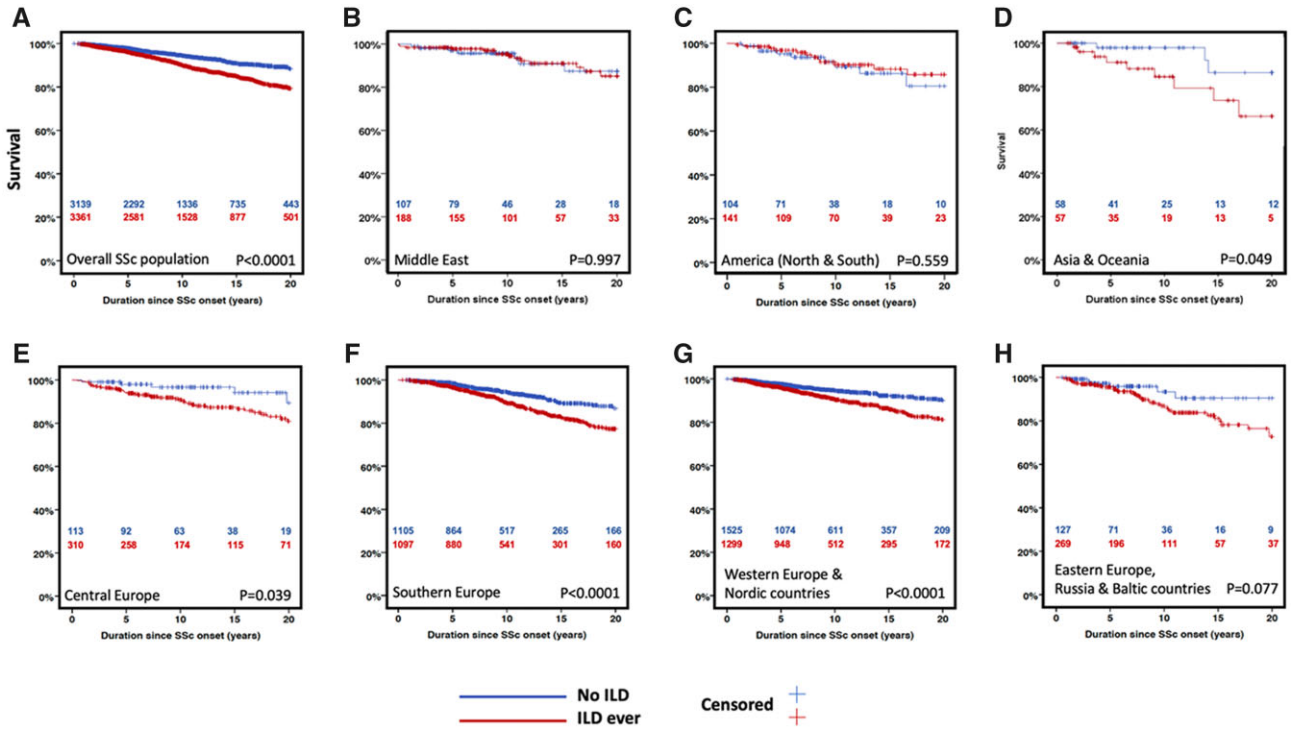

Figure 2. Overall survival with stratification by ILD status in the overall population (**A**); Middle-East (**B**); America (North and South) (**C**); Asia and Oceania (**D**); Central Europe (**E**); Southern Europe (**F**); Western Europe and Nordic countries (**G**); and Eastern Europe, Russia and Baltic countries (**H**). ILD: interstitial lung disease

