# Systemic Sclerosis Sine Scleroderma: A Multicenter Study of 1417 Subjects

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*ABSTRACT.* ***Objective.*** To describe the clinical and serological features of systemic sclerosis sine scleroderma (ssSSc) in a multicentered SSc cohort.

***Methods.*** Data from 1417 subjects in the Canadian Scleroderma Research Group registry were extracted to identify subjects with ssSSc, defined as SSc diagnosed by an expert rheumatologist, but without any sclerodactyly or skin involvement prior to baseline study visit or during followup. Clinical and serological features of ssSSc subjects were compared to limited (lcSSc) and diffuse cutaneous SSc (dcSSc) subjects.

***Results.*** At the first registry visit, only 57 subjects (4.0%) were identified as having ssSSc. Of these, 30 (2.1%) were reclassified as lcSSc within 1.9 years. Thus, only 27 ssSSc subjects (1.9%) remained, with mean followup of 2.4 years. Clinical profiles of ssSSc were generally similar or milder compared to lcSSc, and milder than dcSSc, including rates of interstitial lung disease (25.9% ssSSc, 25.4% lcSSc, 40.3% dcSSc). Patients with ssSSc had serological profiles similar to those with lcSSc, including high rates of anticentromere antibodies (50.0% ssSSc, 47.5% lcSSc, 12.1% dcSSc), and low rates of antitopoisomerase I (16.7% ssSSc, 7.0% lcSSc, 21.8% dcSSc) and anti-RNA polymerase III (0 ssSSc, 11.1% lcSSc, 34.9% dcSSc).

***Conclusion.*** The condition ssSSc is rare and resembles lcSSc. These observations suggest that ssSSc is most likely a forme fruste of lcSSc, and that the absence of skin involvement may in part be related to misclassification arising from early or subtle skin involvement. There is little evidence to consider ssSSc as a distinct clinical or serological subset of SSc. (First Release Oct 1 2014; J Rheumatol 2014;41:2179–85; doi:10.3899/jrheum.140236)

*Key Indexing Terms:*
SCLERODERMA SINE SCLERODERMA
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Systemic sclerosis sine scleroderma (ssSSc), a subtype of scleroderma without sclerodactyly or more proximal skin involvement, was first described in 1954 by Abrams, *et al*[1]. Since then, there have been over 100 published cases of ssSSc. A study of 48 patients with ssSSc by Poormoghim, *et al* reported that ssSSc had features and prognosis similar to limited cutaneous SSc (lcSSc)[2]. Hunzelmann, *et al* reached a similar conclusion in their analysis of 22 patients with ssSSc from the German Network for Systemic Scleroderma[3]. In contrast, both the Spanish registry comprising 69 patients with ssSSc and a Brazilian cohort of 79 patients with ssSSc identified clinical differences such as more cardiac involvement and less telangiectasia in ssSSc, which they believed differentiated ssSSc from lcSSc[4,5]. Further, in a 2009 literature review by Toya and Tzelepis, the prevalence of antitopoisomerase I (Scl-70) antibodies, an antibody highly correlated with diffuse cutaneous SSc (dcSSc), was reported to be as common as anticentromere antibodies in ssSSc[6]. This suggests that the clinical and laboratory features as well as prognosis of ssSSc may be more heterogeneous than previously reported. However, several studies also reported that some cases originally

classified as ssSSc eventually progressed to lcSSc[2,4,5]. Thus, some inconsistencies could also be attributed to misclassification because of subtle or slowly evolving skin involvement.

We undertook our study to describe the clinical and serological features of ssSSc subjects in a large, multicenter SSc cohort, and to compare ssSSc subjects to subjects with lcSSc or dcSSc using a strict definition of ssSSc, excluding subjects who ever had skin involvement, including during followup.

## MATERIALS AND METHODS

*Patient source*. Our study subjects were patients with SSc enrolled in the multicenter Canadian Scleroderma Research Group (CSRG) cohort. Ethics committee approval for the CSRG data collection protocol and our study was obtained at all participating study sites. All subjects provided informed written consent to participate. The subjects included in our study were those whose baseline visit was between September 2004 and July 2013.

