Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 14 July 2021 | doi:10.4414/smw.2021.20528
Cite this as: Swiss Med Wkly. 2021;151:w20528

The burden of systemic sclerosis in Switzerland – the Swiss systemic sclerosis EUSTAR cohort

Hernández Jasmin[a], Jordan Suzana[a], Dobrota Rucsandra[a], Iudici Michele[b], Hasler Paul[c], Ribi Camillo[d], Villiger Peter[e], Vlachoyiannopoulos Panayiotis[f], Vacca Alessandra[g], Garzanova Ludmila[h], Giollo Alessandro[i], Rosato Edoardo[j], Kötter Ina[k], Carreira Patricia E.[l], Doria Andrea[m], Henes Jörg[n], Müller-Ladner Ulf[o], Smith Vanessa[p], Distler Jörg[q], Gabrielli Armando[r], Hoffman-Vold Anna-Maria[s], Walker Ulrich[t], Distler Oliver[a], the EUSTAR collaborators *

[a] Department of Rheumatology, University Hospital Zurich, University of Zurich, Switzerland
[b] Rheumatology Unit, Geneva University Hospitals, Geneva, Switzerland
[c] Department of Rheumatology, Kantonsspital Aarau, Switzerland
[d] Department of Clinical Immunology and Allergy, Lausanne, Switzerland
[e] Department of Rheumatology and Clinical Immunology/Allergology, Inselspital, University of Bern, Switzerland
[f] Department of Pathophysiology Medical School, National University of Athens, Greece
[g] Rheumatology Unit, University Hospital of Cagliari, Monserrato (CA), Italy
[h] Laboratory of microcirculation and inflammation, VA Nasonova Institute of Rheumatology, Moscow, Russian Federation
[i] Rheumatology Section, Department of Medicine, University of Verona, Italy
[j] Department of Translational and Precision Medicine, Sapienza University of Rome, Italy
[k] Asklepios Clinic Altona, Medical Department, Rheumatology, Immunology, Nephrology, Hamburg, Germany
[l] Rheumatology Department. University Hospital 12th of October, Madrid, Spain
[m] Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padova, Italy
[n] University Hospital Tuebingen, Centre for Interdisciplinary Clinical Immunology, Rheumatology and Auto-inflammatory Diseases and Department of Internal Medicine II (Haematology, Oncology, Immunology and Rheumatology), Germany
[o] Department of Rhumatology and Clinical Immunology, Justus-Liebig-University Giessen, Kerckhoff-Clinic Bad Nauheim, Germany
[p] Department of Rheumatology, University of Ghent, Belgium
[q] Department of Internal Medicine 3, University Clinic Erlangen, Germany
[r] Marche Polytechnic University, Institute of Clinical Medicine, University of Ancona, Italy
[s] Department of Rheumatology, Rikshospitalet University Hospital, Oslo, Norway
[t] Department of Rheumatology, University Hospital Basel, Switzerland

Summary

OBJECTIVES: Characteristics of Swiss patients with systemic sclerosis have not been described so far. The aim of the current study was to identify unmet needs in comparison with other European countries that could inform specific interventions to improve the care of systemic sclerosis patients.

METHODS: We analysed Swiss and other European systemic sclerosis patients registered in European Scleroderma Trials And Research (EUSTAR) and the Very Early Diagnosis Of Systemic Sclerosis (VEDOSS) cohort. Demographics, clinical profiles, organ involvement and survival of established, early/mild and very early / very mild systemic sclerosis patients were described and compared between the cohorts.

RESULTS: We included 679 Swiss and 8793 European systemic sclerosis patients in the analysis. Over 95% of patients in both cohorts were Caucasian, disease subsets were similar, and no age difference was found. The Swiss cohort had more male patients (25% vs 16% European, p = 0.005) and higher prevalence of early/mild and very early / very mild patients (26.1 vs 8.5% European and 14.9% vs 6.7% European, respectively, both p <0.0001). Disease duration in established systemic sclerosis patients at first presentation was numerically shorter but not significant in the Swiss cohort: 5.0 years (1–12) Swiss vs 6.0 years (2–12) years European, p = 0.055). Despite the earlier referral of Swiss patients to systemic sclerosis expert centres, they showed evidence of more severe disease, particularly in the limited cutaneous systemic sclerosis subset, but no differences in overall survival on longitudinal follow-up were observed.

CONCLUSION: This is the first report of the national Swiss EUSTAR cohort. It identifies earlier referral to systemic sclerosis expert centres, before major organ damage occurs, and when outcome can still be modified, as a priority to improve care of patients with systemic sclerosis.

Correspondence:
Prof. Oliver Distler, MD, Department of Rheumatology, University Hospital Zurich, University of Zurich, Gloriastrasse 25, CH-8091 Zurich, oliver.distler[at]usz.ch

Introduction

Systemic sclerosis (SSc) is a heterogeneous multisystem autoimmune disorder, characterised by vasculopathy and extensive tissue fibrosis with multiple organ involvement [1, 2]. With estimates of prevalence from 3 to 50 per 100,000, SSc is an orphan disease, and is associated with high morbidity and disease-related mortality [3, 4]. At present, there is no licensed therapy that can prevent overall disease progression [5].

The aetiology of the disease is still unclear, but genetic and environmental factors have been implicated [6]. There is a higher susceptibility in females as well as in Afro-Americans, and geographical variations with higher prevalence of SSc in the USA and Australia than in Japan and Europe [7, 8]. Within Europe, a north-south gradient with higher prevalence in southern countries and higher prevalence of more severe organ manifestations in eastern centres has been described. However, differences between European countries might be due to referral-and investigator-related bias in the specific healthcare systems rather than true differences in prevalence and severity [3, 6].

The American College of Rheumatology (ACR) classification criteria from 1980 have been the most widely used in epidemiological studies of SSc [3, 9]. However, as the ACR criteria 1980 were developed for patients with long-standing SSc, they show insufficient sensitivity for early/mild and very early / very mild SSc patients [10–12]. The lack of early diagnostic criteria and predictors of disease progression are important limiting factors for identification and treatment in the early and very early stages of the disease [13]. Especially as internal organ involvement occurs early and is often subclinical, detection of disease in the so-called "window of opportunity", which refers to the time between first manifestations to development of irreversible organ damage, is of great interest [13–16]. In 2013, the new ACR / European Alliance of Associations for Rheumatology (EULAR) classification criteria including immunological, vascular and fibrotic features of the disease were published. These criteria were validated as highly sensitive and specific for SSc, and allow inclusion of more patients into clinical studies [17–19]. Further, the European Scleroderma Trials and Research (EUSTAR) group defined preliminary criteria for diagnosis of very early SSc. These included puffy fingers, (SSc-specific) antinuclear antibodies, and microvascular alterations detected by nailfold capillaroscopy in addition to Raynaud's phenomenon [20]. These criteria aim to identify patients with a predisposition to develop SSc fulfilling the classification criteria SSc [21, 22].

In Switzerland, a national strategy for the management of rare diseases offering prospects of improved medical care and government-funded support has been developed and approved [23]. In this context, it is essential to have a good understanding of the specific needs of SSc patients in Switzerland. The EUSTAR database was formed in June 2004, and since then has prospectively followed SSc patients in most European countries. It provides a unique opportunity to assess Swiss and European SSc patients. Further, a comparison of Swiss with European SSc patients leads to a better understanding of the geographical epidemiology of SSc and to identification of specificities of clinical manifestations of SSc patients. To date, no characterisation of Swiss SSc patients has been published.

In this study, we aimed to address this unmet need. This analysis could represent a valuable asset to set priorities in the clinical management strategy of SSc and thus guide the direction of medical efforts and resources towards the best care of patients.

Patients and methods

For this observational study, all SSc patients from the EUSTAR centres in Switzerland (Zurich, Basel, Geneva, Aarau, Bern, Lausanne) and Europe (excluding Swiss centres, all included centres are listed in supplementary table S1 in appendix 2) with visits entered into the EUSTAR or the associated VEDOSS database (for patient with very early / very mild SSc) between 01 January 2009 and 30 October 2017 (date of data export) were analysed cross-sectionally. The first visit after 01 January 2009 was used to characterise patients. This date was chosen because by then the online documentation was introduced and more complex clinical data, including detailed information on therapies, were available. Collection of the data from the VEDOSS cohort started in July 2010 with participation of all EUSTAR centres including patients with a predisposition to develop early SSc according to recently developed criteria [20].

All patients agreed to participate in the EUSTAR/VEDOSS database by signing informed consent forms approved by the local ethics committees. Ethics approval has been obtained from the local ethics committees by all participating EUSTAR and VEDOSS centres and the corresponding ethics committee in Zurich gave approval for our study (KEK-BASEC-Nr. 2017-02102). The study was conducted in accordance with the principles of the Declaration of Helsinki, local laws and guidelines for Good Clinical Practice.

The database covers demographic aspects, disease duration, organ involvement, and laboratory and therapy data, which have been described in detail previously [7, 24]. For the present analysis, patients were grouped into late/established (patients fulfilling the ACR 1980 classification criteria), early/mild (patients fulfilling only the ACR/EULAR 2013, but not the ACR 1980 classification criteria) and very early / very mild patients (patients not fulfilling any of the classification criteria, but with evidence for SSc based on the VEDOSS criteria) [9, 17, 20]. Patients from non-European centres and patients with missing information for the classification criteria were excluded from the analysis.

