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ORIGINAL RESEARCH

Systemic sclerosis sine scleroderma: clinical and serological features and relationship with other cutaneous subsets in a large series of patients from the national registry 'SPRING' of the Italian Society for Rheumatology

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ABSTRACT

Objective To describe demographic, clinical and laboratory features of systemic sclerosis sine scleroderma (ssSSc) in a large multicentre systemic sclerosis (SSc) cohort.

Methods Data involving 1808 SSc patients from Italian Systemic sclerosis PRogression INvestiGation registry were collected. The ssSSc was defined by the absence of any cutaneous sclerosis and/or puffy fingers. Clinical and serological features of ssSSc were compared with limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) subsets.

Results Among patients with SSc, only 61 (3.4%) were classified as having ssSSc (F/M=19/1). Time from Raynaud's phenomenon (RP) onset to diagnosis was longer in ssSSc (3 years, IQR 1–16.5) than lcSSc (2 years, IQR 0–7), and dcSSc (1 year, IQR 0–3) (p<0.001). Clinical ssSSc phenotype was comparable to lcSSc, except for digital pitting scars (DPS) (19.7% vs 42%, p=0.01), but significantly milder than dcSSc, particularly for digital ulcers (DU) (6.6% vs 35.7%, p<0.001), oesophagus (46.2% vs 63.5%, p=0.009), lung (mean diffusion capacity for carbon monoxide 72.2±19.6 vs 62.4±22.8, p=0.009; mean forced vital capacity 105.6±21.7 vs 89.2±20.9, p<0.001) and major videocapillaroscopic alterations (late pattern 8.6% vs 47.6%, p<0.001). Moreover, in ssSSc the percentages of anticentromere and antitopoisomerase were comparable to lcSSc (40% and 18.3% vs 36.7% and 26.6%), but divergent respect to dcSSc (8.6% and 67.4%, p<0.001).

Conclusion The ssSSc is a quite rare disease variant characterised by clinico-serological features comparable to lcSSc, but significantly different from dcSSc. Overall,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Currently, the literature is conflicting concerning demographics and clinico-laboratory hallmark of systemic sclerosis (SSc) sine scleroderma (ssSSc), a quite rare SSc subset without distinctive cutaneous signs, generating diagnostic uncertainties.

WHAT THIS STUDY ADDS

⇒ The analysis of the large SSc population from Systemic sclerosis PRogression INvestiGation Italian national registry allowed for an updated description of the ssSSc phenotype, mainly characterised by a longer Raynaud's phenomenon duration at diagnosis, reduced frequencies of peripheral vascular involvement, less microcirculatory abnormalities and anticentromere positivity. The comparative analysis with other subsets revealed that ssSSc visceral involvement was nearly similar to limited cutaneous SSc and significantly milder than diffuse cutaneous SSc.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may provide some important suggestions for future investigations on the biological bases of the variable distribution of both skin/visceral fibrosis and microangiopathy through the whole scleroderma spectrum, as well as on the complex etiopathogenesis of the SSc, which may lead to a novel disease subsetting.

longer RP duration, low percentages of DPS and peripheral microvascular abnormalities, and increased anti-centromere seropositivity distinguish ssSSc. Further investigations based on national registries might provide useful insights on the actual relevance of the ssSSc within the scleroderma spectrum.

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease affecting skin and internal organs, characterised by autoimmunity, microvascular injury and collagen deposition.[1 2] In SSc, widespread skin and visceral fibrosis are associated with a reduction of quality of life, poor patients' outcomes and increased mortality.[1 3] The hallmark of the disease is the remarkable heterogeneity of clinical manifestations.[3] The disease is clinically classified according to the extension of skin involvement in two main subsets, limited cutaneous SSc (lcSSc) and diffuse cutaneous (dcSSc), that also include SSc-specific autoantibodies, nailfold capillaroscopic patterns and fibrosis of internal organ.[2 3] The two subsets have well-recognised differences with respect to disease severity and prognosis.[2 4] Furthermore, SSc sine scleroderma (ssSSc) is considered as a separate subset first described in detail by Rodnan and Fennell.[5] Its clinical presentation can be misleading, generating diagnostic uncertainties because of the lack of skin involvement, although it may have the involvement of lung, heart and gastrointestinal (GI) system.[6 7] Currently, the literature is conflicting concerning the real prevalence of ssSSc, the female/male ratio, and the presence/severity of both visceral organ and peripheral vascular involvement, mostly depending on the characteristics of the studied population.[8–14]

In 2014, the Italian Society for Rheumatology promoted the development of the national SPRING (Systemic sclerosis PRogression INvestiGation) registry, which includes the clinical conditions preceding the onset of definite SSc and the main disease subsets.[15] The overall baseline data have already been published[15 16] while the assessment of more than 2400 consecutive patients is still in progress. The aim of the present work was to analyse the main demographic, clinical and laboratory features of patients with ssSSc in comparison with lcSSc and dcSSc subsets within the SPRING registry. Moreover, the observed findings were compared with other similar studies present in the literature.