Patients in the CSRG cohort must have a diagnosis of SSc confirmed by a rheumatologist, be ≥ 18 years of age, be fluent in English or French, and likely to be compliant with study procedures and visits. When the CSRG cohort was created in 2004, we were aware that the 1980 preliminary criteria for the classification of SSc[7] lacked sensitivity, in particular for subjects with limited disease, and importantly for the subject at hand, no skin involvement. Therefore, the gold standard for cohort entry was physician diagnosis. Recently, the classification criteria for SSc were updated and reported to have greater sensitivity for SSc[8]. Indeed, we recently examined the performance of the 2013 criteria in the CSRG cohort and found that, overall, over 98% of the subjects met those criteria, compared to 88% who met the 1980 criteria. Among those with limited disease, 99% of the subjects in the CSRG cohort met the 2013 criteria, compared to 86% who met the 1990 criteria. Finally, among those with sine disease, 74% of the subjects met the 2013 criteria, compared to 11% for the 1990 criteria[9].

*Definitions of SSc subsets based on extent of skin involvement*. Skin involvement was assessed using the modified Rodnan skin score, a widely used clinical assessment measure where the examining rheumatologist records the degree of skin thickening ranging from 0 (no involvement) to 3 (severe thickening) in 17 areas (total score range 0–51)[10]. Patients with ssSSc were defined as those included into the cohort, and thereby diagnosed with SSc by an expert rheumatologist, but without any sclerodactyly or more proximal skin involvement at any time either prior to their baseline registry visit or during followup. Those with skin involvement were classified into limited (skin involvement distal to the elbows and knees with or without facial involvement) or diffuse (skin involvement proximal to the elbows and knees with or without truncal involvement) cutaneous subsets[11].

*Study variables*. Demographic information regarding age, sex, and ethnicity was collected by patient self-report. Disease duration was recorded by the study physician based on the time between the onset of the first non-Raynaud disease manifestation and baseline study visit. Study physicians recorded the presence of Raynaud phenomenon (RP), sclerodactyly, calcinosis, telangiectasias, digital pits, digital ulcers, digital tuft resorption, esophageal dysmotility, and a history of inflammatory polyarthritis, inflammatory myositis, or scleroderma renal crisis based on detailed clinical assessments including standardized histories and physical examinations. Abnormal nailfold capillaries (dropouts, enlarged, or giant capillaries) were identified by study physicians using a Dermlite dermatoscope. Study physicians also reported the concomitant presence of overlap diseases, including systemic lupus erythematosus, Sjögren syndrome (SS), rheumatoid arthritis, polymyositis, dermatomyositis, and/or mixed connective tissue disease.

To assess gastrointestinal (GI) involvement, patients answered yes or no to a series of 14 questions concerning appetite loss, difficulty swallowing, regurgitation of acid, nocturnal choking, heartburn, early satiety, abdominal bloating, nausea and vomiting, constipation, diarrhea, need for antibiotics for diarrhea, greasy stools, fecal incontinence, and need for parenteral nutrition. In addition, the presence of malabsorption, hyperalimentation, and/or pseudoobstruction were reported by study physicians.

Interstitial lung disease (ILD) was considered present if a high-resolution computed tomography (HRCT) scan of the lungs was interpreted by an experienced radiologist as showing ILD or, in the case where no HRCT was available, if either a chest radiograph was reported as showing either increased interstitial markings (not thought to be caused by congestive heart failure) or fibrosis, and/or if a study physician reported findings indicative of ILD on physical examination[12].

Systolic pulmonary artery pressure (sPAP) was measured using the Doppler flow measurement of the tricuspid regurgitant jet on echocardiography. Pulmonary hypertension was defined as an estimated sPAP ≥ 45 mmHg (an estimate that correlates strongly with right heart catheter studies)[13].

Function and disease severity were measured using the Scleroderma-Health Assessment Questionnaire (S-HAQ). It consists of the self-reported HAQ-Disability Index, a widely used instrument intended to assess functional ability in arthritis[14], and scales to measure the severity of symptoms specific for SSc in the past week[15]. The disease-specific questions in the S-HAQ relate to RP, digital ulcers, GI symptoms, and dyspnea. Each question is scored separately. Unlike the visual analog scales originally used for the S-HAQ, the assessments in our study were made using 11-point numerical rating scales ranging from 0 (representing no disease) to 10 (representing very severe disease).