First, a descriptive analysis from the Swiss cohort with EUSTAR and VEDOSS patients including disease characteristics, organ involvement, antibody profile and laboratory parameters was performed. Skin fibrosis was assessed by the modified Rodnan skin score [25]. Presence of organ involvement was defined as follows: interstitial lung disease (by low-dose high-resolution computed tomography [CT] and/or X-ray), kidney involvement (presence of renal crisis), conduction blocks (by electrocardiography), heart involvement on echocardiography (any of the following: pericardial effusion, diastolic dysfunction or left ventricular ejection fraction <50%), and clinical diagnosis of joint synovitis. The New York Heart Association (NYHA) functional classification was used to determine cardiac insufficiency. Clinical experts in the respective EUSTAR centres determined the presence of organ involvement or certain SSc parameters based on EUSTAR definitions [26, 27].

In a second step, characteristics of the Swiss EUSTAR patients were compared with European EUSTAR patients. Disease characteristics, organ involvement, antibody profile and survival were compared between the Swiss and

European cohort by the subgroups diffuse cutaneous (dcSSc) and limited cutaneous SSc (lcSSc), according to the Le Roy criteria 1988 [28].

Statistical analysis

For this cross-sectional study and longitudinal survival analysis, continuous variables were tested for normal distribution with the Kolmogorov-Smirnoff test, and mean and standard deviation (SD) or median and interquartile range (IQR) were calculated. Categorical variables were presented as frequencies (percentages). Statistical evaluation between two groups was performed using the chi-square or Fisher's exact test for categorical variables and the t-test or Mann-Whitney U test as appropriate for continuous variables. To address multiple testing, a Bonferroni correction (α/number of tests) was applied and only p-values ≤0.0011 (0.05/45) were considered statistically significant and marked as p*-values. Vital status was obtained at the latest follow up. Survival curves were computed with Kaplan-Meier analysis and survival estimates were statistically tested with the log-rank test. Statistical analysis was performed in IBM SPSS Statistics v. 23 software.

Results

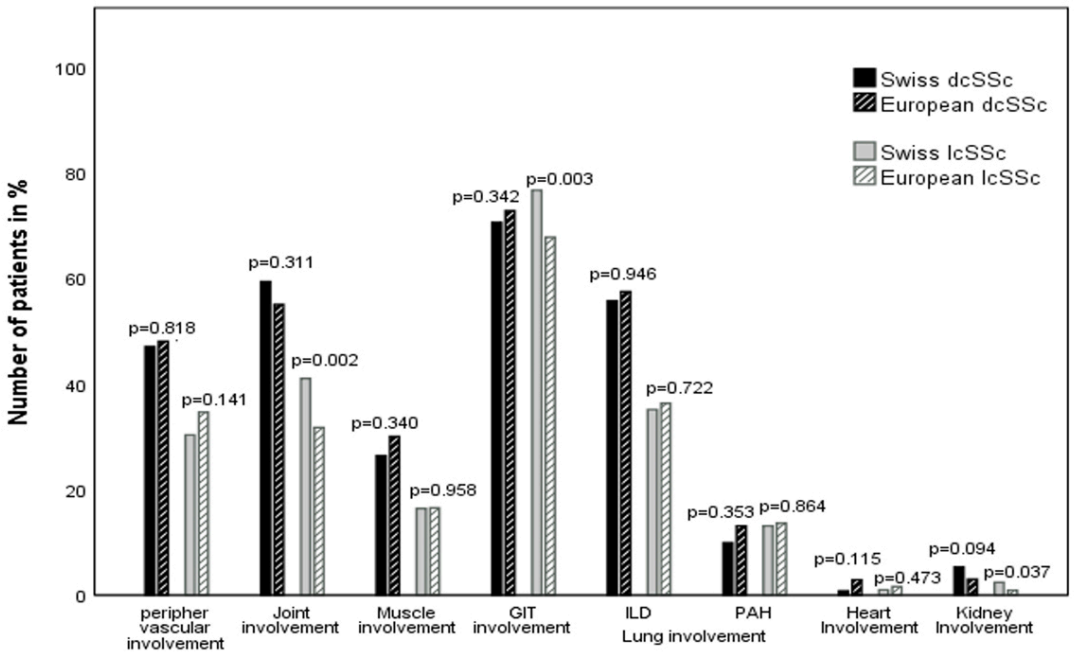
Study population

At the time of data export, the EUSTAR registry comprised a total of 10,863 European SSc patients (EUSTAR: 529 Swiss / 8036 European; VEDOSS: 150 Swiss / 757 European) with at least one available visit after 01 January 2009. Excluded were 383 patients with missing data for classification criteria (EUSTAR: 7 Swiss / 192 European; VEDOSS: 1 Swiss / 183 European) and 1008 Patients from EUSTAR fulfilling neither the ACR 1980 classification criteria nor ACR/EULAR 2013 (80 Swiss / 928 European). Thus, the final number of patients included in the analysis were 679 patients from Switzerland and 8793 patients from other European countries.

Analysis of the Swiss cohort

Of 679 Swiss patients, we found 401 (59.1%) established, 177 (26.1%) early/mild and 101 (14.9%) very early / very mild cases. Demographics and disease characteristics, organ involvement and antibody status are summarised in table 1 and table 2. There were 66% female patients among the established group and 88% in the early/mild and very early / very mild group. Age was similar in the established and early/mild groups (56.81 ± 13.61 and 57.46 ± 14.72 years, respectively) and lower in very early / very mild patients (47.70 ± 14.75 years). Over 94% in all groups were Caucasian and over 95% had Raynaud's phenomenon. Age at onset of Raynaud's phenomenon was again similar between established and early/mild (46.76 ± 16.53 and 47.23 ± 17.73 years, respectively) and lower for very early / very mild patients (39.93 ± 16.55 years). Age at onset of first non-Raynaud's phenomenon symptom (disease onset) was lower in established (47.81 ± 15.2 years) than in early/mild patients (51.02 ± 16.4 years).

Figure 1: Disease characteristics and organ involvement Switzerland and Europe.Peripheral vasculopathy: digital ulcers ever; joint involvement: any of joint contracture, joint synovitis or tendon friction rubs; muscular involvement: any of muscle weakness or muscle atrophy; GIT (gastrointestinal tract) involvement: any of oesophageal (dysphagia, reflux), stomach or intestinal symptoms; ILD (interstitial lung disease): lung fibrosis on x-ray or HRCT; PAH (pulmonary artery hypertension): PAPsys >40 mm Hg by echo; heart involvement: left ventricular ejection fraction <45%; kidney involvement: renal crisis.



Peripheral vasculopathy: Digital ulcers ever; joint involvement: any of joint contracture, joint synovitis or tendon friction rubs; muscular involvement: any of muscle weakness or muscle atrophy; GIT (gastrointestinal tract) involvement: any of esophageal (dysphagia, reflux), stomach (..) or intestinal (..) symptoms; ILD (interstitial lung disease): Lung fibrosis in x-ray or HRCT; PAH (pulmonary artery hypertension): PAPsys > 40mmHg by Echo; Heart involvement: Left ventricular ejection fraction < 45%; Kidney involvement: renal crisis;

Specific analysis of the subgroups revealed certain characteristics: the very early / very mild patients showed typical early/mild disease features: abnormal nailfold capillaroscopy pattern in 58.4% patients, followed by presence of SSc-specific anti-centromere antibodies (ACA) in 42.6%, oesophageal involvement in 27%, puffy fingers (20.8%) and telangiectasia (13%). Presence of anti-Scl70 antibodies, anti-RNA polymerase antibodies (RNAP) III and digital ulcers was very low (4.0%, 7.4% and 4.0%, respectively). Creatine kinase and the inflammation markers C-reactive protein and erythrocyte sedimentation rate were elevated in a small number of the very early / very mild patients (9.1%, 7.0% and 5.3%, respectively).

In the early/mild group, an abnormal scleroderma pattern on nailfold capillaroscopy was present in 80.3% of the patients, followed by ACA antibodies (73.7%), puffy fingers (70.7%) and telangiectasia (50.9%), a typical feature of lcSSc [29]. As expected, organ involvement was more frequent than in very early / very mild patients: oesophageal involvement 50.0%, lung fibrosis 17.4%. Similarly, early/mild patients had more cardiovascular, gastrointestinal and vascular manifestations, as well as higher inflammation markers (table 2).

As expected, in established SSc, organ manifestations became even more frequent (table 2). Although the appearance of organ manifestations increased with disease severity, features that characterise early/mild SSc, such as puffy fingers and ACA, were less frequent in established patients. The number of males was more than two-fold higher in established SSc in comparison with early/mild and very early patients, consistent with previous studies in SSc [30–36]. Dyspnoea NYHA II was similar in all groups, but with more severe cases (NYHA III/IV) in established patients. As expected, lung involvement was highest in established patients with 44.5% of the patients having interstitial lung disease based on chest CT or X-ray.

Cardiovascular involvement with diastolic dysfunction and palpitation occurred often in established (33.8% and 16.6%) as well as early/mild patients (33.1% and 14.4%). Left ventricular ejection fraction (LVEF) <45% was rare in established (0.9%) and absent in early/mild and very early / very mild patients.