Patients and methods

The non-profit national multicentre SPRING registry, involving 37 tertiary referral centres, collects more than 150 disease variables, such as demographic, clinical and imaging investigations, as well as ongoing treatments.

Data were collected and handled using the tool REDCap (Research Electronic Data Capture), a web-based application for assistance in data collection. Since multicentre registries are greatly heterogeneous in collecting and entering data, we minimised this issue by introducing clear-cut definitions of all registry variables; moreover, periodic quality checks were performed by the coordinating centre.[15]

Definitions

For the current study, data concerning patients with definite SSc aged >18, enrolled up to June 2022, were taken into account. The SPRING database has been previously described,[15 16] consisting of patients classified into four different cohorts: (1) primary Raynaud's phenomenon (RP); (2) suspected secondary RP; (3) Very Early Diagnosis of Systemic Sclerosis; (4) definite SSc according to ACR/EULAR 2013 classification criteria.[17] A thorough medical chart review for all consecutive patients with definite SSc was made and cutaneous subsets were classified as dcSSc, lcSSc and ssSSc. In particular, the ssSSc was classified based on the absence of puffy fingers and skin thickening, in any skin areas, including fingers (sclerodactyly), hands, limbs and trunk. All ssSSc patients had a modified Rodnan skin score=0.[2 4 7]

Information collected at registration included age of disease onset, that is, that of the first non-RP sign(s)/symptom(s), time from SSc onset to diagnosis, time from RP onset to SSc diagnosis, as well the following clinical variables: oesophageal dysfunction symptoms (dysphagia, reflux), cardiopulmonary signs and symptoms (dyspnoea, arrhythmias, heart failure), sicca syndrome (dry eyes/mouth), renal crisis (sudden onset of severe arterial hypertension with acute renal failure), skin signs (sclerodactyly, puffy fingers, calcinosis, telangiectasia), peripheral vascular signs (fingertip pitting scars (DPS), digital ulcers (DUs), gangrene) and musculoskeletal (tenosynovitis, arthritis defined as inflammatory changes observed in more than two joints, joint

contractures, tendon friction rubs, osteomyelitis, carpal tunnel syndrome, myositis). Capillaroscopic patterns at nailfold videocapillaroscopy (NVC) were classified according to the current guidelines as normal (N), early (E), active (A) and late (L).[18] Laboratory findings included antinuclear antibodies (ANA), antiextractable nuclear antigens, particularly the SSc-related antibodies (anticentromere/CENP-B, antitopoisomerase I/Scl-70 and anti-RNA polymerase III), as earlier described.[15 16] Non-invasive cardiac diagnostic testing was performed by trans-thoracic Doppler echocardiography, collecting the following data: systolic pulmonary arterial pressure (sPAP), left ventricular ejection fraction (LVEF), anomalous diastolic function, pericardial effusion. The current algorithm was used to screen SSc patients and identify those with a high-risk of pulmonary arterial hypertension (PAH). Those with a high PAH probability underwent right hearth catheterisation (RHC).[19]

Investigations for lung involvement consisted of pulmonary function tests (predicted value of total lung capacity (TLC), forced vital capacity (FVC)), diffusion capacity for carbon monoxide (DLCO) and high-resolution CT (HRCT) (ground glass fibrosis, reticulation, honeycombing). Finally, information about previous/current treatments included both vasoactive/vasodilating drugs (bosentan, sildenafil, vardenafil, tadalafil, iloprost, PGE1, inhaled-INN iloprost, epoprostenol, riociguat, nifedipine, nicardipine, amlodipine, felodipine, diltiazem) and immunosuppressants (cyclophosphamide, methotrexate, leflunomide, aziatoprine, micophenolic acid, cyclosporine, rituximab, imatinib, anti-TNF-alpha, tocilizumab, abatacept) was collected.

Statistical analysis

Descriptive analyses were reported as absolute and relative frequencies for categorical variables, mean and SD for continuous ones. Median (IQR) has been provided in place of mean (SD) when significant asymmetry of distributions was present. To evaluate the differences among groups either the Pearson's χ^2 test or the Fisher's exact test were employed, while quantitative variables were examined using the non-parametric Mann-Whitney test or the t-test, as appropriate. To avoid family-wise error rate the Simes-Benjamini-Hochberg correction was applied. Multivariable statistical analysis was also performed by using a logistic regression model. P values <0.05 were considered statistically significant.

All analyses were carried out using R statistical software (Foundation for Statistical Computing, V.4.2).

RESULTS

Demographic, clinical and laboratory findings of the whole SSc series and cutaneous subsets are provided in table 1, whereas data regarding internal organ involvement, peripheral microcirculation abnormalities and previous/current treatments are given in table 2. Moreover, figure 1 gives a comprehensive depiction of the similarities and difference between the three cutaneous subsets. Finally, table 3 summarises the main cohort and multicentre studies on ssSSc available in the world literature.

