# Prevalence and clinical presentation of SSc-associated ILD according to worldwide spatial repartition in the EUSTAR database

Lescoat A[1], Huscher D[2], Hachulla E[3], Denton CP[4], Matucci-Cerinic M[5], Riemekasten G[6], Del Galdo F[7], Caimmi C[8], Truchetet ME[9], Schoof N[10], Distler O[11], Allanore Y,[12] on behalf of EUSTAR investigators

1-CHU Rennes, Internal medicine and clinical immunology and IRSET UMR 1085, Rennes, France
2-Institute of Biostatistics and Clinical Epidemiology, Charité Universitätsmedizin Berlin and Berlin Institute of Health, Berlin, Germany
3-Lille, INSERM U995, CHU Lille, Département de Médecine Interne et d'Immunologie clinique, Centre National de Référence Maladies Systémiques et Auto-Immunes Rares, European Reference Network on Rare Connective Tissue and Musculoskeletal Diseases (ReCONNECT), Lille, France
4-Department of Rheumatology, University College London, Royal Free Hospital, London United Kingdom
5-Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Florence, Italy
6-Department of Rheumatology and Clinical Immunology, Justus Liebig Universitat Giessen, Bad Nauheim, Germany
7-Leeds Biomedical Research Centre and Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom
8-Rheumatology Unit, University of Verona, Verona, Italy
9-Rheumatology Department, Bordeaux University Hospital, Bordeaux, France
10-Boehringer Ingelheim GmbH, Ingelheim, Germany
11-Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
12-Department of Rheumatology, Cochin Hospital, University of Paris Descartes, Paris, France

## Context

Systemic sclerosis (SSc) is a **heterogeneous disease** with a wide range of clinical presentations. Some SSc-associated characteristics differ between countries, ethnicities, and geographical regions[1]. SSc-associated interstitial lung disease **(SSc-ILD) is considered as the leading cause of death in SSc**. Nonetheless, little is known about the direct comparison of the characteristics of SSc-ILD between geographical regions worldwide.

**This study aims to determine and compare the prevalence, clinical presentation, management and prognosis of SSc-ILD among predefined geographical regions.**

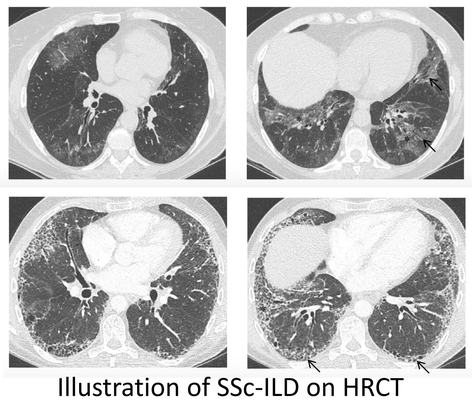


Illustration of SSc-ILD on HRCT

## Methods

**EUSTAR** inclusion centres were located within 39 different countries that were clustered into **7 pre-defined geographical regions:** "Southern Europe", "Western Europe and Nordic countries", "Eastern Europe, Russia and Baltic countries", "Central Europe", "Africa and Middle East", "America (north and south)", "Asia and Oceania"[2]. Only patients enrolled since January 2009 in the EUSTAR database and fulfilling ACR/EULAR 2013 or ACR 1980 classification criteria were included. Data were extracted from the database in February 2019.