Table 1: Demographic and disease characteristics of Swiss SSc patients

	Missing data % (n)	Established SSc* n/total (%)	Early/mild SSc† n/total (%)	Very early / very mild SSc‡ n/total (%)
Total patients	679	401/679 (59.1)	177/679 (26.1)	101/679 (14.9)
Age, mean ± SD	–	56.81 ± 13.61	57.46 ± 14.72	47.70 ± 14.75
Sex	–			
– Male		100/401 (24.9)	17/177 (9.6)	10/101 (9.9)
– Female		301/401 (75.1)	160/177 (90.4)	91/101 (90.1)
Race	2.5 (17)			
– Caucasian		372/392 (94.9)	167/170 (98.2)	96/100 (96.0)
– African-American / African		13/392 (3.3)	1/170 (0.6)	2/100 (2.0)
– Asian		4/392 (1.0)	0/170	0/170
– Other		3/392 (0.8)	2/170 (1.2)	2/100 (2.0)
Disease subset le Roy	0.4 (2)			
– dcSSC		151/399 (37.8)	0	NA
– lcSSc		248/399 (62.2)	128/128 (100)	NA
mRSS, median (IQR)		8.0 (4–14)	0.0 (0–2)	0.0 (0–0)
Raynaud's phenomenon	0.4 (3)	378/399 (94.7)	177/177 (100)	99/100 (99.0)
Age at onset of first RP symptom, mean ± SD	11.9 (81)	46.76 ± 16.53	47.23 ± 17.73	39.93 ± 16.55
Age at onset of first non-RP symptom, mean ± SD	7.9 (42)	47.81 ± 15.2	51.02 ± 16.14	NA
Disease duration (years) median (IQR)	8.3 (44)	5.0 (1–12)	3.0 (1–9.5)	NA
Difference first RP to first non-RP symptom (months), median (IQR)	41.3 (165)	5.0 (0–48)	24.0 (0–125)	NA
Digital ulcers (ever)	0.9 (6)	176/395 (44.6)	22/177 (12.4)	4/101 (4.0)
Digital ulcers active	3.4 (23)	68/378 (18.0)	13/177 (7.3)	4/101 (4.0)
Puffy fingers (ever)	5.3 (36)	217/368 (59.0)	123/174 (70.7)	21/101 (20.8)
Pitting scars	40.1 (272)	68/139 (48.9)	19/167 (11.4)	2/101 (2.0)
Joint synovitis	0.4 (3)	55/398 (13.8)	27/177 (15.3)	15/101 (14.9)
Joint contractures	1.7 (9)	152/393 (38.7)	11/127 (8.2)	NA
Muscle weakness	1.1 (6)	70/394 (17.8)	10/129 (7.8)	NA
Muscle atrophy	1.3 (7)	46/393 (11.7)	1/129 (0.8)	NA
Tendon friction rubs	1.9 (13)	48/391 (12.3)	7/174 (4.0)	1/101 (1.0)
Scleroderma pattern	25.3% (176)	200/229 (87.3)	139/173 (80.3)	59/101 (58.4)
Scleroderma pattern if present	8.4 (25)			NA
– Early pattern		42/181 (23.2)	34/90 (37.8)	NA
– Active pattern		60/181 (44.2)	45/90 (50.0)	NA
– Late pattern		59/181 (32.6)	11/90 (12.2)	NA
Telangiectasia	39.5 (268)	86/143 (60.1)	85/167 (50.9)	13/101 (12.9)

dcSSc = diffuse cutaneous systemic sclerosis; IQR = interquartile range; lcSSc = limited cutaneous systemic sclerosis; mRSS = modified Rodnan skin score; NA = data not available for VEDOSS patients; RP = Raynaud's phenomenon; SD = standard deviation; SSc = systemic sclerosis * established SSc patients – ACR 1980 criteria positive; † early/mild – ACR 1980 criteria negative and ACREULAR 2013 criteria positive; ‡ very early / very mild patients for both ACR 1980 and ACR/EULAR 2013 criteria negative

Gastrointestinal symptoms were very common in all groups and oesophageal symptoms were most often reported. Renal crisis was rare and only present in established patients. ANA (anti-nuclear antibodies) were found in all groups, in from 93–98%. Similarly, joint synovitis had a stable distribution among the groups, as did creatine kinase elevation.

Comparison of Swiss and European patients

Demographic information of all included Swiss and other European patients are listed in table 3. There was no difference found in age (55.7 ± 14.5 years Swiss / 55.4 ± 14.2 years European), and over 95% in both cohorts were Caucasian. There were more male patients in Switzerland (25% vs 16% European, p = 0.005). A significant difference in disease classification was found, with a higher prevalence of established patients in other European countries (84.7% vs 59.1% Swiss, p <0.0001) and consequently higher prevalence of early/mild (26.1% vs 8.5% European, p <0.0001) and very early / very mild patients (14.9% vs 6.7% European, p <0.0001) in Switzerland. Disease subsets according to Le Roy were similar: dcSSc 37.8% Swiss / 35.4% European and lcSSc 62.2% Swiss / 64.6% European [28].

Univariable comparison of Swiss and European established patients summarised in figures 1 and 2 revealed no major differences after correction for disease subsets. (Details in supplementary tables S2 and S3 in appendix 2.)

Consistent differences were found for disease duration, which was significantly shorter in established Swiss patients: 5.0 years (1–12) vs 7.0 years (3–13) European, p* <0.0001). However, as only visits after 2009 were included in this analysis, this difference might be caused by a higher recruitment of patients into the database after 2009 in Switzerland without true differences in disease duration. To correct for this potential bias, we performed a subanalysis including only patients who had their first visit after 2009. In this subanalysis (82.1% of Swiss established SSc patients and 62.4% of European established SSc pa-

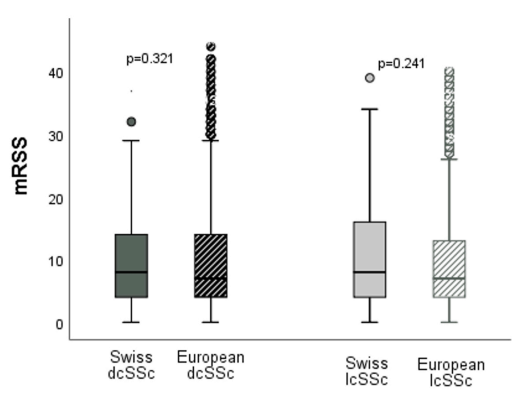
Table 2: Organ involvement, autoantibody profile and laboratory of Swiss SSc patients

	Missing data % (n)	Established SSc* n/total (%)	Early/mild SSc† n/total (%)	Very early / very mild SSc‡ n/total (%)
Total patients		401/679 (59.1)	177/679 (26.1)	101/679 (14.9)
Lung				
Dyspnoea	14.6 (99)	44/310 (14.2)	19/169 (11.2)	14/101 (13.9)
NYHA	15.2 (103)			
– Stage I		156/313 (49.8)	105/168 (62.5)	82/95 (86.3)
– Stage II		113/313 (36.1)	55/168 (32.7)	13/95 (13.7)
– Stage III		38/313 (12.1)	7/168 (4.2)	0/95
– Stage IV		6/313 (1.9)	1/168 (0.6)	0/95
PH by echocardiography	9.0 (61)	64/351 (18.2)	12/169 (7.1)	1/98 (1.0)
PAPsys by echocardiography >40 mmg Hg	34.2 (232)	30/255 (11.8)	8/122 (6.6)	0/70
Lung fibrosis: HRCT or X-ray	12.4 (84)	153/344 (44.5)	28/161 (17.4)	2/90 (2.2)
FVC <80% predicted	11.6 (79)	80/341 (23.5)	13/168 (7.7)	8/91 (8.8)
DLCO <70	11.5 (78)	167/346 (48.3)	46/165 (27.9)	10/90 (11.1)
Cardiovascular				
Arterial hypertension (BP >130/80 mm Hg)	3.2 (22)	108/398 (27.1)	42/170 (24.7)	19/89 (21.3)
Palpitation	2.3 (12)	65/392 (16.6)	18/125 (14.4)	NA
Conduction blocks	20.9 (142)	39/294 (13.3)	13/147 (8.8)	9/96 (9.4)
LEVF <45%	12.8 (87)	3/339 (0.9)	0/162	0/91
Diastolic function abnormal	8.8 (80)	121/358 (33.8)	54/163 (33.1)	17/98 (17.3)
Pericardial effusion	12.1 (82)	31/344 (9.0)	3/159 (1.9)	0/94
Gastrointestinal				
Oesophageal symptoms	0.4 (3)	252/399 (63.2)	88/176 (50.0)	28/101 (27.7)
Stomach symptoms	2.1 (11)	111/394 (28.2)	30/124 (24.2)	NA
Intestinal symptoms	1.7 (9)	111/393 (28.2)	39/126 (31.0)	NA
Renal crisis	0.3 (2)	14/399 (3.5)	0/171	0/101
Antibodies				
ANA	1.2 (8)	383/393 (97.5)	174/177 (98.3)	94/101 (93.1)
ACA	4.6 (31)	133/372 (35.8)	129/175 (73.7)	43/101 (42.6
Anti-Scl70	2.7 (18)	139/389 (35.7)	23/171 (13.5)	4/101 (4.0)
Anti U1RNP	18.7 (127)	10/302 (3.3)	2/156 (1.3)	3/94 (3.2)
Anti RNA polymerase III	28.9 (196)	30/240 (12.5)	7/104 (6.7)	7/94 (7.4)
Laboratory data				
CK elevation	5.9 (40)	47/370 (12.7)	17/170 (10.0)	9/99 (9.1)
Proteinuria	5.0 (34)	44/382 (11.5)	8/165 (4.8)	2/98 (2.0)
ESR >25 mm/h	11.5 (78)	88/335 (26.3)	29/166 (17.5)	5/95 (5.3)
CRP elevation	4.7 (32)	96/374 (25.7)	28/636 (16.2)	7/100 (7.0)