Whole SSc series: demographic features and subsetting

Up to 30 June 2022, among the whole 1808 patients' series with definite SSc included in the study, 61 (3.4%) were classified as ssSSc (table 1) that were characterised by the absence of cutaneous involvement but fulfilling the classification criteria of SSc.[17] All patients with ssSSc reached the cut-off of ≥9 that satisfied the subitem scores, excluding scleroderma skin involvement, in accordance with the point score system of ACR/EULAR 2013 criteria.[17]

In particular, 6 (9.8%) had a total score of 9, and 33 (54.1%) a total score of 10. Next, patients (8.2%) reached the total score of 11 and 10 (16.4%) the total score of 12. Finally, seven patients (11.4%) had a score ≥13.[17]

These ssSSc patients had a mean age at disease onset of 52.8±14.7 years, with a 95.1% (F/M ratio 19/1) of females. The lcSSc subset consisted of 1377 patients, accounting for 76.2% of the whole cohort (F/M ratio 8.5:1), while 370 patients (20.4%) had dcSSc variant (F/M ratio 4.9:1) (table 1).

ssSSc: clinical variables and autoantibodies

ssSSc patients showed a variable percentage of other SSc signs/symptoms. Namely, telangiectasias (63.9%), oesophageal involvement (42.6%) and sicca syndrome (44.3%) were common, while DPS and DUs were less represented (19.7% and 6.6%, respectively). Musculoskeletal involvement was globally present in around one-third of patients (tenosynovitis 4.9%, arthritis 11.9% and myositis 11.9%). Joint contractures and tendon friction rubs were only anecdotally reported (only two and one case). In all ssSSc patients, serum ANA were present. Among SSc-specific autoantibodies, anticentromere were detected in 40%, followed by antitopoisomerase I in 18.3% and anti-RNA polymerase III in 2.6% of ssSSc (table 1).

ssSSc: internal organ and microcirculation abnormalities

Hearth involvement was observed in 13 out of total ssSSc patients (21.3%). Doppler echocardiography examination revealed diastolic dysfunction (22%), pericardial effusion (5.9%), mean sPAP of 25.8±17 mm Hg, and mean LVEF % of 61.7±4, while PAH at RHC was found in 5.9% of assessed individuals (table 2). More than one-third of ssSSc patients (37.7%) had ILD at HRCT. The mean values of % predicted DLCO, FVC and TLC were 72.2±19.6, 105.6±21.7 and 103.9±19.1, respectively. Among capillaroscopic findings, a normal or early pattern was more frequent and was found in almost 50% of ssSSc patients (12.1% and 36.2%, respectively), whereas late pattern was uncommon (8.6%). In ssSSc patients, vasoactive/vasodilating treatments were frequently used

Table 1 Demographic, clinical characteristics and laboratory characteristics of SSc patients by cutaneous subtype classification

	All (N=1808)	ssSSc N=61 (3.4)	lcSSc N=1377 (76.2)	dcSSc N=370 (20.4)	P value ssSSc vs lcSSc	P value ssSSc vs dcSSc	P value lcSSc vs dcSSc
Demographics							
Female sex, n/N (%)	1594/1803 (88.4)	58/61 (95.1)	1229/1372 (89.6)	307/370 (83)	0.71	0.06	**0.001**
Age of onset, years, mean (SD)	49.6 (14)	52.8 (14.7)	50.6 (13.9)	45.4 (13.4)	0.70	**0.003**	**<0.001**
SSc onset to diagnosis, years, median (IQR)	0 (0–1)	0 (0–1.5)	0 (0–1)	0 (0–1)	0.99	0.9	0.22
RP onset to diagnosis, years, median (IQR)	2 (0–6)	3 (1–16.5)	2 (0–7)	1 (0–3)	0.27	**<0.001**	**<0.001**
Clinical							
Skin							
Digital pitting scars, n/N (%)	855/1798 (47.6)	12/61 (19.7)	574/1367 (42)	369/370 (72.7)	**0.01**	**<0.001**	**<0.001**
Digital ulcers, n/N (%)	403/1802 (22.4)	4/61 (6.6)	267/1371 (19.5)	132/370 (35.7)	0.18	**<0.001**	**<0.001**
Gangrene, n/N (%)	18/1796 (1)	0/61 (0)	10/1365 (0.7)	8/370 (2.2)	0.99	0.79	0.05
Telangiectasia, n/N (%)	1072/1801 (59.5)	39/61 (63.9)	783/1370 (57.2)	250/370 (67.6)	0.77	0.83	**0.001**
Calcinosis, n/N (%)	219/1795 (12.2)	2/61 (3.3)	153/1364 (11.2)	64/370 (17.3)	0.44	**0.02**	**0.005**
Musculoskeletal							
Tenosynovitis, n/N (%)	110/1798 (6.1)	3/61 (4.9)	76/1367 (5.6)	31/370 (8.4)	0.99	0.66	0.09
Arthritis, n/N (%)	207/1790 (11.6)	7/61 (11.5)	138/1359 (10.2)	62/370 (16.8)	0.99	0.60	**0.001**
Osteomyelitis, n/N (%)	12/1795 (0.7)	0/61	7/1365 (0.5)	5/369 (1.4)	0.99	0.99	0.20
Carpal tunnel syndrome, n/N (%)	83/1794 (4.6)	0/61	61/1364 (4.5)	22/369 (6)	0.47	0.12	0.35
Myositis, n/N (%)	265/1796 (14.8)	7/61 (11.5)	177/1365 (13)	81/370 (21.9)	0.99	0.18	**<0.001**
Oesophageal symptoms, n/N (%)	894/1801 (49.6)	26/61 (42.6)	633/1370 (46.2)	235/370 (63.5)	0.99	**0.009**	**<0.001**
Sicca syndrome, n/N (%)	499/1797 (27.8)	27/61 (44.3)	380/1366 (27.8)	92/370 (24.9)	0.11	**0.009**	0.35
Renal crisis, n/N (%)	21/1796 (1.2)	1/61 (1.6)	11/1366 (0.8)	9/369 (2.4)	0.83	0.99	**0.03**
Autoantibodies							
ANA, n/N (%)	1725/1783 (96.7)	60/60 (100)	1308/1358 (96.3)	357/365 (97.8)	0.73	0.82	0.26
Antitopoisomerase I, n/N (%)	616/1781 (34.6)	11/60 (18.3)	61/1359 (26.6)	244/362 (67.4)	0.76	**<0.001**	**<0.001**
Anti-RNA polymerase III, n/N (%)	27/1437 (1.9)	1/39 (2.6)	14/1094 (1.3)	12/304 (3.9)	0.81	0.99	**0.01**
Anti-centromere, n/N (%)	515/1655 (31.1)	22/55 (40)	464/1264 (36.7)	29/336 (8.6)	0.99	**<0.001**	**<0.001**