Disease severity was also assessed globally, using physician- and patient-reported global assessments of disease severity, and by organ, using the Medsger Disease Severity Scale. The global assessments were made using 11-point numerical rating scales ranging from 0 (representing no disease) to 10 (representing very severe disease). The Medsger Disease Severity Scale assesses disease severity in 9 organ systems, namely, general health, peripheral vascular, skin, joint/tendon, muscle, GI tract, lungs, heart, and kidneys[16]. Each organ is scored separately from 0 to 4 depending on whether there is no, mild, moderate, severe, or endstage involvement.

*Serology*. Using a standardized operating protocol, sera were collected at baseline registry visits and sent to a central laboratory (Mitogen Advanced Diagnostics Laboratory, University of Calgary). Aliquots were stored at –80°C until needed for diagnostic assays. All immunoassays were performed by technologists with > 8 years of experience. Antinuclear antibodies and antibodies against centromere proteins (CENP) were detected by indirect immunofluorescence performed on HEp-2 cells (HEp-2000; ImmunoConcepts). CENP-B (recombinant full-length human CENP-B) and CENP-A ELISA (Dr. Fooke Laboratorien GmbH) were performed according to the manufacturer's AI-Line instructions and reported using a modified cutoff, as previously described[17]. Antibodies to topoisomerase I (Scl-70), Ro52/TRIM21, U1-RNP, SSA/Ro60, and SSB-La were assayed by an addressable laser bead immunoassay using a commercially available kit (QUANTAPlex ENA 8, INOVA Diagnostics Inc.) in a Luminex 100 (Luminex Corp.) assay platform. Anti-RNA polymerase III antibodies were assayed by QUANTA Lite RNA Pol III (INOVA Diagnostics Inc.), as previously described[18]. An ELISA with the synthetic peptide PM1-Alpha, PM/Scl-100's major epitope, was performed according to the manufacturer's directions (Dr. Fooke Laboratorien GmbH)[19].

Of the 1417 subjects included in our study, the first 1158 (82%) had antibody testing done centrally. However, because of funding issues, we subsequently suspended this centralized testing. Thus, antinuclear antibody testing was not available for about 18% of the subjects included in our study. However, this represents data missing completely at random and should therefore not bias the estimates reported.

*Statistical analysis*. Descriptive statistics were used to summarize the baseline characteristics of the patients. Kaplan-Meier survival analysis was

performed to compare survival between disease subsets. Time to death was defined as the time between the onset of the first non-Raynaud disease symptom and date of death or date of last visit if the patient was still alive. P values less than 0.05 were considered significant. However, given the small number of ssSSc subjects and the exploratory nature of the analysis, both numerical and statistical differences were considered clinically informative, and correction for multiple testing was not done. All statistical analyses were performed with SAS v.9.2 (SAS Institute).

## RESULTS

There were 1417 patients included in our study. At baseline study visit, 57 (4.0%) were identified as having ssSSc (i.e., without sclerodactyly or any skin involvement ever noted prior to that visit). Of these, 30 (2.1%) were reclassified as lcSSc because of skin involvement noted at subsequent visits, on average 1.9 years (interquartile range 1.0–3.0 yrs) after baseline visits. Thus, using a strict definition of ssSSc, our study consisted of 27 ssSSc subjects (1.9%) with a mean duration of followup of 2.4 years. In addition, there were 873 subjects (61.6%) with lcSSc and 517 (36.5%) with dcSSc.

Baseline demographic and clinical characteristics of the study subjects are presented in Table 1. The demographic features of ssSSc subjects were generally similar to those of lcSSc subjects, including the proportion of women (89% ssSSc and 90% lcSSc vs 79% diffuse) and whites (96% ssSSc and 91% lcSSc vs 79% dcSSc). Both ssSSc and lcSSc subjects had slightly longer disease duration compared to dcSSc subjects (11.2, 11.5, and 9.0 yrs, respectively). However, age at disease onset was similar in all 3 groups (about 45 yrs).