ACA = anti-centromere antibody; ANA = anti-nuclear antibody; BP = blood pressure; CK = creatine kinase; CRP = C-reactive protein; DLCO = diffusing capacity of the lung for carbon monoxide; ESR = erythrocyte sedimentation rate; FVC = forced vital capacity; HRCT = High resolution computed tomography; LEVF = left ventricular ejection fraction; NA = not available; NYHA = New York Heart Association; PAPsys = systolic pulmonary artery pressure; RNA = ribonucleic acid; Scl-70 = antitopoisomerase I antibody; SSc = systemic sclerosis; U1RNP = uridine-rich ribonucleic protein * established SSc patients – ACR 1980 criteria positive; † early/mild – ACR 1980 criteria negative and ACREULAR 2013 criteria positive; ‡ very early / very mild patients for both ACR 1980 and ACR/EULAR 2013 criteria negative

tients) there was still a shorter disease duration in the Swiss patients, but without reaching statistical significance: 5.0 years (1–12) vs 6.0 years (2–12) European, p = 0.055). Still, when looking at the whole cohort, disease duration was shorter in Swiss patients across subgroups: in dcSSc 4.0 years (1–9) Swiss / 5.0 years (2–11) European, p = 0.003; in lcSSc 6.0 years (2–13) years Swiss / 8.0 (4–15) years European, p = 0.015) and in Swiss early/mild patients (3.0 (1–9) Swiss / 5.0 years (2–11) European, p = 0.016). However, it did not reach statistical significance after conservative correction for multiple testing using the Bonferroni method (p-values ≤0.0011, marked as p*).

Figure 2: Skin fibrosis in Switzerland and Europe. dcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis; mRSS = modified Rodnan skin score



dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; mRSS: modified roadnen skin score

Despite the shorter disease duration, Swiss patients showed overall evidence of a more severe disease, particularly in the lcSSc subset. In patients with lcSSc, significantly higher percentage had tendon friction rubs (10.2% Swiss / 3.9% European, p* <0.0001), and diastolic dysfunction (39.0% Swiss / 21.7% European, p* <0.0001). Similarly, joint involvement (31.4% Swiss / 22.8% European, p = 0.002), gastro-intestinal tract involvement (76.6% Swiss / 67.7% European, p = 0.003) and renal crisis (2.4% Swiss / 0.9% European, p = 0.037) were more prevalent in Swiss lcSSc patients, but without reaching statistical significance after Bonferroni correction. In Swiss dcSSc patients, significant differences were found only for more prevalent RNA pol III antibodies (20.2% Swiss / 7.9% European, p* <0.0001). However, Swiss dcSSc patients did not show a milder disease than European dcSSc patients, despite of their shorter disease duration (table S2).

Survival analysis

During the median follow up (duration from disease onset to last visit / death) of 8.0 years (4–13) Swiss / 9.0 years (4–14) European for dcSSc and 10 years (5–16) Swiss / 12.0 years (6–18) European for lcSSc patients, 13/151 (8.6%) Swiss / 250/2526 (9.5%) European dcSSc and 16/

Table 3: Demographic information of Swiss and European patients

	Missing data % (n)	Swiss SSc patients n/total (%)	Missing data % (n)	European SSc patients n/total (%)	p-value
Total Patients		679		8793	
Age, mean ± SD	-	55.70 ± 14.46	-	55.39 ± 14.22	p = 0.589
Sex	-		-		p = 0.005
Male		127/679 (18.7)		1294/8793 (14.7)	
Female		552/679 (81.3)		7499/8793 (85.3)	
Race	2.5 (17)		13.5 (1190)		p = 0.073
Caucasian		635/662 (95.9)		7375/7603 (97.0)	
African-American/ African		16/662 (2.4)		96/7603 (1.3)	
Asian		4/662 (0.6)		72/7603 (0.9)	
Other		7/662 (1.1)		60/7603 (0.8)	
Disease classification	-		-		
Established		401/679 (59.1)		7451/8793 (84.7)	p* <0.0001
Mild/early		177/679 (26.1)		751/8793 (8.5)	p* <0.0001
Very early		101/679 (14.9)		591/8793 (6.7)	p* <0.0001
Disease subset*	0.4 (2)		0.5 (39)		p = 0.323
dcSSC		151/399 (37.8)		2625/7412 (35.4)	
lcSSc		248/399 (62.2)		4787/7412 (64.6)	
Age at onset of first RP symptom*, mean ± SD	20.0 (80)	46.76 (16.53)	39.4 (2937)	44.13 (15.43)	p = 0.003
dcSSC		47.14 ±14.94		44.01 ± 14.97	p = 0.028
lcSSc		46.72 ±17.39		44.19 ± 15.71	p = 0.030
Age at onset of first non-RP symptom, mean ± SD	*6.7 (27)*	47.81 (15.2)	12.3 (917)	46.84 (14.49)	p = 0.210
dcSSC		46.66 ± 14.29		44.98 ± 14.29	p = 0.175
lcSSc		48.56 ± 15.41		47.90 ± 14.56	p = 0.504
Disease duration, median (IQR)*	6.7 (27)	5.0 (1-12)	12.3 (917)	7.0 (3-13)	p* <0.0001
dcSSC		4.0 (1–9)		5.0 (2–11)	p = 0.003
lcSSc		6.0 (2–13)		8.0 (4–15)	p = 0.015
Incident dcSSc		15.0 (10–23)		17.0 (9–25)	p = 0.244

dcSSc = diffuse cutaneous systemic sclerosis; incident dcSSc = dcSSc patients with disease duration <3 years; IQR = interquartile range; lcSSc = limited cutaneous systemic sclerosis; p* = p-value significant after Bonferroni correction (p-values ≤0.0011); RP = Raynaud's phenomen; SSc = systemic sclerosis; SD = standard deviation *comparison of established SSc Patients only,

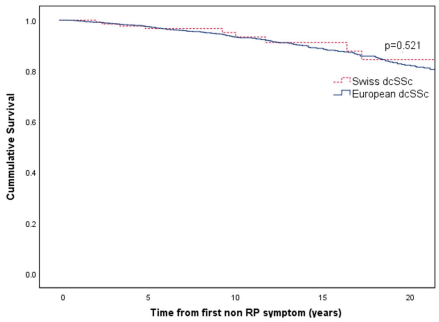
248 (6.5%) Swiss / 295/4787 (6.1%) European lcSSc patients died. As illustrated in figures 3 and 4, there was no significant difference of survival between Switzerland and Europe in either dcSSc or lcSSc patients. The 10-year survival estimate (standard error) in dcSSc was 91.8% (3.2%) Swiss / 93.1% (0.6%) European, and 15-year survival was 88.6% (4.5%) / 88.1% (1.0%), respectively. In lcSSc patients, 10-year survival was 92.2% (2.2%) Swiss / 97.1% (0.3%) European and 15-year survival was 91.1% (2.5%) / 94.0% (0.5%), respectively.

Discussion

This is the first description of the Swiss EUSTAR cohort. Our cross-sectional analysis provides a detailed overview of the clinical profile of the Swiss SSc patients. Application of ACR 1980 classification criteria, the ACR/EULAR 2013 classification criteria and inclusion of patients from the VEDOSS database with very early / very mild and early/mild disease allowed us to include a wide range of SSc patients.

The current analysis showed that the Swiss EUSTAR/VEDOSS registry includes a larger part of the Swiss SSc population. Considering that the published prevalence estimates for Europe are 3 to 50 per 10^5 [3, 4], the Swiss EUSTAR registry covers, with 8 per 10^5, a remarkable part of the expected number of patients in Switzerland [37]. In general, prevalence numbers have to be interpreted with caution because they strongly depend on the definition of SSc and on the quality of the epidemiological data. In addition, prevalence data do not exist for Switzerland and are thus estimated from other European countries. However, even considering these limitations, the calculated 8 per 10^5 lies within the expected range and allows us to assume a remarkable coverage of SSc patients in Switzerland. Still, one has to realise that the EUSTAR Swiss cohort does not cover all SSc patients, as registration is not mandatory. A centre effect with registration of more severe patients into the EUSTAR SSc expert centres can therefore not be excluded.

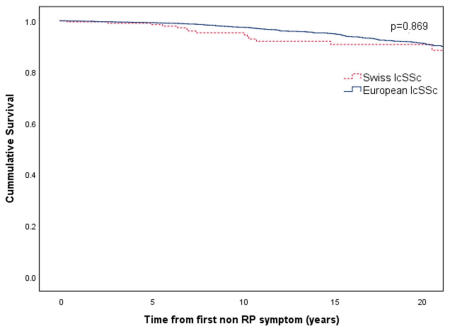
Figure 3: Kaplan-Meier survival analysis dcSSc patients. dcSSc = diffuse cutaneous systemic sclerosis; RP = Raynaud's phenomenon.