Significant p-values are outlined in bold
ANA, antinuclear antibodies; dcSSc, diffuse cutaneous SSc; lcSSc, limited cutaneous SSc; RP, Raynaud's phenomenon; SSc, systemic sclerosis; ssSSc, SSc sine scleroderma.

(62.3%), while immunosuppressants in around 24.6% of patients (table 2).

ssSSc versus limited and diffuse cutaneous subsets

The results of comparative analysis among the three SSc subsets are shown in tables 1 and 2 and figure 1.

The ssSSc and lcSSc exhibit several similarities as regards both demographic and clinical parameters, except for DPS (ssSSc 19.7% vs lcSSc 42 %, p=0.01).

Conversely, the ssSSc and the dcSSc subsets markedly differ for the rate of female sex (95.1% vs 83%, p=0.001), the age of disease onset (52.8±14.7 vs 45.4±13.4 years; p=0.003), as well as time interval (years) from RP onset to SSc diagnosis (median, IQR=3, 1–16.5 vs median, IQR=1, 0–3; p<0.001) (table 1).

The oesophageal involvement and sicca syndrome were significantly lower in ssSSc than dcSSc (p=0.009, for both), as well as DPS (p<0.001), DU (p<0.001) and calcinosis (p=0.02).

Among SSc-specific autoantibodies, anticentromere were more frequently detected in ssSSc (40%) compared with dcSSc (8.6%, p<0.001), while an opposite distribution was observed for antitopoisomerase I antibodies (18.3% vs 67.4%, p<0.001).

The frequency of ILD was similar in ssSSc and lcSSc (37.7% and 36.8%, respectively), but higher in dcSSc

Table 2 Results of diagnostic tests and treatments in SSc patients by cutaneous subtype classification

