The Scleroderma Patient-Centered Intervention Network (SPIN) Cohort: baseline clinical features and comparison to other large scleroderma cohorts

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CONFLICTS OF INTEREST:

ABSTRACT:

Objective: The SPIN Cohort is a longitudinal web-based study to develop, evaluate and test disease specific psychosocial and rehabilitation support. The aim was to present the baseline demographic, medical, and patient reported outcomes (PROs) features of the Scleroderma Patient-centered Intervention Network (SPIN) Cohort and to assess the comparability with other large systemic sclerosis (SSc) cohorts.

Methods: Descriptive statistics were used to summarize SPIN Cohort characteristics, and these were compared to published data of European Scleroderma Trials and Research (EUSTAR) and Canadian Scleroderma Research Group (CSRG) cohorts.

Results: Regarding demographics, organ involvement and antibody profiles, the SPIN Cohort was broadly comparable to the EUSTAR and CSRG SSc cohorts. There was a high proportion of women and of whites in all cohorts though relative proportions did differ. Scl 70 antibody frequency was highest in EUSTAR, followed by SPIN and lowest in CSRG. This was reflected in the higher proportion of interstitial lung disease among diffuse cutaneous SSc patients in SPIN compared to CSRG (48.5% vs 40.3%). RNA polymerase III antibody frequency was highest in SPIN and remarkably lower in EUSTAR (21.1% vs 2.4%) consistent with the higher prevalence of SSc renal crisis (4.5% vs 2.1%) in SPIN. Disease burden, determined by the prevalence of organ involvement and multiple validated PROs, was greater among diffuse cutaneous SSc patients than limited cutaneous patients in SPIN.

Conclusions: The SPIN Cohort is comparable to other large prevalent SSc cohorts and therefore insights gained from the SPIN Cohort should be generalizable to the SSc population at large.

Introduction

Patients living with rare diseases often lack access to disease-specific psychosocial and rehabilitation interventions that are important components of disease management and patient centered care. In more common chronic illnesses such as chronic obstructive pulmonary disease, asthma, diabetes and arthritis, existing evidence suggests that strategies to improve self-management can positively impact disease specific outcomes and quality of life (1-5). However, in the context of more rare diseases like systemic sclerosis (SSc, or scleroderma), there is a lack of evidence to support disease-specific interventions. To address this problem the Scleroderma Patient-centered Intervention Network (SPIN) was launched in 2013 as an international collaboration to develop and test psychosocial and rehabilitation interventions for patients living with SSc (6).

Recognizing that rare diseases present a major barrier to conducting adequately powered trials, SPIN utilizes the cohort multiple randomized controlled trial (cmRCT) design (7). In this design, a cohort of patients with SSc is followed longitudinally and consented to participate in web-based randomized interventions providing a basis for comparison of a given intervention. Upon enrollment, physicians provide basic medical data, and patients complete a core set of patient reported outcome measures (PROs) every 3 months that provide the basis for measuring impact of SSc on quality of life and disability (6).

The objectives of this study were to summarize baseline demographic and clinical characteristics of current participants in the SPIN Cohort and to compare these baseline data to two other large SSc cohorts: the Canadian Scleroderma Research Group (CSRG) Registry and the European Scleroderma Trials and Research (EUSTAR) group cohort, to

determine similarities or differences among these cohorts which could affect the generalizability of SPIN findings to the overall SSc patient population.

Patients and Methods

SPIN Cohort

This was a cross-sectional study including baseline data of patients enrolled in the SPIN Cohort who completed study questionnaires from April 2014 through October 2016. Patients in the SPIN Cohort were enrolled at 32 centers Canada, USA, UK, and France. To be eligible for the SPIN Cohort, patients must have a diagnosis of SSc according to the 2013 ACR/EULAR classification criteria (8), confirmed by a SPIN physician, be at least 18 years of age, having the ability to give informed consent, and be fluent in English or French. Exclusion criteria for participation in the SPIN Cohort include not having access to the internet or otherwise not being able to respond to questionnaires via the internet. The SPIN sample is a convenience sample. Eligible patients are invited by the attending physician or a supervised nurse coordinator to participate in the SPIN Cohort, and written informed consent is obtained. The local SPIN physician or supervised nurse coordinator then completes a medical data form that is submitted online to initiate patient registration in the SPIN Cohort. After completion of online registration, an automated welcoming email is sent to participants with instructions to on how to activate their SPIN online account and how to complete the SPIN Cohort patient measures online. SPIN Cohort patients complete PROs via the internet upon enrollment and subsequently every 3 months. The SPIN Cohort study was approved by the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada and by