Patients at risk					
Swiss dcSSc	[142]	[98]	[51]	[28]	[17]
European dcSS	[2407]	[1772]	[1075]	[590]	[302]

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; RP: Raynaud's phenomenon

Figure 4: Kaplan-Meier survival analysis lcSSc patients. lcSSc = limited cutaneous systemic sclerosis; RP = Raynaud's phenomenon



Patients at risk:					
Swiss lcSSc	[229]	[174]	[118]	[70]	[41]
European lcSSc	[4098]	[3417]	[2485]	[1545]	[888]

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; RP: Raynaud's phenomenon

EUSTAR centres are requested to include all consecutive patients into the registry to avoid selection biases. Indeed, in the Swiss EUSTAR cohort, the frequencies of organ manifestations for different subsets of the disease, as well as other disease features, are very similar to those in other databases [3, 6, 24]. Accordingly, comparison of Swiss and European patients revealed no major differences after correction for disease subsets in the current analysis. These data support the assumption that the Swiss EUSTAR cohort is a representative cohort for Swiss SSc patients and can be used to further define specific national needs, to monitor the use of certain treatments and treatment responses, document the natural course of the disease over time and possibly even for socioeconomic estimates.

The only remarkable difference between the Swiss and European EUSTAR SSc patients was the shorter disease duration when first registered into the database. Even though the difference did not remain statistically significant after correction for potential confounding factors, a meaningful difference of a 1-year shorter disease duration for Swiss SSc patients remained. The most likely explanation for the difference is that the highly developed Swiss healthcare system allows early referral of patients with rare, orphan diseases such as SSc to expert tertiary centres. Early referral is of high importance for the care of SSc patients, as it provides a window of opportunity for early intervention and risk stratification before irreversible organ damage occurs. Delayed inclusion in the registry after the patient was seen and inclusion of selected rather than consecutive patients in other European SSc centres could also have played a role.

Early intervention has been shown to improve long-term outcome in other chronic inflammatory diseases [38]. However, despite their earlier referral, the Swiss EUSTAR SSc patients did not show a better long-term outcome. Survival was not significantly different in Swiss SSc patients compared with other European patients. Swiss patients with lcSSc even presented with evidence for more severe disease compared with the SSc patients from other European countries. Several possible explanations can be considered:

1. SSc interstitial lung disease is the most frequent cause of death in SSc [39]. Treatments have been implemented only during very recent years, including a more frequent use of mycophenolate mofetil and nintedanib, the first registered targeted therapy for SSc interstitial lung disease [40–45]. These novel treatments possibly affect survival only in the long term, which cannot be analysed when these changes

in treatment occurred only recently. Longer-term follow up and re-analyses in several years could address this hypothesis.

2. With the exception of haematopoietic stem cell transplantation [46], which is recommended only for a small subgroup of patients with rapidly progressive SSc at high risk of organ failure [47], treatments modifying the overall disease course of SSc beyond single organ manifestations are not available at present. This does not exclude beneficial effects of early intervention with standard of care on specific organ manifestations and patient well-being, but it might not lead to an overall improvement in survival.

3. Most importantly, earlier referral as seen for the Swiss SSc patients might not be early enough. Indeed, a recent analysis of the EUSTAR database showed that patients who were seen as early as within the first year after onset of Raynaud's phenomenon already had meaningful and frequent organ involvement [48]. This is further supported by data from the Norwegian national SSc cohort, which showed that SSc interstitial lung disease is already frequently detected at first presentation to the SSc centres, and only a few patients develop interstitial lung disease at follow up [49]. Thus, our and other data indicate that even more efforts are needed to be made to identify patients with SSc as early as possible, before meaningful organ damage occurs, to ensure referral to an expert centre and to initiate very early risk stratification and treatment.

Our study also has limitations: The EUSTAR registry is an observational real-life database. As such, it has missing data, which limited some of the analysis. For example, because of missing data, the ACR/EULAR criteria could not be calculated in 9.1% of EUSTAR patients, who then were not included into the analysis. However, for all key SSc characteristics, the EUSTAR database has a remarkably low amount of missing data (tables 1 and 2). After all, the EUSTAR database is run by mostly academic tertiary expert centres. There is no financial compensation for putting patients into the registry, which makes it difficult for smaller centres and private practices to contribute. Thus, while the Swiss SSc EUSTAR cohort covered remarkably a high percentage of the expected Swiss SSc patients, a recruitment bias for more severe patients cared for in tertiary centres cannot be excluded.

Taken together, our study provides the first report on the national Swiss EUSTAR cohort. Clinical profiles for different subforms of the disease were reported. We showed that the recruited patients are representative for a typical European SSc population, which emphasises the high burden of disease for SSc patients in Switzerland. Compared with other European centres, we could show an earlier referral of SSc patients. Despite this early referral, outcomes were not different in the Swiss SSc patients. This indicates that more efforts need to be made to allow referral of SSc patients at risk even before severe organ damage has occurred.

*** EUSTAR collaborators:**

Marco Matucci Cerinic, Florence (Italy); Bettina Bannert, Basel (Switzerland); Florenzo Iannone, Bari (Italy); Britta Maurer, Zurich (Switzerland); Radim Becvar, Prague (Czech Republic); Otylia Kowal Bielecka, Bialystok (Poland); Maurizio Cutolo, Genova (Italy); Gabriele Valentini, Naples (Italy); Elise Siegert, Berlin (Germany); Simona Rednic, Cluj-Napoca(Romania); Yannick Allanore, Paris (France); P. Vlachoyiannopoulos, Athens (Greece); C. Montecucco, Pavia (Italy); Jiri Stork, Prague (Czech Republic); Murat Inanc, Capa, Istanbul (Turkey); Patricia E. Carreira (MD), Madrid (Spain); Srdan Novak, Rijeka (Croatia); László Czirják, Pecs (Hungary); Danièle Allali, Geneva (Switzerland); Eugene J. Kucharz, Katowice (Poland); Elisabetta Zanatta, Padova (Italy); Katja Perdan-Pirkmajer, Ljubljana (Slovenia); Bernard Coleiro, Balzan (Malta); Lucia Manfredi, Ancona (Italy); Dominique Farge Bancel, Paris (France); Paolo Airò, Brescia (Italy); Roger Hesselstrand, Lund (Sweden); Mislav Radic, Split (Croatia); Andrea Lo Monaco, Ferrara (Italy); Nicolas Hunzelmann, Köln (Germany); Raffaele Pellerito, Torino (Italy); Bertoldo Eugenia, Verona (Italy); Jadranka Morovic-Vergles, Zagreb (Croatia); Christopher Denton, London (United Kingdom); Nemanja Damjanov, Belgrade (Serbia); Ann-Christian Pecher, Tübingen (Germany); Vera Ortiz-Santamaria, Granollers Barcelona (Spain); Stefan Heitmann, Stuttgart (Germany); Dorota Krasowska, Lublin (Poland); Samuel Kretzschmar, Aarau (Switzerland); Michaela Köhm, Frankfurt am Main (Germany); Ivan Foeldvari, Hamburg (Germany); Gianluigi Bajocchi, Reggio Emilia (Italy); Maria João Salvador, Coimbra (Portugal); Bojana Stamenkovic, Niska Banja (Serbia); Carlo Francesco Selmi, Rozzano, Milano (Italy); Ludmila Garzanova, Moscow (Russia); Ariane Herrick, Salford (United Kingdom); Ulf Müller-Ladner, Bad Nauheim (Germany); Simone Negrini, Genova (Italy); Merete Engelhart, Hellerup (Denmark); Gabriela Szücs, Debrecen (Hungary); Anna-Maria Hoffmann-Vold, Oslo (Norway); Eric Hachulla, Lille (France); Valeria Riccieri, Roma (Italy); Ruxandra Maria Ionescu, Bucharest (Romania); Ana Maria Gheorghiu, Bucharest (Romania); Cord Sunderkötter, Münster (Germany); Jörg Distler, Erlangen (Germany); Francesca Ingegnoli, Milano (Italy); Luc Mouthon, Paris (France); Vanessa Smith, Gent (Belgium); Francesco Paolo Cantatore, Foggia (Italy); Susanne Ullman, Copenhagen (Denmark); Maria Rosa Pozzi, Monza (Italy); Kilian Eyerich, Munich (Germany); Piotr Wiland, Wroclaw (Poland); Marie Vanthuyne, Brussels (Belgium); Juan Jose Alegre-Sancho, Valencia (Spain); Kristine Herrmann, Dresden (Germany); Ellen De Langhe, Leuven (Belgium); Branimir Anic, Zagreb (Croatia); Maria Üprus, Tallin (Estonia); Sule Yavuz, Altunizade-Istanbul (Turkey); Brigitte Granel, Marseille (France); Svetlana Agachi, Chisinau (Republic of Moldova); Margarita Pileckyte, Kaunas (Lithuania); Alessandra Vacca, Monserrato (CA) (Italy); Douglas Veale, Dublin (Ireland); Jacek Olas, Cracow (Poland); Edoardo Rosato, Roma (Italy); Fahrettin Oksel, Bornova, Izmir (Turkey); Cristina-Mihaela Tanaseanu, Bucharest (Romania); Rosario Foti, Catania (Italy); Codrina Ancuta, Iasi (Romania); Sabine Adler, Bern (Switzerland); Jacob van Laar, Middlesbrough (United Kingdom); Marzena Olesinska (MD), Warsaw (Poland); Paloma García de la Peña Lefebvre, Madrid (Spain); Patrick Carpentier, Grenoble (France); Camille Francès, Paris (France); Jean Sibilia, Strasbourg (France); Francesco Del Galdo, Leeds (United Kingdom); Goda Seskute, Vilnius (Lithuania); Ivan Castellví, Barcelona (Spain); Jasminka Milas-Ahic, Osijek (Croatia); Massimiliano Limonta, Bergamo (Italy; Maura Couto, Viseu (Portugal); Camillo Ribi, Lausanne (Switzerland); Antonella Marcoccia, Roma (Italy); Sarah Kahl, Bad Bramstedt (Germany); Thierry Martin, Strasbourg (France); Sergey Moiseev, Moscow (Russia); Tim Schmeiser, Wuppertal-Elberfeld (Germany); Dominik Majewski, Poznan (Poland); Zbigniew Zdrojewski, Gdansk (Poland); Julia Martínez-Barrio, Madrid (Spain); Vera Bernardino, Lisboa (Portugal); Gabriela Riemekasten, Lübeck (Germany); Lelita Santo, Coimbra (Portugal); Elena Rezus, Lasi (Romania); Omer Nuri Pamuk, Edirne (Turkey); Piercarlo Sarzi Puttini, Milano (Italy); Marek Brzosko, Szczecin (Poland); Martin Krusche, Hamburg (Germany); Giovanna Cuomo, Naples (Italy); Francis Gaches, Toulouse (France); Laura Belloli, Milano (Italy); Petros Sfikakis, Athens (Greece)