	All (N=1808)	ssSSc N=61 (3.4)	lcSSc N=1377 (76.2)	dcSSc N=370 (20.4)	P value ssSSc vs lcSSc	P value ssSSc vs dcSSc	P value lcSSc vs dcSSc
Hearth							
PAH, n/N (%)	29/1494 (1.9)	3/51 (5.9)	17/1126 (1.5)	9/317 (2.8)	0.30	0.40	0.24
sPAP, mm Hg, mean (SD)	23.3 (16.4)	25.8 (17)	23 (16.1)	24 (17.2)	0.73	0.83	0.22
LVEF, mean (SD)	61.1 (5.8)	61.7 (4.1)	61.2 (5.7)	61 (6.2)	0.99	0.92	0.83
Diastolic dysfunction, n/N (%)	20/1452 (22)	11/50 (22)	240/1078 (22.3)	69/324 (21.3)	0.99	0.99	0.81
Pericardial effusion, n/N (%)	109/1474 (7.4)	3/51 (5.9)	72/1099 (6.6)	34/324 (10.5)	0.99	0.66	**0.04**
Lung							
ILD, n/N (%)							
Ground glass	371/1808 (20.5)	11/61 (18)	244/1377/17.7)	116/370 (31.4)	0.99	0.11	**<0.001**
Reticulation	294/1808 (16.3)	11/61 (18)	208/1377 (15.1)	75/370 (20.3)	0.99	0.95	**0.03**
Honeycomb	97/1808 (5.4)	1/61 (1.6)	55/1377 (4)	41/370 (11.1)	0.95	0.09	**<0.001**
DLCO % predicted, mean (SD)	68.6 (20.6)	72.2 (19.6)	69.8 (19.7)	63.4 (22.8)	0.73	**0.009**	**<0.001**
FVC % predicted, mean (SD)	101 (22.8)	105.6 (21.7)	104.1 (22.3)	89.2 (20.9)	0.99	**<0.001**	**<0.001**
TLC % predicted, mean SD	96.6 (20.4)	103.9 (19.1)	98.5 (20.1)	87.6 (19.5)	0.44	**<0.001**	**<0.001**
Nailfold videocapillaroscopy							
Scleroderma pattern, n/N (%)							
Normal (N)	105/1609 (6.5)	7/58 (12.1)	92/1215 (7.6)	6/336 (1.8)	0.73	**0.003**	**<0.001**
Early (E)	336/1609 (20.9)	21/58 (36.2)	265/1215 (21.8)	50/336 (14.9)	0.19	**0.001**	**0.013**
Active (A)	746/1609 (46.4)	25/58 (43.1)	601/1215 (49.5)	120/336 (35.7)	0.79	0.58	**<0.001**
Late (L)	422/1609 (26.2)	5/58 (8.6)	257/1215 (21.2)	160/336 (47.6)	0.25	**<0.001**	**<0.001**
Treatments							
Vasoactive drugs, n/N (%)	1391/1808 (76.9)	38/61 (62.3)	1036/1377 (75.2)	317/370 (85.7)	0.23	**<0.001**	**<0.001**
Immunosuppressants, n/N (%)	500/1808 (27.7)	15/61 (24.6)	299/1377 (21.7)	186/370 (50.3)	0.99	**0.001**	**<0.001**

Significant p-values are outlined in bold
dcSSc, diffuse cutaneous SSc; DLCO, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; lcSSc, limited cutaneous systemic sclerosis; lcSSc, diffuse cutaneous SSc; LVEF, left ventricular ejection fraction; NVC, nailfold videocapillaroscopy; PAH, pulmonary arterial hypertension by hearth catheterisation; sPAP, systolic pulmonary arterial pressure; SSc, systemic sclerosis; ssSSc, SSc sine scleroderma; TLC, total lung capacity.

(62.7%). ssSSc and dcSSc differed for DLCO (mean DLCO 72.2±19.6 vs 62.4±22.8, p=0.009) and other functional tests (mean FVC predicted 105.6±21.7 vs 89.2±20.9, TLC 103.9±19.1 vs 87.6±19.5, p<0.0001 for both) (table 2).

The proportion of normal and early patterns were more frequent in ssSSc (12.1% and 36.2%) compared with both lcSSc (7.6% and 21.8%) and dcSSc (1.8% and 14.9%) (p=0.003 and 0.001, respectively), whereas the late pattern was uncommon (8.6%) in ssSSc, with an increasing prevalence from lcSSc (21.2%) to dcSSc (47.6%, p<0.001). Finally, both vasoactive/vasodilating and immunosuppressive therapies were more frequently used in dcSSc (p=0.001, table 2).

Multivariable logistic regression analysis, after adjustment for sex and age at onset, indicates that longer time