Clinical signs and symptoms in ssSSc subjects were, in general, considerably less prevalent compared to dcSSc subjects and to a lesser extent those with lcSSc, including RP, calcinosis, esophageal dysmotility, telangiectasia, digital pits, ulcers and tuft resorption, inflammatory polyarthritis, inflammatory myositis, and GI symptoms. Overlap disease was also considerably less frequent in ssSSc, with only 1 subject (4%) reported to have SS compared to 159 lcSSc (19%) and 78 dcSSc (16%) subjects with overlap disease. ILD was as common in ssSSc (26%) and lcSSc (25%), but less common than in dcSSc (40%). The notable exception was pulmonary hypertension, which was similarly present in 11% of all 3 subsets. The frequency of scleroderma renal crisis was very low, with only 1 case among ssSSc subjects, precluding a firm comparison to lcSSc and dcSSc.

*Table 1*. Baseline demographic and clinical characteristics of the study cohort.

| Characteristics | Diffuse, n = 517 | | Limited, n = 873 | | Sine, n = 27 | |
|---|---|---|---|---|---|---|
| | Mean or % | SD or N | Mean or % | SD or N | Mean or % | SD or N |
| Age, yrs | 53 | 11.7 | 57.1 | 12.3 | 56.4 | 13.6 |
| Female | 78.5 | 406 | 90.2 | 787 | 88.9 | 24 |
| White | 86.1 | 427 | 91.4 | 734 | 96 | 24 |
| Disease duration, yrs | 9 | 8.5 | 11.5 | 9.9 | 11.2 | 8.8 |
| Age at disease onset, yrs | 44 | 13.2 | 45.5 | 13.9 | 44.4 | 14.6 |
| Modified Rodnan skin score | 18.1 | 10.3 | 5.1 | 4.2 | 0 | 0 |
| Raynaud phenomenon | 96.3 | 496 | 97.5 | 849 | 92.6 | 25 |
| Calcinosis | 30.6 | 158 | 25.7 | 224 | 15.4 | 4 |
| Esophageal dysmotility | 70 | 319 | 68.9 | 557 | 56 | 14 |
| Sclerodactyly | 96.3 | 496 | 91.7 | 800 | 0 | 0 |
| Telangiectasias | 71.7 | 352 | 76.4 | 654 | 69.2 | 18 |
| Nailfold capillary abnormalities | 74.4 | 384 | 74.7 | 651 | 74.1 | 20 |
| Digital pits | 54.9 | 282 | 43.6 | 380 | 11.1 | 3 |
| Fingertip ulcers | 58.4 | 302 | 48.1 | 420 | 18.5 | 5 |
| Digital tuft resorption | 46.7 | 237 | 31.7 | 274 | 11.1 | 3 |
| Inflammatory polyarthritis | 37.1 | 185 | 28.1 | 237 | 11.5 | 3 |
| Inflammatory myositis | 15.7 | 81 | 7.7 | 67 | 3.7 | 1 |
| No. GI symptoms, 0–14 | 4.3 | 3 | 4.1 | 3.2 | 3.6 | 3 |
| Malabsorption | 16.6 | 85 | 11.9 | 103 | 0 | 0 |
| Pseudoobstruction | 4.7 | 24 | 3.4 | 29 | 0 | 0 |
| Hyperalimentation | 4.3 | 22 | 1.7 | 15 | 0 | 0 |
| Scleroderma renal crisis | 7.6 | 39 | 1.9 | 16 | 3.7 | 1 |
| Interstitial lung disease | 40.3 | 203 | 25.4 | 218 | 25.9 | 7 |
| Pulmonary hypertension | 10.5 | 46 | 11.1 | 82 | 11.5 | 3 |
| Any overlap disease | 15.6 | 78 | 18.6 | 159 | 4 | 1 |
| Sjögren syndrome | 6.3 | 32 | 8.6 | 74 | 4 | 1 |
| Rheumatoid arthritis | 2.8 | 14 | 4.8 | 41 | 0 | 0 |
| Systemic lupus erythematosus | 3 | 15 | 3.8 | 33 | 0 | 0 |
| Polymyositis/dermatomyositis | 5.3 | 27 | 3 | 26 | 0 | 0 |
| Mixed connective tissue disease | 2.8 | 14 | 2.6 | 22 | 0 | 0 |

GI: gastrointestinal.

Disease severity was generally milder in ssSSc compared to dcSSc, and either milder or comparable to lcSSc (Table 2). A notable exception was the severity of patient-reported breathlessness, which was comparable in all 3 subsets (ranging from 2.0–2.2, on a scale of 0–10).