Financial disclosure

There was no specific funding for this study. Authors were supported by their respective institutions.

Conflict of interests

JH, SJ, MI, PH, CR, PeV, Pa V, AV, LG, AlG, ER, IK, PEC, AD, UML VS, JD, ArG, UW: None. RD: grants from Articulum Fellowship, sponsored by Pfizer (2013-2014), grants from Actelion, personal fees from Actelion, outside the submitted work. JCH has/had consultancy relationship and/or has received research funding in the area

of potential treatments of scleroderma and its complications from (last three years): Amgen, Bayer, Boehringer Ingelheim, Janssen, Novartis, Pfizer, Roche. AMHV has received research funding and/or consulting fees and/or other remuneration from Actelion, Boehringer Ingelheim, Roche, Bayer, Merck Sharp & Dohme, ARXX, Lilly and Medscape. OD has/had consultancy relationship and/or has received research funding in the area of potential treatments of scleroderma and its complications from (last three years): Abbvie, Acceleron Pharma, Amgen, AnaMar, Bayer, Boehringer Ingelheim, Catenion, Drug Development International Ltd, CSL Behring, ChemomAb, GSK, Horizon (Curzion) Pharmaceuticals, Inventiva, Italfarmaco, iQvia, Lilly, Medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Sanofi, Serodapharm, Target Bio Science and UCB. He has a patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143).

References

1 Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009;360(19):1989–2003. doi: http://dx.doi.org/10.1056/NEJMra0806188. PubMed.

2 Wirz EG, Jaeger VK, Allanore Y, Riemekasten G, Hachulla E, Distler O, et al.; EUSTAR coauthors. Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR database. Ann Rheum Dis. 2016;75(7):1285–92. doi: http://dx.doi.org/10.1136/annrheumdis-2015-207271. PubMed.

3 Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum. 2008;37(4):223–35. doi: http://dx.doi.org/10.1016/j.semarthrit.2007.05.003. PubMed.

4 Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69(10):1809–15. doi: http://dx.doi.org/10.1136/ard.2009.114264. PubMed.

5 Herrick AL, Pan X, Peytrignet S, Lunt M, Hesselstrand R, Mouthon L, et al. Treatment outcome in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study (ESOS). Ann Rheum Dis. 2017;76(7):1207–18. doi: http://dx.doi.org/10.1136/annrheumdis-2016-210503. PubMed.

6 Walker UA, Tyndall A, Czirják L, Denton CP, Farge-Bancel D, Kowal-Bielecka O, et al.; EUSTAR co-authors. Geographical variation of disease manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research (EUSTAR) group database. Ann Rheum Dis. 2009;68(6):856–62. doi: http://dx.doi.org/10.1136/ard.2008.091348. PubMed.

7 Walker UATA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66(6):754–63. doi: http://dx.doi.org/10.1136/ard.2006.062901. PubMed.

8 Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev. 2010;9(5):A311–8. doi: http://dx.doi.org/10.1016/j.autrev.2009.11.003. PubMed.

9 Masi AT. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum. 1980;23(5):581–90. doi: http://dx.doi.org/10.1002/art.1780230510. PubMed.

10 LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28(7):1573–6. PubMed.

11 Scussel Lonzetti L, Joyal F, Raynauld JP, Roussin A, Goulet JR, Rich E, et al. Updating the American College of Rheumatology preliminary classification criteria for systemic sclerosis: Addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. 2001;??:735–6.

12 Wollheim FA. Classification of systemic sclerosis. Visions and reality. Rheumatology (Oxford). 2005;44(10):1212–6. doi: http://dx.doi.org/10.1093/rheumatology/keh671. PubMed.

13 Matucci-Cerinic M, Allanore Y, Czirják L, Tyndall A, Müller-Ladner U, Denton C, et al. The challenge of early systemic sclerosis for the EULAR Scleroderma Trial and Research group (EUSTAR) community. It is time to cut the Gordian knot and develop a prevention or rescue strategy. Ann Rheum Dis. 2009;68(9):1377–80. doi: http://dx.doi.org/10.1136/ard.2008.106302. PubMed.

14 Matucci-Cerinic M, Bellando-Randone S, Lepri G, Bruni C, Guiducci S. Very early versus early disease: the evolving definition of the 'many faces' of systemic sclerosis. Ann Rheum Dis. 2013;72(3):319–21. doi: http://dx.doi.org/10.1136/annrheumdis-2012-202295. PubMed.

15 Valentini G, Cuomo G, Abignano G, Petrillo A, Vettori S, Capasso A, et al. Early systemic sclerosis: assessment of clinical and pre-clinical organ involvement in patients with different disease features. Rheumatology (Oxford). 2011;50(2):317–23. doi: http://dx.doi.org/10.1093/rheumatology/keq176. PubMed.

16 Bellando-Randone S, Matucci-Cerinic M. From Raynaud's Phenomenon to Very Early Diagnosis of Systemic Sclerosis- The VEDOSS approach. Curr Rheumatol Rev. 2013;9(4):245–8. doi: http://dx.doi.org/10.2174/15733971090414041712481 9. PubMed.

17 van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72(11):1747–55. doi: http://dx.doi.org/10.1136/annrheumdis-2013-204424. PubMed.

18 Andréasson K, Saxne T, Bergknut C, Hesselstrand R, Englund M. Prevalence and incidence of systemic sclerosis in southern Sweden: population-based data with case ascertainment using the 1980 ARA criteria and the proposed ACR-EULAR classification criteria. Ann Rheum Dis. 2014;73(10):1788–92. doi: http://dx.doi.org/10.1136/annrheumdis-2013-203618. PubMed.

19 Jordan S, Maurer B, Toniolo M, Michel B, Distler O. Performance of the new ACR/EULAR classification criteria for systemic sclerosis in clinical practice. Rheumatology (Oxford). 2015;54(8):1454–8. doi: http://dx.doi.org/10.1093/rheumatology/keu530. PubMed.

20 Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al.; EUSTAR Group. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis. 2011;70(3):476–81. doi: http://dx.doi.org/10.1136/ard.2010.136929. PubMed.

21 Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirják L, et al.; EUSTAR co-workers; EUSTAR co-workers. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis. 2014;73(12):2087–93. doi: http://dx.doi.org/10.1136/annrheumdis-2013-203716. PubMed.

22 Blaja E, Jordan S, Mihai CM, Dobrota R, Becker MO, Maurer B, et al. The Challenge of Very Early Systemic Sclerosis: A Combination of Mild and Early Disease? J Rheumatol. 2021;48(1):82–6. doi: http://dx.doi.org/10.3899/jrheum.190976. PubMed.

23 Federal Office of Public Health HaAID. Nationales Konzept Seltene Krankheiten 3003 Bern: Federal Office of Public Health; 2014 [updated 15 October 2015. Available from: https://www.bag.admin.ch/bag/de/home/themen/mensch-gesundheit/seltene-krankheiten/nationales-konzept-seltene-krankheiten.html.

24 Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al.; EUSTAR Co-authors. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis. 2012;71(8):1355–60. doi: http://dx.doi.org/10.1136/annrheumdis-2011-200742. PubMed.

25 Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017;2(1):11–8. doi: http://dx.doi.org/10.5301/jsrd.5000231. PubMed.

26 Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66(6):754–63. doi: http://dx.doi.org/10.1136/ard.2006.062901. PubMed.

27 Valentini G, Bencivelli W, Bombardieri S, D'Angelo S, Della Rossa A, Silman AJ, et al. European Scleroderma Study Group to define disease activity criteria for systemic sclerosis. III. Assessment of the construct validity of the preliminary activity criteria. Ann Rheum Dis. 2003;62(9):901–3. doi: http://dx.doi.org/10.1136/ard.62.9.901. PubMed.