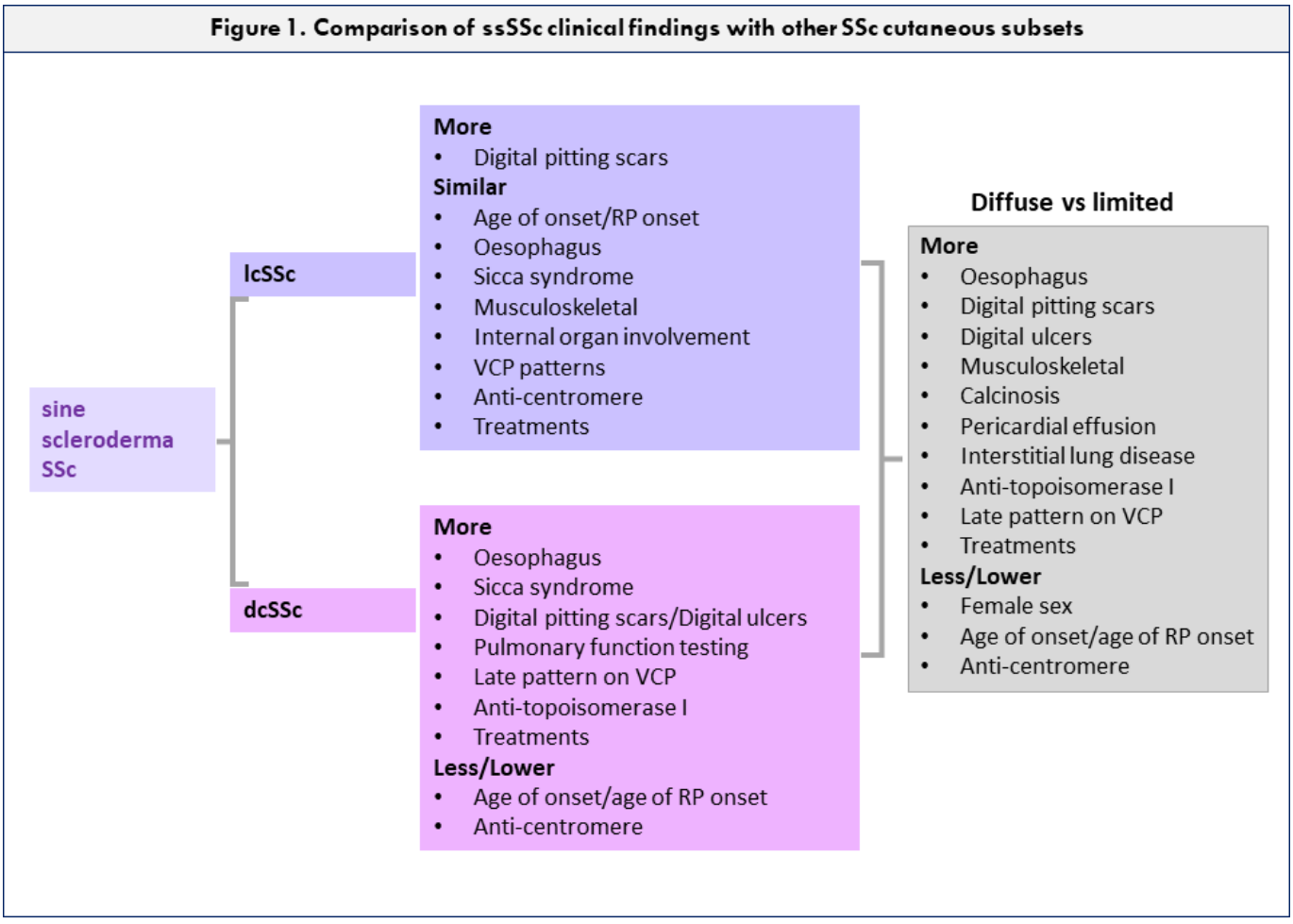

Figure 1 Comparison of SSc sine scleroderma clinical findings with other SSc cutaneous subsets. VCP, videocapillaroscopy; dcSSc, diffuse cutaneous SSc; lcSSc, limited cutaneous SSc; RP, Raynaud's phenomenon; SSc, systemic sclerosis.

from RP onset to diagnosis (OR 1.031; 95% CI 1.004 to 1.057; p=0.016) and higher prevalence of DPS (OR 0.394; 95% CI 0.188 to 0.767; p=0.009) may distinguish ssSSc from lcSSc patients, whereas longer time from RP onset to diagnosis (OR 1.062; 95% CI 1.024 to 1.105; p=0.002), higher DPS (OR 0.158; 95% CI 0.067 to 0.346, p<0.001), anticentromere positivity (OR 2.486; 95% CI 1.038 to 5.972; p=0.04) and antitopoisomerase 1 negativity (OR 0.219; 95% CI 0.086 to 0.515; p=0.001) may distinguish ssSSc from dcSSc patients.

As expected, lcSSc and dcSSc significantly differed in several clinical and laboratory findings (oesophageal involvement, renal crisis, DPS and DU, telangiectasias, calcinosis, arthritis, and myositis), including cardiopulmonary involvement (pericardial effusion and ILD in all items), with a relevant higher frequency of antitopoisomerase I and late capillaroscopic pattern in dcSSc. Taken together these differences showed a significant higher prevalence of worse clinical-prognostic parameters in the dcSSc compared with lcSSc (figure 1).

DISCUSSION

This cross-sectional study indicates that ssSSc subset accounts for approximately 3% of the SSc patients' population recorded in the Italian SPRING registry. Except for cutaneous involvement, this subset fulfils the current classification criteria of SSc by exhibiting the typical disease manifestations, including the main visceral organ damages. Our national registry study, focusing on the largest SSc population so far investigated, allows for valuable comparative analysis between the three skin subgroups.

In particular, the data show that the clinical features and the autoantibodies of the ssSSc subset overlap with those of the lcSSc subset, while both differ significantly from the dcSSc subset, which is characterised by more severe microvascular and fibrotic organ involvement and increased antitopoisomerase I and anti-RNA polymerase rates. Of note, a significantly longer time interval from RP onset to SSc diagnosis was observed either in ssSSc and lcSSc compared with dcSSc, as well as an increasing trend in DU rates through the three subsets (ssSSc<lcSSc<dcSSc). Overall, a longer RP duration at diagnosis, reduced DPS frequency, less microcirculatory abnormalities and anticentromere positivity were the main features of the ssSSc subset.