The serological profiles of patients with ssSSc were generally similar to those of lcSSc subjects (Table 3), in particular in the high rates of anti-CENP antibodies detected by indirect immunofluorescence, as well as CENP-A and CENP-B as detected by ELISA. Antitopoisomerase I were less frequent in both ssSSc (17%) and lcSSc (11%), compared to dcSSc (22%). Anti-RNA polymerase III antibodies were much less frequent in lcSSc (7%) compared to dcSSc (35%) subjects, and none of the patients with ssSSc had anti-RNA polymerase III, PM/Scl, SSA/Ro60, or SSB/La autoantibodies. It was noted that the frequency of anti-Ro52/TRIM21 was about 20% in lcSSc and dcSSc, and only 10% in ssSSc.

Of subjects for whom vital status was available, 12% (143/1180) died. Mean time to death from disease onset was 14.0, 13.1, and 11.9 years in the ssSSc, lcSSc, and dcSSc groups, respectively (Figure 1). There was a significant difference (p = 0.0006) in survival between patients with dcSSc and patients with lcSSc, but no significant difference in survival between lcSSc, dcSSc, and ssSSc, although the number of deaths in the ssSSc subset was small.

## DISCUSSION

Even in the context of a cohort of patients with SSc, ssSSc is relatively rare. At the first registry visit, only 57 of 1400 subjects in the CSRG cohort were identified as having ssSSc. However, 30 of these were later reclassified as lcSSc because of skin involvement noted on average within 1.9 years. Thus, only 27 ssSSc subjects (1.9% of the whole cohort) remained, and these also had relatively short durations of followup (mean 2.4 yrs). The clinical profiles of

*Table 2*. Measures of disease severity.

| | Diffuse, n = 517 | | Limited, n = 873 | | Sine, n = 27 | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| MD's global assessments of severity, 0–10 | 3.7 | 2.5 | 2.4 | 2 | 1.9 | 1.7 |
| Patient's global assessments of severity, 0–10 | 4.2 | 2.7 | 3.2 | 2.5 | 3.2 | 2.6 |
| Medsger disease severity scores | | | | | | |
| General | 1.1 | 1.3 | 0.8 | 1.1 | 0.9 | 1.1 |
| Skin | 1.8 | 0.8 | 1 | 0.3 | 0 | 0 |
| Lung | 1.4 | 1.1 | 1.3 | 1.1 | 1.1 | 1.1 |
| Heart | 0.6 | 1.1 | 0.4 | 0.9 | 0.5 | 0.9 |
| Joint/tendon | 1.2 | 1.4 | 0.4 | 1 | 0 | 0 |
| Gastrointestinal | 2 | 0.8 | 1.9 | 0.8 | 1.9 | 0.5 |
| Peripheral/vascular | 1.8 | 1.2 | 1.5 | 1.2 | 0.8 | 1 |
| Muscle | 0.4 | 0.9 | 0.2 | 0.7 | 0 | 0.2 |
| Kidney | 0.2 | 0.8 | 0.1 | 0.4 | 0.1 | 0.6 |
| HAQ, 0–3 | 1 | 0.7 | 0.7 | 0.7 | 0.4 | 0.5 |
| Severity of Raynaud phenomenon, 0–10 | 3.3 | 3 | 2.7 | 2.9 | 2 | 2.5 |
| Severity of dyspnea, 0–10 | 2.2 | 2.7 | 2 | 2.5 | 2.1 | 2.3 |
| Severity of GI symptoms, 0–10 | 1.9 | 2.6 | 1.7 | 2.5 | 1.2 | 2.2 |
| Severity of finger ulcers, 0–10 | 2.5 | 3.3 | 1.6 | 2.7 | 0.6 | 2 |

HAQ: Health Assessment Questionnaire; GI: gastrointestinal.

*Table 3*. Serological profiles.