28 LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202–5. PubMed.

29 Cutolo M, Pizzorni C, Sulli A. Die Video-Kapillarmikroskopie der Nagelfalz bei systemischer Sklerose [Nailfold video-capillaroscopy in systemic sclerosis]. Z Rheumatol. 2004;63(6):457–62. doi: http://dx.doi.org/10.1007/s00393-004-0673-5. PubMed.

30 Mayes MD, Lacey JV, Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 2003;48(8):2246–55. doi: http://dx.doi.org/10.1002/art.11073. PubMed.

31 Arias-Nuñez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, et al. Systemic sclerosis in northwestern

Spain: a 19-year epidemiologic study. Medicine (Baltimore). 2008;87(5):272–80. doi: http://dx.doi.org/10.1097/MD.0b013e318189372f. PubMed.

32 Simeón CP, Armadans L, Fonollosa V, Solans R, Selva A, Villar M, et al. Mortality and prognostic factors in Spanish patients with systemic sclerosis. Rheumatology (Oxford). 2003;42(1):71–5. doi: http://dx.doi.org/10.1093/rheumatology/keg033. PubMed.

33 Joven BE, Almodovar R, Carmona L, Carreira PE. Survival, causes of death, and risk factors associated with mortality in Spanish systemic sclerosis patients: results from a single university hospital. Semin Arthritis Rheum. 2010;39(4):285–93. doi: http://dx.doi.org/10.1016/j.semarthrit.2009.06.002. PubMed.

34 Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis. 1998;57(11):682–6. doi: http://dx.doi.org/10.1136/ard.57.11.682. PubMed.

35 Hoffmann-Vold AM, Molberg Ø, Midtvedt Ø, Garen T, Gran JT. Survival and causes of death in an unselected and complete cohort of Norwegian patients with systemic sclerosis. J Rheumatol. 2013;40(7):1127–33. doi: http://dx.doi.org/10.3899/jrheum.121390. PubMed.

36 Czirják L, Kumánovics G, Varjú C, Nagy Z, Pákozdi A, Szekanecz Z, et al. Survival and causes of death in 366 Hungarian patients with systemic sclerosis. Ann Rheum Dis. 2008;67(1):59–63. doi: http://dx.doi.org/10.1136/ard.2006.066340. PubMed.

37 Federal Office of Public Health FOPH. Switzerland's population 2016 Neuchatel, Switzerland 2016 [updated 2016] Available from: https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung.html.

38 van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996;124(8):699–707. doi: http://dx.doi.org/10.7326/0003-4819-124-8-199604150-00001. PubMed.

39 Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al.; EUSTAR group. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis. 2017;76(11):1897–905. doi: http://dx.doi.org/10.1136/annrheumdis-2017-211448. PubMed.

40 Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al.; SENSCIS Trial Investigators. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019;380(26):2518–28. doi: http://dx.doi.org/10.1056/NEJMoa1903076. PubMed.

41 Hoffmann-Vold A-M, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. The Lancet Rheumatology. 2020;2(2):e71–83. doi: http://dx.doi.org/10.1016/S2665-9913(19)30144-4.

42 Kuwana M, Distler O. Recent progress and missing gaps to achieve goal in the care of systemic sclerosis–associated interstitial lung disease. J Scleroderma Relat Disord. 2020;5(2_suppl):3–5. doi: http://dx.doi.org/10.1177/2397198320902551.

43 Volkmann ER, Fischer A. Update on Morbidity and Mortality in Systemic Sclerosis-Related Interstitial Lung Disease. J Scleroderma Relat Disord. 2021;6(1):11–20. doi: http://dx.doi.org/10.1177/2397198320915042. PubMed.

44 Volkmann ER. Natural History of Systemic Sclerosis-Related Interstitial Lung Disease: How to Identify a Progressive Fibrosing Phenotype. J Scleroderma Relat Disord. 2020;5(2_suppl):31–40. doi: http://dx.doi.org/10.1177/2397198319889549. PubMed.

45 Roofeh D, Distler O, Allanore Y, Denton C, Khanna D. Treatment of systemic sclerosis–associated interstitial lung disease: Lessons from clinical trials. J Scleroderma Relat Disord. 2020;5(2_suppl):61–71. doi: http://dx.doi.org/10.1177/2397198320903208.

46 Walker UA, Saketkoo LA, Distler O. Haematopoietic stem cell transplantation in systemic sclerosis. RMD Open. 2018;4(1):e000533. doi: http://dx.doi.org/10.1136/rmdopen-2017-000533. PubMed.

47 Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al.; EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327–39. doi: http://dx.doi.org/10.1136/annrheumdis-2016-209909. PubMed.

48 Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al.; EUSTAR co-authors. Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study. PLoS One. 2016;11(10):e0163894. doi: http://dx.doi.org/10.1371/journal.pone.0163894. PubMed.

49 Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, et al. Tracking Impact of Interstitial Lung Disease in Systemic Sclerosis in a Complete Nationwide Cohort. Am J Respir Crit Care Med. 2019;200(10):1258–66. doi: http://dx.doi.org/10.1164/rccm.201903-0486OC. PubMed.

Appendix: Supplementary tables

Table S1: List of all included European centres.

Countries (number of centres)	Centres (centre number)
Belgium (3)	Brussels (122), Gent (113), Leuven (126)
Croatia (5)	Osijek (181), Rijeka (024), Split (041), Zagreb (051,128)
Czech Republic (2)	Prague (007, 020)
Denmark (2)	Copenhagen (116), Hellerup (086)
Estonia (1)	Tallin (130)
France (11)	Grenoble (170), Paris (017, 035, 112, 171), Lile (093), Marseille (134), Strasbourg (172,189), Toulouse (211), Valence (138)
Germany (17)	Bad Bramstedt (187), Bad Nauheim (081), Berlin (015), Bon (060), Dresden (125), Erlangen (106), Frankfurt (124), Frankfurt am Main (063), Hamburg (064, 209), Köln (044), Lübeck (199), Münster (102), Munich (119), Stuttgart (058), Tübingen (056), Wuppertal (192)
Greece (2)	Athens (018, 213)
Hungary(2)	Debrecen (087), Pecs (025)
Italy (27)	Ancona (034),Bari (004), Bergamo (182), Brescia (038), Cagania (161), Florence (001), Foggia (115), Genova (011, 085), Ferrera (043), Milano (074, 083, 110, 205, 212), Monserrato (CA) (142), Monza (118), Napoli (013,210), Padova (031), Pavia(019),Reggio Emilia (066), Roma (094, 158, 186), Torino (049), Verona (050)
Ireland (1)	Dublin (149)
Lithuania (2)	Kaunas (140), Vilnius (176)
Malta (1)	Blaza (033)
Moldova (1)	Chisinau (137)
Norway(1)	Oslo (092)
Poland (9)	Bialystock (008), Cracow (157), Gdansk (194), Katowice (029), Lublin (059), Poznan (193), Szczecin (206), Warsaw (166), Wroclaw (120)
Portugal (4)	Bissaia Barreto (200), Coimbra (068), Lisboa (198), Viseu (184)
Romania (6)	Bucharest (096, 100, 160), Cluj-Napoca (016), Iasi (162, 202)
Russa (2)	Moscow (078, 190)
Serbia and Montenegro (2)	Belgrade (055), Niska Banja (073)
Slovenia (1)	Ljublijana (032)
Spain (6)	Barcelona (057, 180), Madrid (023, 169, 196), Valencia (123)
Sweden (1)	Lund (040)
Turkey (4)	Bornova Izmir (159), Edirne (203); Istanbul (021,133)
United Kingdom (4)	Leeds (175), London (052), Middlesbrough (165), Salford (080)

Table S2: Demographics and disease characteristics of Swiss and European established SSc patients