the Institutional Reviews Boards of each participating center. A protocol to maximize data collection and participation was in place as outlined in the SPIN Cohort protocol (6). The present paper summarizes the baseline medical and PRO data for the SPIN enrollees with limited or diffuse cutaneous SSc available at the time of this analysis.

Comparison Cohorts: EUSTAR and CSRG

A detailed description of enrolment in the CSRG and EUSTAR cohorts can be found elsewhere (9,10).

In short, patients in the CSRG cohort were enrolled between September 2004 and July 2013. Patients in the CSRG are adults with a diagnosis of SSc confirmed by a rheumatologist who complete measures in English or French. Of patients in the CSRG cohort, 98% meet the 2013 ACR/EULAR classification criteria. SPIN Cohort baseline data are compared with data from the CSRG at baseline

Patients in EUSTAR were enrolled between June 2004 and June 2011 from 174 (mainly European) centres. EUSTAR is a multinational, prospective and open scleroderma cohort. Participating centres seek ethics committee approval, followed by the entry of the Minimal Essential Data set (MEDS) for all consecutive consenting patients (9, 11). Patients who have been classified according to the 1980 ACR were included, and diffuse versus limited cutaneous SSc subset classification was done according to the leRoy criteria.

Measures

Sociodemographic and Medical Data. Patients provided demographic data. SPIN physicians completed a medical data form including all items of the 2013 ACR/EULAR SSc classification criteria (8) as well as variables that were deemed to be important by SPIN rheumatologists (approximately 13 experts in the treatment of SSc). Recruiting physicians provided time since first non-Raynaud's phenomenon symptoms, onset of Raynaud's phenomenon, and diagnosis; SSc subtype (limited cutaneous SSc [lcSSc] or diffuse cutaneous SSc [dcSSc]) (12) modified Rodnan skin score (mRSS) (13); presence of overlap syndromes (systemic lupus erythematosus, rheumatoid arthritis, Sjögrens syndrome, idiopathic inflammatory myositis, primary biliary cirrhosis, and/or autoimmune thyroid disease); and presence of joint contractures (*no/mild (0-25%)* versus *moderate/severe (>25%)* limit in range of motion). Lung disease was defined as "pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of "Velcro" crackles on auscultation, not due to another cause such as congestive heart failure" (*yes*/*no*), and pulmonary hypertension was defined as "pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions (*yes*/*no*)."

Cochin Hand Function scale (CHFS). The 18-item CHFS (14,15) measures the ability to perform daily hand-related activities. Items are scored on a Likert scale from 0 (*yes, without difficulty*) to 5 (*impossible*), and are grouped into five content categories: kitchen, dressing oneself, hygiene, the office, and other. Total scores range from 0 to 90, and higher scores indicate more hand disability. Despite the different content categories, only the total score is used and not subscale scores, and there is no evidence for whether any one category is more or less useful than others. The CHFS has been validated in SSc

(16).

Health Assessment Questionnaire - Disability Index (HAQ-DI). Functional disability was measured using the Disability Index of the Health Assessment Questionnaire (HAQ-DI) (17). The HAQ-DI assesses 8 disability categories over the past 7 days (dressing/grooming, arising, eating, walking, hygiene, reach, grip, common daily activities). Items are rated on a 4-point scale, ranging from 0 (*without any difficulty*) to 3 (*unable to do*), with higher scores indicating greater functional disability. The total score is the mean of the highest scores of each of the 8 categories, ranging from 0 (*no disability*) to 3 (*severe disability*). The HAQ-DI is widely used in rheumatic diseases and has been validated in SSc (17).