Demographic and clinical hallmarks of the present ssSSc series and those previously published are summarised

Table 3 Summary of main registry studies on systemic sclerosis sine scleroderma (ssSSc) published in the world literature

Author, country, year (ref)	Data source	n/N (%)	F (%)	DPS-DU (%)	ILD (%)	Hearth (%)	PAH (%)	SRC (%)	OES (%)	MS (%)	AA (%)	Entry criteria
Poormoghim *et al*, Massachusetts, 2000[8]	Monocentric registry	48/556 (8.6)*	85.4	**60.4**†	38.6	**8.8**	22.9	**0**	–	47.9	Scl-70: 6.25 ACA: 31.2	No skin thickening on physical examination
Hunzelmann *et al*, Germany, 2008[9]	Multicentric inter-disciplinary registry	22/1483 **(1.4)**	90.9	33.3‡	**59.1**	13.6	13.6	**22.7**	72.7	45.5	Scl-70: **40** ACA: 35	No skin alterations
Simeón-Aznar *et al*, Spain, 2012[10]	Multicentric registry	67/916 (7.3)	92.5	14.5‡	39.1	**49.3**	24.6	1.4	44.9	**52.2**	Scl-70: 9.5 ACA: 41.5	1980 ACR 2001 LeRoy-Medsger
Marangoni *et al*, Brazil, 2013[11]	Retrospective bi-centric database	79/947 (8.3)	**96.2**	24.1‡	56.9	–	22.8	2.5	**83.1**	46.9	Scl-70: 7.8 ACA: 41.7	No skin thickening on physical examination
Diab *et al*, Canada, 2014[12]	Multicentre registry	27/1417 (1.9)	88.9	29.6†	25.9	–	11.5	3.7	51.8	**14.8**	Scl-70: 16.6 ACA: 60	Physician diagnosis
Tolosa-Vilella *et al*, Spain, 2016[13]	Multicentric registry	118/1326 **(8.9)**	91.5	16.1‡	27.9	29.6	25.8	1.4	**19.1**	21.8	Scl-70: 12.7 ACA: 46.6	1980 ACR 2001 LeRoy-Medsger 2013 ACR-EULAR
De Almeida Chaves *et al*, France, 2021[14]	Retrospective bi-centric database	33/375 (8.8)	**84.8**	**9.1**‡	**9.1**	15.1	**9.1**	3	–	42.4	Scl-70: 12.1 ACA: **78.7**	2001 LeRoy-Medsger 2013 ACR-EULAR
Present study, 2022	Multicentric registry	61/1808 (3.3)	95.1	26.2†	37.7	27.4	5.9	1.6	42.6	32 .7	Scl-70: 18.3 ACA: 40	2013 ACR-EULAR

Lowest and highest values for each item are highlighted in bold
*lcSSc+ssSSc.
†DPS+DU.
‡DU.
AA, autoantibodies; ACA, anticentromere; DPS, digital pitting scars; DU, digital ulcer; ILD, interstitial lung disease; lcSSc, limited cutaneous systemic sclerosis; MS, musculoskeletal; OES, oesophageal involvement; PAH, pulmonary hypertension; SRC, scleroderma renal crisis.

in table 3. The papers are characterised by a significant heterogeneity for what concerns the number, the modalities of patients' recruitment (mono/multicentre), and the classification criteria adopted.[8–14] This condition may account for the variability in the ssSSc prevalence (from 1.4% to 8.9%), as well as in the clinical phenotype, namely peripheral vascular, heart, lung, renal, oesophageal and musculoskeletal involvement. Whereas, similar data are reported concerning the higher occurrence of anticentromere antibodies, which exceeds that of antitopoisomerase in the majority of the ssSSc series. Given the large time interval of more than 20 years from the first to the last study, it may be noted that only the last three reports, including ours, used the 2013 ACR/EULAR classification criteria (table 3). Overall, the findings reported in the world literature suggested a few considerations that are addressed and developed in the discussion.

The occurrence of ssSSc might be underestimated in clinical practice, being its identification and diagnosis difficult in some cases, due to the absence of any skin involvement paralleled by mild disease manifestations. Moreover, the recognising of SSc, particularly in the early stage, is based on some cardinal signs, namely Raynaud's phenomenon, DPS, puffy fingers, cutaneous sclerosis, sclerodactyly and/or capillaroscopic/autoantibody alterations.[2 4]

The ACR/EULAR 2013 classification criteria for SSc have improved the sensitivity and specificity of previous 1980 ACR criteria,[20] even in the absence of oedematous/fibrotic skin involvement. However, the variable prevalence of ssSSc among the main studies of the literature might be explained by the use of different classification criteria.[8–14] It is supposable that these differences are real and may reflect the variable contribution of genetic and/or geographical/environmental factors among SSc populations from different ethnic groups or geographical areas.[21 22] Furthermore, the low rate of ssSSc observed in some reports,[9 12] including the present study, could also be related to an inadequate network of specialised tertiary referral centres of some geographic areas where a number of ssSSc may be diagnosed very late or completely overlooked.[22]