## Results

**Table 1 : Prevalence of SSc-ILD in the different pre-determined geographical regions**

| | Total | | | Southern Europe | | | Western Europe and nordic countries | | | Eastern Europe, Russia & Baltic countries | | | Central Europe | | | Africa & Middle East | | | America (North & South) | | | Asia & Oceania | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | no ILD | ILD | ILD Prevalence | no ILD | ILD | ILD Prevalence | no ILD | ILD | ILD Prevalence | no ILD | ILD | ILD Prevalence | no ILD | ILD | ILD Prevalence | no ILD | ILD | ILD Prevalence | no ILD | ILD | ILD Prevalence | no ILD | ILD | ILD Prevalence |
| N | 3846 | 3534 | **47.9%** | 1286 | 1058 | **45.1%** | 1780 | 1269 | **41.6%** | 146 | 312 | **68.1%** | 210 | 383 | **64.6%** | 152 | 205 | **57.4%** | 160 | 144 | **47.4%** | 112 | 163 | **59.3%** |

**7380 patients were included in the cross-sectional evaluation.**

**The mean prevalence of SSc-ILD (attested by the presence of signs of lung fibrosis on HRCT and/or X-rays, or when a date for a diagnosis of ILD was informed) was 47.9%, with high differences among regions:** the region "Eastern Europe, Russia and Baltic countries" had the highest prevalence (68.1%) of SSc-ILD, whereas "Western Europe and Nordic countries" had the lowest (41.6%) (p<0.0001). FVC (%pred) was significantly lower in patients with SSc-ILD than in unaffected patients (86.6±21.6 vs 101.8 ±19.6; p<0.0001) and this remains valid in all geographical regions taken separately except in "Eastern Europe, Russia and Baltic countries" where FVC only tended to be lower in SSc-ILD patients (82.9±20.4 vs 90.0 ±15.9; p=0.055). SSc-associated characteristics also differed according to regions: Scl70 antibodies were associated with SSc-ILD in all regions (p<0.001) except in America where this association was not statistically significant (positive in 19.6% of patients without ILD and positive in 29.9% of patients with ILD, p>0.99).

**Table 2: Seven geographical regions, country selection and included SSc-ILD patients from the EUSTAR Database**

| Geographical region (N) | Countries | N (%) |
|---|---|---|
| Southern Europe (N=1058) | Italy | 854 (80.7) |
| | Spain | 154 (14.6) |
| | Portugal | 25 (2.4) |
| | Greece | 23 (2.2) |
| | Malta | 2 (0.2) |
| Western Europe and nordic Countries (N=1269) | Germany | 491 (38.7) |
| | Switzerland | 240 (18.9) |
| | France | 229 (18.0) |
| | United Kingdom | 128 (10.1) |
| | Belgium | 104 (8.2) |
| | Netherlands | 42 (3.3) |
| | Denmark | 14 (1.1) |
| | Norway | 11 (0.9) |
| | Ireland | 10 (0.8) |
| Eastern Europe, Russia and Baltic countries (N=312) | Romania | 193 (61.9) |
| | Russia | 91 (29.2) |
| | Lithuania | 17 (5.4) |
| | Republic of Moldova | 6 (1.9) |
| | Estonia | 5 (1.6) |
| Central Europe (N=383) | Hungary | 140 (36.6) |
| | Poland | 95 (24.8) |
| | Croatia | 71 (18.5) |
| | Czech Republic | 44 (11.5) |
| | Serbia | 33 (8.6) |
| Africa and Middle East (N=205) | Turkey | 111 (54.1) |
| | Israel | 68 (33.2) |
| | Egypt | 26 (12.7) |
| America (north and south) (N=144) | USA | 40 (27.8) |
| | Brasil | 38 (26.4) |
| | Dominican Republic | 35 (24.3) |
| | Argentina | 31 (21.5) |
| Asia and Oceania (N=163) | China | 132 (81.0) |
| | New Zealand | 23 (14.1) |
| | Iran | 8 (4.9) |