	Missing data % (n)	Swiss established SSc n/total (%)	Missing data % (n)	European established SSc n/total (%)	p-value
Total patients		401/679 (59.1)		7451/8793 (84.7)	
Le Roy disease subset	0.4 (2)		0.5 (39)		p = 0.323
– dcSSC		151/399 (37.8)		2625/7412 (35.4)	
– lcSSc		248/399 (62.2)		4787/7412 (64.6)	
Age, mean ± SD	-		-		
– dcSSC		53.82 ± 12.59		52.49 ± 13.48	p = 0.237
– lcSSc		58.56 ± 13.9		57.96 ± 13.53	p = 0.499
Sex					
– dcSSC	-		-		p = 0.003
Male		52/151 (34.4)		624/2625 (23.8)	
Female		99/151 (65.6)		2001/2625 (76.2)	
– lcSSc	-		-		p* <0.0001
Male		48/248 (19.4)		519/4787 (10.8)	
Female		200/248 (80.6)		4268/4787 (89.2)	
Raynaud's					
– dcSSC	-	142/151 (94.0)	1.0 (25)	2530/2600 (97.3)	p = 0.038
– lcSSc	0.8 (2)	235/246 (95.5)	1.4 (68)	4599/4719 (97.5)	
mRSS, median (IQR)					
– dcSSC	4.6 (7)	14.0 (10–22)	12.4 (325)	14.0 (8–21)	p = 0.312
– lcSSc	3.2 (8)	5.0 (2-9)	15.1 (721)	5.0 (2-8)	p = 0.240
Digital ulcers(ever)					
– dcSSC	1.3 (2)	70/149 (47.0)	3.3 (87)	1217/2538 (48.0)	p = 0.818
– lcSSc	1.6 (4)	73/241 (30.3)	4.7 (226)	1576/4561 (34.6)	p = 0.141
Joint synovitis					
– dcSSC	0.7 (1)	22/150 (14.7)	3.2 (84)	447/2541 (17.6)	p = 0.359
– lcSSc	0.8 (2)	32/246 (13.0)	4.2 (200)	552/4587 (12.0)	p = 0.648
Joint contractures					
– dcSSC	*2.6 (4)*	75/147 (51.0)	3.7 (96)	1160/2529 (45.9)	p = 0.223
– lcSSc	*1.2 (3)*	77/245 (31.4)	4.5 (216)	1041/4571 (22.8)	p = 0.002
Tendon friction rubs					
– dcSSC	4.0 (6)	23/145 (15.9)	4.7 (124)	337/2501 (13.5)	p = 0.415
– lcSSc	*1.6 (4)*	25/244 (10.2)	5.1 (244)	175/4543 (3.9)	p*<0.0001
Muscle weakness					
– dcSSC	*1.3 (2)*	35/149 (23.5)	3.7 (96)	677/2529 (26.8)	p = 0.379
– lcSSc	*1.6 (4)*	35/244 (14.3)	4.9 (235)	651/4552 (14.3)	p = 0.985
Muscle atrophy					
– dcSSC	*2.6 (4)*	25/147 (17.0)	4.0 (105)	368/2520 (14.6)	p = 0.424
– lcSSc	*1.2 (3)*	21/245 (8.6)	5.2 (247)	259/4540 (5.7)	p = 0.063
Telangiectasia					
– dcSSC	67.5 (102)	29/49 (59.2)	66.6 (1748)	501/877 (57.1)	p = 0.777
– lcSSc	62.9 (156)	57/92 (62.0)	71.2 (3409)	849/1378 (61.6)	p = 0.947
Abnormal NFC					
– dcSSC	46.4 (70)	72/81 (88.9)	56.4 (1480)	1046/1145 (91.4)	p = 0.419
– lcSSc	40.7 (101)	128/147 (87.1)	27.5 (722)	1697/1903 (89.2)	p = 0.412

dcSSc = diffuse cutaneous systemic sclerosis; IQR = interquartile range; lcSSc = limited cutaneous systemic sclerosis; NFC = nailfold capillaroscopy; RP = Raynaud's phenomenon; SD = standard deviation; SSc = systemic sclerosis; p* = p-value significant after Bonferroni correction (p-values ≤0.0011)

Table S3: Organ involvement and antibody profiles of Swiss and European established SSc patients

	Missing data % (n)	Swiss established SSc n/total (%)	Missing data % (n)	European established SSc n/total (%)	p-value
Total patients		401/679 (59.1)		7451/8793 (84.7)	p* <0.0001
Le Roy disease subset	0.4 (2)		0.5 (39)		p = 0.323
– dcSSC		151/399 (37.8)		2625/7412 (35.4)	
– lcSSc		248/399 (62.2)		4787/7412 (64.6)	
Lung					
Dyspnoea					
– dcSSC	23.2 (35)	20/116 (17.2)	9.6 (252)	330/2373 (13.9)	p = 0.313
– lcSSc	22.6 (56)	23/192 (12.0)	11.5 (550)	440/4237 (10.4)	p = 0.480
PH by echocardiography					
– dcSSC	9.9 (15)	22/136 (16.2)	17.9 (471)	359/2154 (16.7)	p = 0.882
– lcSSc	13.7 (34)	42/214 (19.6)	18.8 (900)	648/3887 (16.7)	p = 0.261
PAPsys >40 mmg Hg					
– dcSSC	33.1 (50)	10/101 (9.9)	41.3 (1083)	202/1542 (13.1)	p = 0.353
– lcSSc	38.3 (95)	20/153 (13.1)	38.5 (1844)	399/2943 (13.6)	p = 0.864
Lung fibrosis on HRCT or chest X–ray					
– dcSSC	9.3 (14)	79/137 (57.7)	10.8 (284)	1343/2341 (57.4)	p = 0.946
– lcSSc	17.3 (43)	72/205 (35.1)	16.6 (795)	1451/3992 (36.3)	p = 0.722
FVC <80% predicted					
– dcSSC	13.9 (21)	48/130 (36.9)	24.5 (642)	742/1983 (37.4)	p = 0.910
– lcSSc	15.3 (38)	32/210 (15.2)	22.8 (1091)	624/3696 (16.9)	p = 0.535
DLCOsb <70					
– dcSSC	12.6 (19)	77/132 (58.3)	23.9 (628)	1255/1997 (62.8)	p = 0.300
– lcSSc	14.1 (35)	90/213 (42.3)	23.3 (1116)	1773/3671 (48.3)	p = 0.860
Cardiovascular					
Palpitation					
– dcSSC	2.6 (4)	19/147 (12.9)	3.5 (92)	593/2533 (23.4)	p = 0.003
– lcSSc	1.6 (4)	46/244 (18.9)	6.0 (287)	863/4500 (19.2)	p = 0.900
Conduction blocks					
– dcSSC	25.2 (38)	16/113 (14.2)	14.1 (371)	358/2254 (15.9)	p = 0.624
– lcSSc	27.4 (68)	23/180 (12.8)	17.5 (836)	476/3951 (12.0)	p = 0.769
Left ventricular ejection fraction < 45					
– dcSSC	13.9 (21)	1/130 (0.8)	30.4 (797)	53/1828 (2.9)	p = 0.152
– lcSSc	16.1 (40)	2/208 (1.0)	30.7 (1470)	53/3317 (1.6)	p = 0.770
Diastolic function abnormal					
– dcSSC	7.9 (12)	36/139 (25.9)	20.3 (533)	487/2092 (23.3)	p = 0.480
– lcSSc	12.1 (30)	85/218 (39.0)	21.9 (1050)	810/3737 (21.7)	p* <0.0001
Pericardial effusion					
– dcSSC	11.9 (18)	12/133 (9.0)	26.5 (695)	156/1930 (8.1)	p = 0.702
– lcSSc	15.3 (38)	19/210 (9.0)	27.1 (1296)	220/3491 (6.3)	p = 0.116
Gastrointestinal					
Oesophageal symptoms					
– dcSSC	0.7 (1)	90/150 (60.0)	0.8 (22)	1719/2603 (66.0)	p = 0.130
– lcSSc	0.4 (1)	160/247 (64.8)	1.1 (52)	2804/4735 (59.2)	p = 0.083
Stomach symptoms					
– dcSSC	1.3 (2)	47/149 (31.5)	2.5 (66)	662/2559 (25.9)	p = 0.126
– lcSSc	1.6 (4)	63/244 (25.8)	4.2 (202)	847/4585 (18.5)	p = 0.004
Intestinal symptoms					
– dcSSC	1.3 (2)	38/149 (25.5)	2.2 (58)	644/2567 (25.1)	p = 0.909
– lcSSc	1.6 (4)	73/244 (29.9)	4.1 (194)	1063/4593 (23.1)	p = 0.015
Renal crisis					
– dcSSC	0.7 (1)	8/150 (5.3)	2.2 (58)	77/2567 (3.0)	p = 0.111
– lcSSc	0.4 (1)	6/247 (2.4)	3.9 (188)	43/4599 (0.9)	p = 0.037
Antibody status					
ANA					
– dcSSC	-	144/151 (95.4)	5.1 (134)	2368/2491 (95.1)	p = 0.868
– lcSSc	2.8 (7)	238/241 (98.8)	6.6 (316)	4277/4471 (95.7)	p = 0.019
ACA					
– dcSSC	7.9 (12)	13/139 (9.4)	10.5 (276)	206/2349 (8.8)	p = 0.814
– lcSSc	6.5 (16)	120/232 (51.7)	10.4 (496)	2166/4291 (50.5)	p = 0.711
Anti–Scl70					
– dcSSC	1.3 (2)	82/149 (55.0)	8.0 (209)	1520/2416 (62.9)	p = 0.054

	Missing data % (n)	Swiss established SSc n/total (%)	Missing data % (n)	European established SSc n/total (%)	p-value
– lcSSc	3.6 (9)	57/239 (23.8)	10.8 (515)	945/4272 (22.1)	p = 0.532
Anti U1RNP					
– dcSSC	20.5 (31)	2/120 (1.7)	30.8 (809)	68/1816 (3.7)	p = 0.238
– lcSSc	27.0 (67)	8/181 (4.4)	30.1 (1443)	146/3344 (4.4)	p = 0.972
Anti RNA polymerase III					
– dcSSC	34.4 (52)	20/99 (20.2)	47.6 (1250	108/1375 (7.9)	p* <0.0001
– lcSSc	43.1 (107)	10/141 (7.1)	45.3 (2167)	66/2620 (2.5)	p = 0.005

ACA = anti-centromere antibody; ANA = anti-nuclear antibody; dcSSc = diffuse cutaneous systemic sclerosis; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; HRCT = High resolution computer tomography; lcSSc = limited cutaneous systemic sclerosis; LEVF = left ventricular ejection fraction; PAPsys = systolic pulmonary artery pressure; PH = pulmonary hypertension; RNA = ribonucleic acid; Scl-70 = anti-topoisomerase I antibody; SSc = systemic sclerosis; U1RNP = uridine-rich ribonucleic protein; p* = p-value significant after Bonferroni correction (p-values ≤0.0011)