Patient Health Questionnaire-8 (PHQ-8). Symptoms of depression were measured using the 8-item Patient Health Questionnaire (PHQ-8) (18). The PHQ-8 items measure depressive symptoms over the last 2 weeks on a 4-point scale, ranging from 0 (*not at all*) to 3 (*nearly every day*). A total score is obtained by summing item scores, with higher scores indicating more depressive symptoms. The PHQ-8 performs equivalently to the PHQ-9 (19), which is a valid measure of depressive symptoms in patients with SSc (20).

Patient-Reported Outcomes Measurement Information System -29 (PROMIS-29v2). Patient-reported health status was measured using the 29-item PROMIS-29 profile version 2.0 (21, 22). The PROMIS-29 measures eight domains of health status over the past 7 days with 4 items for each of 7 domains (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference) plus a single item for pain intensity. Each item is scored on a 5-point scale,

ranging from 1 to 5, with different response options for different domains, except for the item measuring pain intensity, which uses an 11-point rating scale ranging from 0 (*no pain*) to 10 (*worst imaginable pain*). Higher scores represent more of the domain being measured; that is, better physical function and ability to participate in social roles and activities, but higher levels of anxiety, depression, fatigue, sleep disturbance, pain interference, and pain intensity. Total raw scores are obtained by summing item scores for each domain, which are then converted into T-scores standardized from the general US population (mean = 50, standard deviation [SD] = 10). The PROMIS-29v2 is a valid measure of health status in patients with SSc (23).

*Satisfaction With Appearance (SWAP) Scal*e. Body image concerns due to changes in appearance from SSc were be assessed with the Satisfaction with Appearance Scale (SWAP). The 14-item SWAP was developed to measure non-weight related body image dissatisfaction among burn survivors (24). The SWAP has been validated for SSc (25,26). Respondents to the SWAP rate the degree to which they feel each item reflects their thoughts and feelings about their appearance on a 7-point scale ranging from 1 (*strongly disagree)* to 7 (*strongly agree)*. The SWAP has a two-factor structure, Perceived Social Impact, reflecting social discomfort, and Subjective Dissatisfaction, reflecting dissatisfaction with various body parts. Higher scores indicate greater body image dissatisfaction (27). A brief six-item version of the SWAP (Brief-SWAP) has also been developed and validated in SSc (28,29).

Self-Efficacy to Manage Chronic Disease Scale (SEMCD). The 6-item SEMCD Scale measures confidence in one's ability to manage fatigue, pain, emotional distress and other symptoms as well as to reduce the need for medical care and reliance on

medications (28). Respondents are asked to rate their confidence in their ability to perform certain tasks regularly at the present time. Each item is rated on a numerical scale ranging from 1 (*not confident at all*) to 10 (*totally confident*). The score for the scale is the mean of all items, with higher scores reflecting greater self-efficacy. The SEMCD scale is a valid measure of self-efficacy in patients with SSc (31).

Statistical Analyses

Descriptive statistics were used to summarize SPIN Cohort characteristics. Means and SDs were calculated for continuous variables, and categorical variables were reported by frequency and percentage. SPIN Cohort characteristics were compared to the EUSTAR and CSRG cohorts using existing published baseline data (9,10). Continuous variables were compared using t-test and categorical variables were compared using a chi-square or Fisher exact test. Statistical significance was set at $p < 0.05$. The analyses were performed with the statistical software Stata version 14.2.

Results

Characteristics of the SPIN Cohort

Baseline demographic, clinical, and PRO measures are presented in Table 1. There were 1125 enrollees included in this analysis, of whom 41% (n=460) were classified as diffuse cutaneous SSc (dcSSc) and 59% (n=665) as limited cutaneous SSc (lcSSc). The mean age was 55.6 years (SD=12.1) and the majority of enrollees were female (87%); this was similar among the subgroups. There was a relatively lower frequency of white patients in the dcSSc subgroup (75%) compared to the lcSSc

subgroup (87%). Mean time since the onset of the first non-Raynaud's symptom at enrollment was longer in the lcSSc (13.4 years) compared to the dcSSc (9.1 years) subgroup.