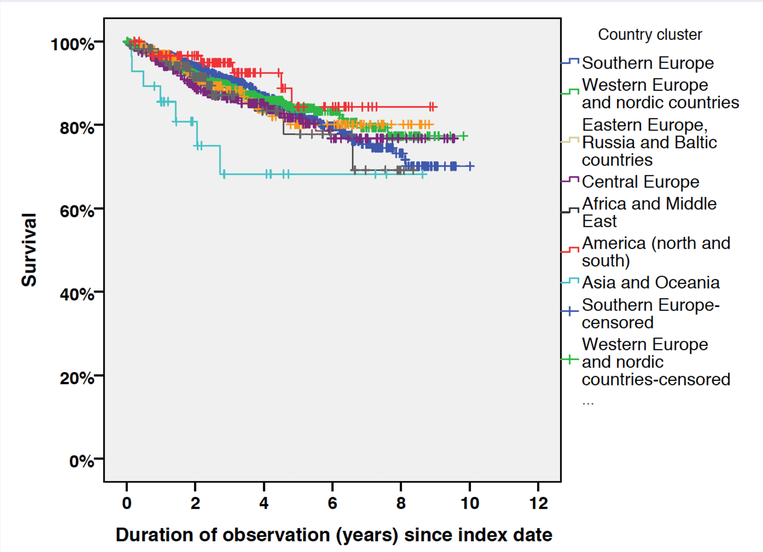
**Table 3: Baseline characteristics of 3534 patients with SSc-ILD in the different pre-determined geographical regions**