Our ssSSc subgroup showed a female/male ratio comparable to that of the Brazilian study[11] and of our earlier reports,[15 16] but significantly higher than that observed in other studies.[8 12 14] According to previous observation for the whole SSc population in Italy,[1 15] the longer time from RP onset to diagnosis seems to characterise the ssSSc subset, a finding also reported by other authors in national registries.[10 14] It may represent a useful prognostic factor at SSc diagnosis in individual patient, suggesting a rather slow progression of the microangiopathic dysfunction that characterises the SSc pathogenesis.[23 24]

The present findings confirmed the lower rate of peripheral vascular complications in ssSSc, namely the DPS and/or DU, compared with other subsets.[10 11 13 14] In particular, our ssSSc patients showed the lowest rate of DU among the three subsets, and a significantly lower percentage of DPS than the lcSSc subset. In this respect, a recent study found that DPS were associated with a severe disease course and worse outcomes.[25] In ssSSc, our data indicate a milder peripheral small vessel vasculopathy as shown by the rarity of major capillaroscopic modifications and the low rate use of vasoactive/vasodilating drugs.

In SSc, lung involvement includes ILD and PAH.[26] The recognition of more than 37% of ssSSc patients presenting ILD on HRCT (with a DLCO close to 70%), with a percentage comparable to lcSSc, is in agreement with previous studies,[8 10] but still higher than others.[12–14] Noteworthy, in our ssSSc cohort, the percentage of honeycombing, which correspond to the most advanced and severe sign of lung injury,[26] was very low. However, our findings demonstrate that, also in ssSSc, ILD should be a concern that should not be neglected.[27] In this respect, additional data from national registries are needed to verify the real occurrence and severity of lung involvement in ssSSc, as well as of other organs manifestations (ie, cardiac, GI and musculoskeletal) that showed a wide range of variability among previously published studies (table 3).

In our ssSSc patients, the autoantibody profile was similar to the data previously reported[8 10 11 13]; namely, anticentromere were detected in 40% or more, with antitopoisomerase I usually belonging 20% or less of patients.[10–14] This specific autoantibody dichotomy seems to be the distinctive immunological marker of the ssSSc subset.

The comparison between ssSSc and lcSSc revealed several similarities concerning demographic, clinical and immunological features. On the contrary, clear-cut differences were found in both ssSSc and lcSSc when compared with dcSSc, being the latter characterised by higher proportion of oesophageal, peripheral vascular (DPS, DU, calcinosis), pulmonary (functional alterations), worse NVC microvascular involvement and higher serum antitopoisomerase I autoantibodies. These findings were consistent with data formerly described.[10 11 13]

A thorough examination of the literature shows a substantial disagreement about including ssSSc within the scleroderma spectrum. Some authors recommend that ssSSc should be a separate condition to avoid misdiagnosis,[4 28] while others consider ssSSc as a mild subvariant of lcSSc.[8 9 12] In this scenario, several data suggested that the investigation of SSc subsets might help to better understand the disease aetiopathogenesis, and to shape the prognosis predicting the severity of organ complications.[1–4] The fact that ssSSc and lcSSc share a similar clinical picture, the autoantibody profile and the peripheral microangiopathy may suggest that these subsets are strongly related, although with a different skin phenotype. The heterogeneity of skin involvement remains a matter of debate in SSc, as well as the variable combination and the severity of microangiopathy/fibrosis-related manifestations in internal organs.[21 29–32]

The strengths and limitations of SSc registry-based multicentric studies have been previously addressed.[12 15 16] Although our SSc population is the largest reported among national registries, the present data are not conclusive. Possibly, long-term follow-up studies may verify the natural course and outcome of ssSSc patients in comparison to the other cutaneous subsets.[14 33]

The aim of our study was to provide an overall assessment of the ssSSc subset recruited at tertiary referral centres in our Italian SPRING registry. First, a relatively low proportion of ssSSc was observed within a large population of definite SSc, a finding that greatly varied among the few reports of the existing literature. Apart from skin involvement, the signs and symptoms of the ssSSc subset were mostly comparable with that of lcSSc. Both subsets were characterised by less frequent and less severe organ involvement, scarce NVC alterations, absence of anti-topoisomerase I positivity and a significantly different clinical pattern respect to dcSSc.

A number of issues still remain unclear: the absence of cutaneous sclerosis, and the clinical overlap between the ssSSc and lcSSc raise the question whether ssSSc represents a distinct SSc subset or a simple phenotypic variant of lcSSc. Overall, future investigations on the biological origin of the different distribution of skin fibrosis among SSc patients[29–32] may provide useful insights on the complex etiopathogenesis of the disease, likewise a novel disease sub-setting.[2 4 33]

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