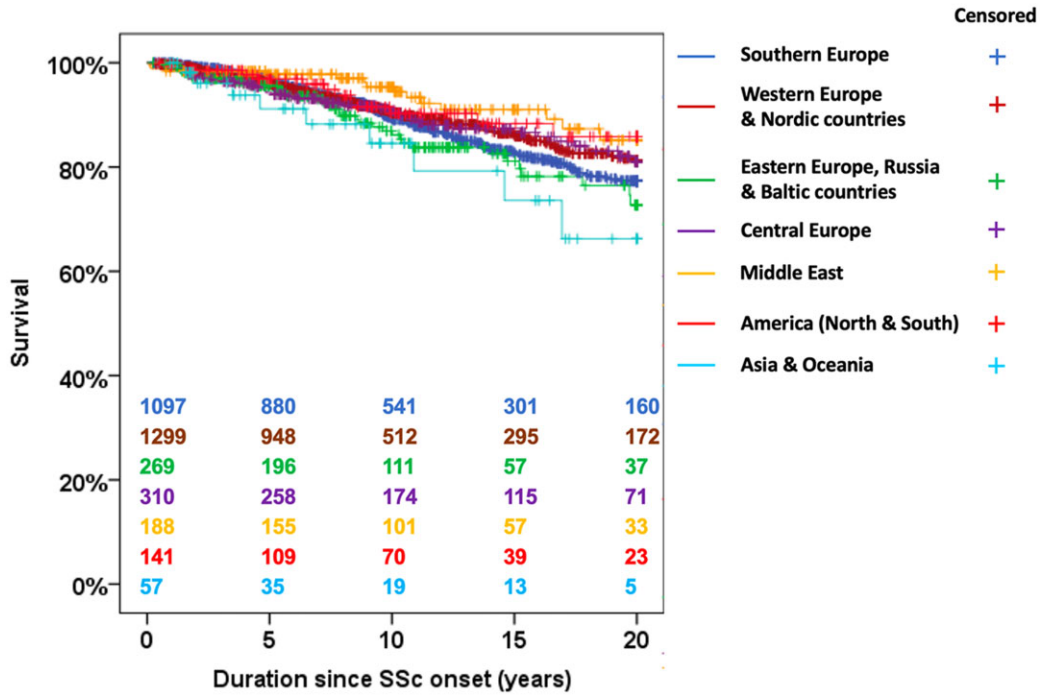

Figure 3. Overall survival in patients with SSc-ILD according to geographical regions. SSc-ILD: SSc-associated interstitial lung disease

(North and South)' and 'Middle East', $P < 0.200$ in all other regions except with 'Eastern Europe, Russia and Baltic countries' ($P = 0.445$)]. Follow-up durations per region are provided in Supplementary Table S4, available at *Rheumatology* online.

Impact of antibody status on overall survival in patients with SSc-ILD within the seven predetermined geographical regions

When considering antibody status as dichotomic variables, patients with anti-centromere antibodies had better survival

rates than patients negative for this antibody subtype in the overall SSc-ILD population ($P = 0.01$). Nonetheless, this difference was only observed in 'Southern Europe' when regions were considered separately ($P = 0.001$ in this region and $P > 0.100$ in all others), and the opposite trend was observed in 'Asia and Oceania' (Supplementary Fig. S1, available at *Rheumatology* online). In the overall SSc-ILD population, there was no difference in terms of survival between patients with and without anti-topoisomerase antibodies (Fig. 4). Nonetheless, when considering each region separately, anti-topoisomerase antibody status significantly discriminated survivors and non-survivors among SSc-ILD patients in 'America (North and South)' ($P = 0.001$ in this region and $P > 0.100$ in all others except 'Asia and Oceania'). The opposite trend was observed in 'Asia and Oceania' (Fig. 4). Patients with anti-RNA polymerase III antibodies tended to have lower survival rates in the overall SSc-ILD population, and this result reached statistical significance in 'Western Europe and Nordic counties' and 'Eastern Europe, Russia and Baltic countries' ($P = 0.026$ and $P = 0.027$, respectively). The opposite trend was observed in 'America (North and South)' (Supplementary Fig. S2, available at *Rheumatology* online).

When considered as separate variables with pairwise comparison, there was no difference in terms of survival among the populations defined by antibody status in the overall SSc-ILD population (Supplementary Fig. S3 and Supplementary Table S5, available at *Rheumatology* online). When considering each region separately, discrepancies were observed in the prognostic values of autoantibodies, as detailed in Supplementary Table S5, available at *Rheumatology* online.

Discussion

The objectives of this study were to explore the differences in terms of prevalence, clinical presentation, prognosis and treatment in patients with SSc-ILD from predetermined geographical regions in the EUSTAR database. Our study highlights the heterogeneity of survival and SSc-ILD prevalence, as its regional prevalence ranged from 44% to 67.5% of patients with SSc. This range is consistent with recent results from national registries and international reviews [4, 22].

Geographical discrepancies may reflect differences in health care organization, access to SSc centres, ILD screening strategies and early management of SSc (including treatments). Our work provides insight into the worldwide regional differences concerning the treatment of SSc-ILD, as about one-third of SSc-ILD patients in 'America (North and South)' and 'Middle East' used MMF at baseline, whereas this proportion fell to 4.3% in 'Asia and Oceania'. Such differences could be explained by discrepancies in terms of drug availability or drug validation by the regulatory agencies in these different regions. Organization of healthcare systems may also help to explain geographical disparities, notably including cost compensation system, health insurance policies and early access to expert centres [23].