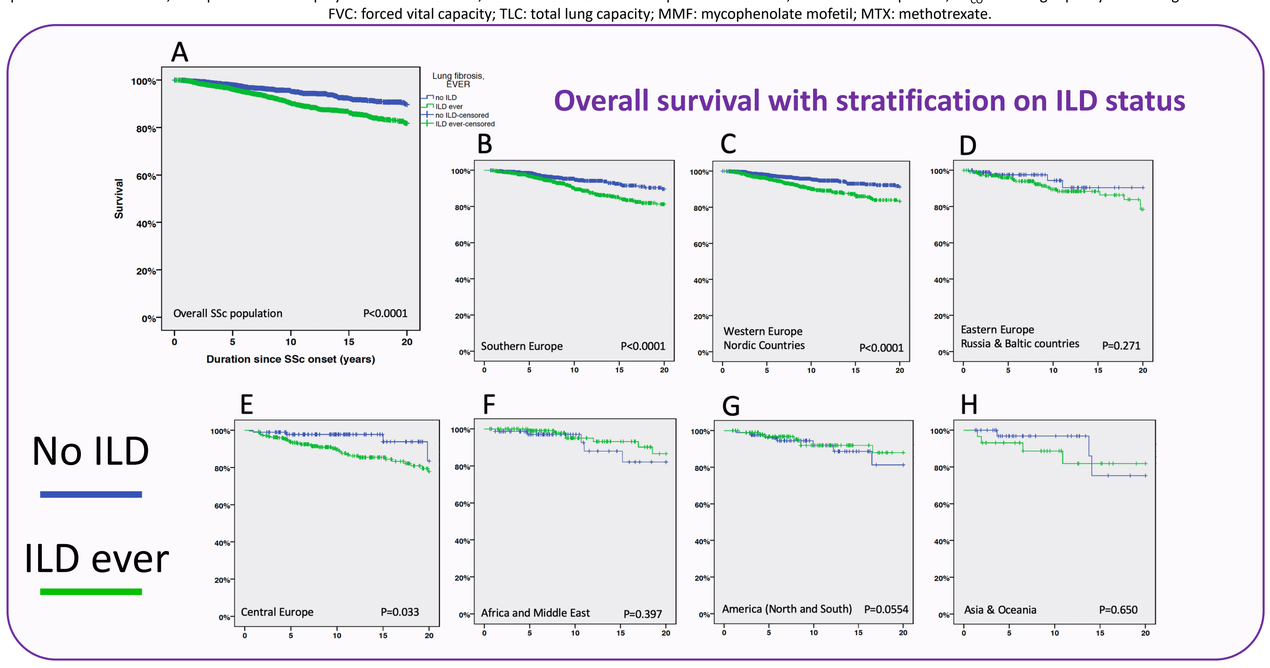
| | Data available (n/3534) | Total | Southern Europe | Western Europe and nordic countries | Eastern Europe, Russia & Baltic countries | Central Europe | Africa & Middle East | America (North & South) | Asia & Oceania | P value |
|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristics** | | | | | | | | | | |
| **N** | 3534/3534 | 3534 | 1058 | 1269 | 312 | 383 | 205 | 144 | 163 | |
| **Age (SD)** | 3534/3534 | 56.6 (13.3) | 58.7 (13.8) | 57.9 (13.0) | 54.1 (11.6) | 57.0 (11.4) | 52.1 (13.0) | 51.1 (12.7) | 47.9 (13.8) | <0.0001 |
| **Male gender (%)** | 3534/3534 | 687 (19.4) | 144 (13.6) | 354 (27.9) | 51 (16.3) | 64 (16.7) | 29 (14.1) | 20 (13.9) | 25 (15.3) | 0.091 |
| **Disease duration since first non-RP symptom** | 3019/3534 | 8.2 (8.1) | 8.3 (8.1) | 7.9 (8.5) | 8.0 (8.2) | 8.7 (7.6) | 9.9 (7.6) | 9.0 (6.8) | 6.9 (7.4) | <0.0001 |
| **dcSSc (%)** | 3521/3534 | 1841 (52.3) | 484 (45.9) | 662 (52.5) | 171 (54.8) | 206 (53.8) | 137 (67.2) | 87 (60.4) | 94 (57.7) | <0.0001 |
| **mRSS** | 3186/3534 | 10.6 (9.0) | 9.5 (8.5) | 9.7 (8.8) | 11.5 (9.6) | 13.0 (8.5) | 15.2 (10.3) | 12.4 (10.1) | 9.3 (8.4) | <0.0001 |
| **DU (%)** | 3414/3534 | 892 (26.1) | 273 (26.3) | 294 (24.3) | 104 (34.4) | 93 (24.6) | 52 (27.5) | 41 (31.3) | 35 (21.5) | 0.834 |
| **Joint synovitis (%)** | 3444/3534 | 522 (15.2) | 147 (14.1) | 145 (11.8) | 87 (28.2) | 60 (15.9) | 55 (28.8) | 17 (12.7) | 11 (6.8) | 0.124 |
| **Tendon friction rubs (%)** | 3395/3534 | 299 (8.8) | 90 (8 .7) | 102 (8.5) | 34 (11.3) | 32 (8.6) | 14 (7.4) | 23 (16.9) | 4 (2.5) | 0.791 |
| **Muscle weakness (%)** | 3438/3534 | 700 (20.4) | 170 (16.3) | 217 (17.8) | 124 (40.3) | 113 (30.1) | 34 (18) | 34 (24.8) | 8 (5.0) | 0.106 |
| **Esophageal symptoms (%)** | 3500/3534 | 2238 (63.9) | 655 (62.6) | 760 (60.7) | 224 (71.8) | 257 (67.1) | 163 (80.7) | 89 (62.7) | 90 (55.6) | 0.061 |
| **Pulmonary hypertension (%)** | 2920/3534 | 629 (21.5) | 196 (20.8) | 178 (17.6) | 68 (24.7) | 69 (26.2) | 56 (33.3) | 27 (24.3) | 35 (23.2) | <0.0001 |
| **ACA+ (%)** | 3253/3534 | 724 (22.3) | 276 (27.4) | 239 (20.3) | 57 (21.8) | 76 (21.5) | 41 (21.5) | 22 (19.1) | 13 (9.2) | <0.0001 |
| **ATA+ (%)** | 3332/3534 | 1734 (52.0) | 511 (50.2) | 616 (50.9) | 190 (66.0) | 180 (49.9) | 129 (66.2) | 35 (31.8) | 73 (48.7) | 0.447 |
| **RNA pol III (%)** | 2302/3534 | 145 (6.3) | 28 (3.6) | 87 (8.9) | 2 (1.7) | 11 (5.2) | 12 (11.1) | 4 (4.9) | 1 (5.9) | <0.0001 |
| **U1 RNP (%)** | 2798/3534 | 198 (7.1) | 39 (4.2) | 50 (4.7) | 19 (9.1) | 11 (4.4) | 18 (15.4) | 24 (24.0) | 37 (27.0) | <0.0001 |
| **High CRP level (%)** | 3217/3534 | 985 (30.6) | 259 (26.8) | 394 (33.1) | 106 (36.2) | 105 (28.8) | 58 (33.1) | 29 (29.0) | 34 (27.0) | 0.566 |
| **DLCO (%pred)** | 2756/3534 | 60.5 (19.3) | 64.5 (20.1) | 58.1 (19.0) | 53.4 (16.8) | 61.2 (19.1) | 62.5 (16.7) | 59.3 (21.3) | 58.2 (16.4) | <0.0001 |
| **FVC (%pred)** | 2932/3534 | 86.0 (21.6) | 89.8 (21.3) | 86.8 (22.1) | 82.9 (20.4) | 86.7 (20.7) | 77.5 (18.6) | 72.5 (21.0) | 79.8 (18.6) | <0.0001 |
| **TLC (% pred)** | 2058/3534 | 85.0 (20.1) | 84.8 (20.0) | 85.8 (19.8) | 78.2 (20.3) | 87.8 (21.9) | 75.4 (17.4) | 84.5 (25.2) | 85.3 (17.2) | <0.0001 |
| **Immunosuppressive therapy** | 2387/3534 | 2077 (58.8) | 640 (60.5) | 768 (60.7) | 205 (65.7) | 198 (51.7) | 169 (82.4) | 83 (57.6) | 14 (8.6) | <0.0001 |
| **MMF** | 2387/3534 | 596 (16.9) | 248 (23.5) | 199 (15.7) | 29 (9.3) | 17 (4.4) | 55 (27.2) | 41 (28.5) | 7 (4.3) | <0.0001 |
| **MTX** | 2385/3534 | 457 (13.0) | 73 (6.9) | 224 (17.7) | 56 (17.9) | 44 (11.5) | 38 (18.5) | 21 (14.6) | 1 (0.6) | 0.732 |
| **CTC** | 2385/3534 | 1355 (38.4) | 483 (45.7) | 452 (35.8) | 136 (43.6) | 138 (36.0) | 92 (44.9) | 43 (29.9) | 11 (6.7) | <0.0001 |
| **Cyclophosphamide** | 2387/3534 | 311 (8.8) | 41 (3.9) | 100 (7.9) | 72 (23.1) | 55 (14.4) | 27 (13.2) | 15 (10.4) | 1 (0.6) | <0.0001 |