| | Diffuse | | Limited | | Sine | |
|---|---|---|---|---|---|---|
| | % | n positive/n tested | % | n positive/n tested | % | n positive/n tested |
| Antinuclear antibodies by IIF | 94.6 | 399/422 | 96 | 689/718 | 94.4 | 17/18 |
| Anti-CENP by IIF | 12.1 | 51/422 | 47.5 | 341/718 | 50 | 9/18 |
| CENP-A | 13.4 | 41/307 | 47.6 | 232/487 | 60 | 6/10 |
| CENP-B | 13.4 | 41/306 | 49.7 | 242/487 | 60 | 6/10 |
| RNA polymerase III | 34.9 | 107/307 | 7 | 34/488 | 0 | 0/10 |
| Antitopoisomerase I | 21.8 | 92/422 | 11.1 | 80/718 | 16.7 | 3/18 |
| PM/Scl | 6.7 | 20/297 | 7.6 | 36/471 | 0 | 0/9 |
| U1 RNP | 5.7 | 24/422 | 7 | 50/718 | 5.6 | 1/18 |
| Ro52/TRIM21 | 19.2 | 68/354 | 21 | 124/591 | 10 | 1/10 |
| SSA/Ro60 | 6.2 | 22/354 | 5.3 | 31/591 | 0 | 0/10 |
| SSB/La | 3.7 | 13/354 | 2.2 | 13/591 | 0 | 0/10 |

IIF: indirect immunofluorescence; CENP: centromere protein.

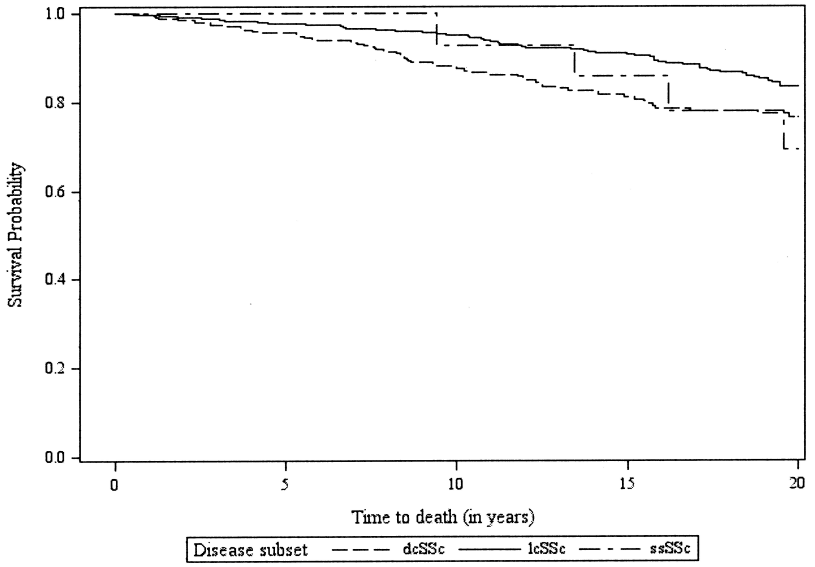


*Figure 1*. Time to death since the first non-Raynaud disease symptom, according to disease subset. Log-rank p values: lcSSc vs ssSSc = 0.2595; dcSSc vs ssSSc = 0.8969; dcSSc vs lcSSc = 0.0006. lcSSc: limited cutaneous systemic sclerosis; ssSSc: systemic sclerosis sine scleroderma; dcSSc: diffuse cutaneous systemic sclerosis.

these patients with ssSSc documented milder disease, but autoantibody profiles similar to those of lcSSc subjects. These observations suggest that ssSSc is most likely a forme fruste of lcSSc, and that the absence of skin involvement may in part be related to misclassification arising from early or subtle skin involvement, or very slowly progressive cutaneous disease.

Published analyses of ssSSc reveal considerable heterogeneity in clinical and laboratory findings (Appendix 1). Our results are consistent with studies that have suggested that ssSSc is related to lcSSc, both clinically and serologically[2,3]. We believe our results are more robust than most previously published, to the extent that we excluded from the ssSSc group subjects who developed skin involvement during followup.

At present, SSc subsets are useful for understanding etiology and predicting organ involvement and prognosis. If one assumes that the autoantibody profiles in SSc reflect an underlying etiology, then the similarities of the antibody profiles between lcSSc and ssSSc suggest that they are etiologically related. The fact that the clinical picture in ssSSc resembled mild lcSSc also suggests that these 2 subgroups are related. A finding of interest and potential unique relevance to the ssSSc cohort is that few of the patients with ssSSc had anti-Ro52/TRIM21, the second most common autoantibody in our[20] and the Australian[21] SSc cohorts and the third most common in the German cohort[22]. It is a biomarker that has been associated with polyautoimmunity[20]. In addition, the absence of antibodies to PM/Scl, a putative marker for an overlap syndrome of PM and SSc[23,24], was reflected in the virtual absence of inflammatory myopathy in the ssSSc group. Finally, the prognosis of ssSSc in terms of time to death was similar to that of lcSSc and longer than that of dcSSc. This implies that even without true sclerodermatous skin changes, ssSSc subjects may be considered to belong to the lcSSc subset. Notwithstanding the aforementioned, subsetting by the extent of skin involvement in SSc may be suboptimal because of problems of misclassification; further studies considering differences in etiology, clinical features, prognosis, and eventually response to treatment are ongoing to identify better SSc subsets.