Regarding phenotype, key risk factors for SSc-ILD onset such as positivity for anti-topoisomerase antibodies (anti-Scl70) were common to all regions when comparing patients with and without SSc-ILD in our study. By contrast, the prognostic values of autoantibodies in terms of survival varied across regions and could not be generalized worldwide based on our data. The heterogeneous predictive value of antibody subtypes in SSc-ILD depending on the region of interest suggests that their predictive value should be considered based on the geographical context [2, 8, 24, 25]. This result may explain the discrepancies between the American registries, where positivity for anti-topoisomerase antibodies (Scl70) was associated with worse prognosis, and the international SENSCIS trial, in which this result was not confirmed [6, 7]. This result may suggest that a double stratification on geographical region and autoantibody status could be useful for randomization in SSc-ILD randomized controlled trials. The variable performances of detection techniques for anti-topoisomerase

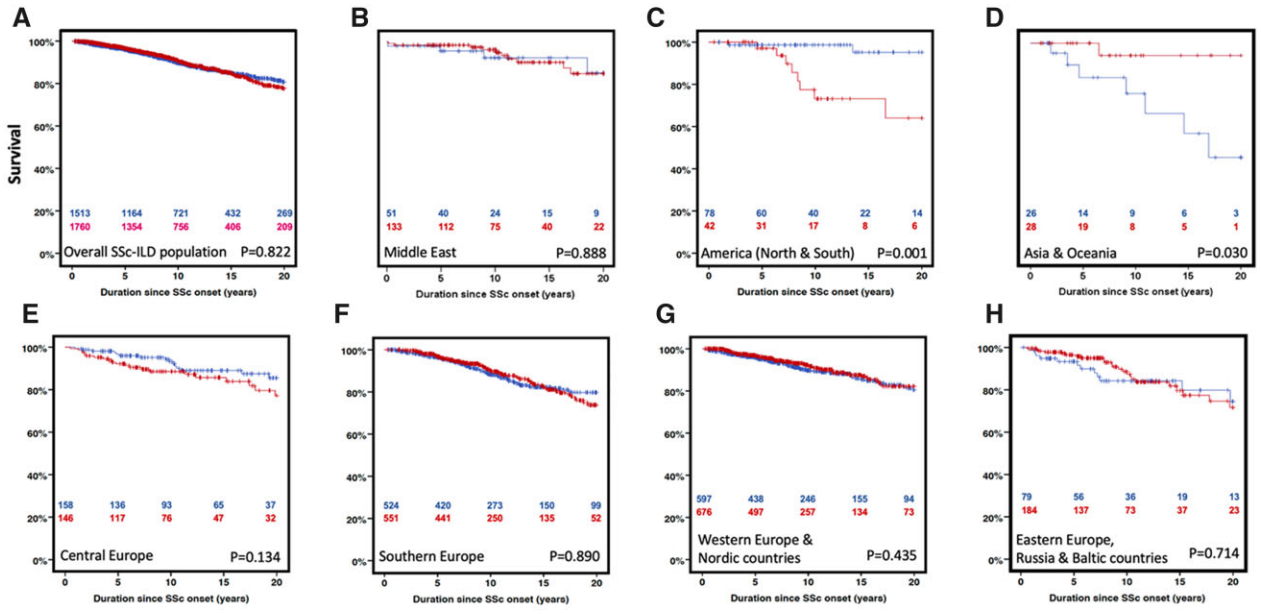

Figure 4. Overall survival of patients with SSc-ILD stratified by anti-topoisomerase antibody status in the overall population (**A**); Middle East (**B**), America (North and South) (**C**); Asia and Oceania (**D**); Central Europe (**E**); Southern Europe (**F**); Western Europe and Nordic countries (**G**); and Eastern Europe, Russia and Baltic countries (**H**). SSc-ILD: SSc-associated interstitial lung disease; TOPO: topoisomerase

antibodies that were available in the different regions may also contribute to these differences [26]. Antibody subtypes have been proposed as a relevant marker for a future sub-classification of SSc, beyond the skin-based classification of dcSSc *vs* limited cutaneous SSc [2]. Their variable prognostic value in SSc-ILD, as illustrated in our study, and the variable availability of the most specific detection techniques across different regions, may suggest that the relevance of such an antibody-based classification should be carefully validated in different regions worldwide before being fully endorsed.