ILD: interstitial lung disease; RP: Raynaud's phenomenon; dcSSc: diffuse cutaneous systemic sclerosis, mRSS: modified Rodnan Skin Score; DU: digital ulcers; ACA: anti-centromere antibodies; ATA: anti-topoisomerase antibodies; RNA pol III: anti-RNA polymerase III antibodies; U1-RNP: anti U1 ribonucleoprotein antibodies; CRP: C-reactive protein; $DL_{CO}$: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; TLC: total lung capacity; MMF: mycophenolate mofetil; MTX: methotrexate.

**Subsequent longitudinal analyses were performed on the 2389 patients with SSc-ILD and at least one follow-up visit:**

"Asia and Oceania" had a significantly worse survival in comparison with all other regions. "Asia and Oceania" had the lowest use of immunosuppressive therapies (8.6%; p<0.0001 in comparison with all other regions). Regarding deaths, the highest proportion of death due to SSc was in "Africa and Middle East" (90.0%) and the lowest in "America" (57.1%).




## Conclusions

**Prevalence, severity and clinical presentation of SSc-ILD significantly varies among geographical regions worldwide. There is a trend for lower use of immunosuppressive drugs in regions with lower survival rate. Socio-environmental, geographical and also health system organisation factors may influence these results.**

***References:***

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