Our study is not without limitations. In particular, the small number of subjects with ssSSc, despite the large originating cohort, may have contributed to low power and inability to identify distinct features unique to this subset. In addition, followup for the ssSSc subjects was relatively short. Finally, as with any large observational longitudinal cohort with detailed data collection, there is inevitably missing data. This is a problem not so much for clinical variables, where missingness for most variables reported in Tables 1 and 2 was largely less than 10%, but more so for investigations, in particular in our study for forced vital capacity (missing data about 14%), DLCO (missing data about 23%), and cardiac echocardiograms (missing data about 15%). In these cases, the causes of missing data are numerous, likely both random and nonrandom, thereby potentially biasing estimates either away and/or toward the null, and with the net effect difficult to know. We acknowledge this important limitation, which is inherent in the study design. Nevertheless, in our study,

the study protocol was the same regardless of skin involvement and the proportion of missingness was also the same in limited and diffuse, and even tended to be lower in sine subjects (data not shown). Thus, the comparisons between groups remain defensible. On the other hand, the strengths of this paper include the longitudinal followup that allowed us to define ssSSc that persisted over time and the detailed clinical and serological data.

Based on a strict definition, and detailed clinical and serological comparisons, ssSSc is a rare entity and could be considered a mild form of lcSSc. Current approach to subsetting SSc based on extent of skin involvement are likely suboptimal and better approaches, possibly based on autoantibodies, are needed.

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**APPENDIX 1.** Comparison of selected clinical and serological features of ssSSc subjects in the Canadian Scleroderma Research Group cohort compared to those in other large cohorts. Adapted from Marangoni, *et al*[5]. Used with permission. All data are represented as n (%) unless specified otherwise.

| | Canada, n = 27 | Pittsburgh 2000[2], n = 48 | Germany 2008[3], n = 22 | Spain 2011[4], n = 69 | Brazil 2013[5], n = 79 |
|---|---|---|---|---|---|
| Total n of cohort | 1417 | 555 | 1483 | 916 | 947 |
| With ssSSc | 27 (2) | 48 (9) | 22 (1.5) | 69 (7.5) | 79 (8.3) |
| Age at disease onset, mean (SD) | 44.4 (14.6) | 51 (range 17–78) | — | 44.9 (18.2) | 46.04 (13.1) |
| Female | 24/27 (88.9) | 41/48 (85) | 20/22 (90.9) | 62/69 (89.8) | 76/79 (96.2) |
| Digital ulcers | 5/27 (18.5) | 16/48 (33) | 7/22 (31.8) | 10/69 (14.5) | 19/79 (24.1) |
| Articular disease | 3/27 (11.5) | 21/48 (44) | 7/22 (31.8) | 9/69 (13) | 35/79 (44.3) |
| Muscular disease | 1/27 (3.7) | 2/48 (4) | 3/22 (13.6) | 2/69 (2.9) | 10/79 (12.7) |
| Esophageal dysmotility | 14/25 (56.0) | 37/48 (77) | 16/22 (72.7) | 31/69 (44.9) | 64/77 (83.1) |
| Interstitial lung disease | 7/27 (25.9) | 32/47 (68) | 16/22 (72.7) | 44/69 (63.7) | 37/65 (56.9) |
| Pulmonary hypertension | 3/26 (11.5) | 11/48 (23) | 3/22 (13.6) | 17/69 (24.0) | 18/79 (22.8) |
| Anticentromere antibodies | 9/18 (50.0) | 15/45 (33) | 8/22 (36.4) | 27/69 (24.6) | 33/79 (41.8) |
| Mortality rate | 4/20 (20) | 19/48 (40) | — | 6/69 (8.7) | 6/79 (7.6) |

ssSSc: systemic sclerosis sine scleroderma.