Studies directly comparing patients from different countries have also underscored the variable severity of SSc among patients depending on their geographical origin. For example, review of the EUSTAR database revealed that Iranian patients with SSc more frequently had dcSSc and a lower FVC value than French patients [27]. Similarly, American patients had more severe phenotypes, with a higher prevalence of dcSSc than French patients [8]. In these studies, phenotypic differences were also associated with significant differences in the prevalence of antibody subtypes such as anti-centromere and anti-topoisomerase I antibodies. The prevalence of digital ulcers in multicentre studies also varies depending on the geographical origin [28].

The strengths of our study include its large sample size, its unique worldwide approach in SSc-ILD and its long-term follow-up. The careful evaluation of validated inclusion criteria of SSc by well-trained clinicians is also a strength in comparison with databases based on International Classification of Diseases-10 codes or other unrepresentative identification methods in nationwide databases [11, 12].

Our study has several limitations. We did not include genetic analyses in our results because these data were not available in the EUSTAR database. This could be considered as a limitation because geographical discrepancies may reflect the influence of genetic background on the clinical presentation and clinical trajectories of SSc-ILD patients [29–31]. Nonetheless, recent studies suggest that antibody subtypes could be surrogate markers of genetic differences in patients with SSc [32]. Within the same geographical region, race may also impact the phenotype and antibody subtypes of patients with SSc [33]. Black patients more frequently have SSc-ILD and a lower prevalence of anti-centromere antibodies as compared with white patients [9, 33, 34]. We did not include ethnicity in our study as this question was recently explored in EUSTAR, with a study showing that black patients had more severe disease when considering the prevalence of dcSSc compared with white patients and that the mortality rate was higher in Asian patients than in white patients [9]. Although this result is in accordance with our results on SSc-ILD in 'Asia and Oceania', there were no data regarding SSc-ILD prevalence or management in this previous EUSTAR study on ethnic differences, and beyond stratification on centres, only two geographical regions were explored (inside/outside Asia and inside/outside sub-Saharan Africa). Our study fills this gap. Differences in the specificity of autoantibodies may contribute to explaining the variable prevalence of visceral involvement such as SSc-ILD among ethnicities [31, 34, 35]. The severity of SSc-ILD may also be influenced by environmental exposures [36, 37] or socio-demographic factors, which may vary according to regions and/or ethnicities as suggested by recent analyses in African-American patients [38–40]. In our work, 10–15% of patients had SSc-ILD diagnosed by X-rays, and this could be considered as a limitation as HRCT is the reference standard for the diagnosis of ILD. Nonetheless, the majority of patients had available HRCT [>90% in all regions except in Eastern Europe, Russia and Baltic countries (87.9%) and Central Europe (77%)].

Another limitation is that the seven geographical regions delineated in our study could be considered arbitrary, although we based this repartition on previous publications and designed them prior to any analyses [20, 21]. Our results may have been different if the regions had been designed differently. The differences across regions may also be a result of the variable demographical parameters and variable statistical power linked to different sample size in each region. Nonetheless, statistical differences in key parameters such as autoantibodies were observed in regions with a small sample size, suggesting that the statistical power was sufficient to highlight relevant differences. Moreover, all regions had at least 175 patients, which could be considered as a large sample size as SSc-ILD is a rare disease. We only included baseline medications, and treatments such as immunomodulatory drugs may have changed during the course of the disease; this underscores the need to interpret the results on management with caution. We did not include any detailed analysis of HRCT parameters such as ILD patterns as these data were not available in EUSTAR. PFT trajectories were not explored in our work as such data have been recently analysed in EUSTAR, although geographical differences were not assessed [14]. The absence of centralized confirmation of antibody status is also a limitation inherent to the worldwide scale of the database [26].

Conclusions

Our study highlights key differences among regions in terms of prognosis and clinical presentation worldwide. This work also demonstrates that the management of SSc-ILD is highly variable among the different regions considered, suggesting that further efforts are needed for standardization of medical practice in the treatment of SSc-ILD, especially as it remains among the leading causes of SSc-related death. These regional discrepancies suggest that further research is warranted to investigate how potential interplays between genetic background and epigenetic influence exerted by different environmental exposure arising from geographic boundaries may impact SSc-ILD onset, clinical phenotype and the prevalence of associated autoantibodies.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

The data that support the findings of this study are available upon reasonable request.

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