As expected, a high overall frequency (99%) of Raynaud's phenomenon was observed. A positive ANA was detected in 93% of patients. The anticentromere antibody was more frequent in the lcSSc (49%) compared to the dcSSc (9%) subgroup, whereas the Scl70 and RNA polymerase III antibodies were more frequent in the dcSSc compared to the lcSSc subgroup (32% vs. 19% and 41% vs. 5%, respectively). The mean modified Rodnan skin score (mRSS) was higher in the dcSSc (13.3) than the lcSSc group (4.2).

Clinical variables related to skin involvement were generally more prevalent in the dcSSc subgroup compared to the lcSSc subgroup: sclerodactyly, digital pitting scars, digital ulceration, abnormal skin pigmentation; whereas the frequencies of abnormal nailfold capillaries, and puffy fingers were similar between the dcSSc and lcSSc subgroups. Telangiectasias were more frequent in the lcSSc (77%) than the dcSSc (68%) subgroup. Regarding other organ involvement, the frequency of joint contractures, tendon friction rubs, and lower GI involvement were all more common in the dcSSc subgroup compared to lcSSc although the frequency of esophageal involvement was similarly prevalent in both groups. Interstitial Lung Disease (ILD) occurred more frequently in dcSSc (49%) compared to lcSSc (28%) whereas Pulmonary Arterial Hypertension (PAH) was more frequent in lcSSc (12%) than dcSSc (8%). SSc renal crisis was also more frequent in dcSSc than lcSSc (9% vs 2%). There were a variety of overlapping autoimmune illness of which Sjogren's syndrome and autoimmune thyroid disease were the most prevalent.

Baseline scores for the six PRO measures are presented in Table 2. The mean scores for the CHFS, HAQ-DI, PHQ-8 and SWAP were higher in the dcSSc compared to the lcSSc subgroup, reflecting greater disability, more depressive symptoms, and greater dissatisfaction with appearance. The SEMCD score was similar in both groups. The PROMIS-29v2 domain scores are reported as a standardized T-scores with the mean for the general population expected to be 50 and the SD expected to be 10. In the SPIN Cohort, the T-score was below the general population mean for the physical function (43.0) and social roles (48.0) domains, and higher for anxiety (51.5), depression (50.9) fatigue (55.3), sleep disturbance (52.3) and pain interference (55.5) domains.

Comparison of SPIN Cohort and CSRG

A comparison of the SPIN and CSRG subgroups (10) is presented in Table 3. Patients were comparable in age. More women were in the SPIN dcSSc subgroup (86% vs 79%) compared to CSRG. There were fewer white patients in the SPIN dcSSc subgroup compared to CSRG (75% vs 83%) ands the lcSSc groups (87% vs 91%). There was a shorter disease duration in the SPIN lcSSc subgroup compared to CSRG (13.4 vs 11.5 years) whereas disease duration in the dcSSc groups was not different. Compared to CSRG (95%) there was a lower frequency of ANA positivity in the dcSSc group in SPIN (91%). There was a higher frequency of the Scl70 in both subsets in SPIN compared to CSRG.

Skin involvement was more substantial in CSRG than SPIN, with higher mean skin scores in both subsets, higher frequency of sclerodactyly and ulcers in both subsets, and a higher frequency of pitting scars in the lsSSc group. Abnormal nailfold capillaries,

on the other hand, were more frequent in SPIN than CSRG in both subsets., and there were no differences in the presence of telangiectasia.

In regard to other organ involvement, there was a higher occurrence of esophageal involvement in SPIN compared to CSRG. Among dcSSc patients, there was a higher frequency of ILD in SPIN than in CSRG (49% vs 40%). The frequency of PAH and SSc renal crisis were no different between the cohorts. There was a higher frequency of Rheumatoid Arthritis and Myositis in the dcSSc subset in SPIN compared to CSRG.

Comparison of SPIN Cohort and EUSTAR

A comparison of baseline features between the SPIN and EUSTAR cohorts (9) is presented in Table 4. Variables were compared where data were available. Patients with dcSSc in the SPIN Cohort were older and less likely to be female compared with EUSTAR. In both subsets, there were fewer White patients in SPIN compared to EUSTAR, and the BMI was higher for SPIN in both subsets. The mean age at first non-Raynaud's phenomenon was higher in the EUSTAR lcSSc subset than SPIN, and time since onset of non-Raynauds symptoms was longer in SPIN in bith subsets.

Among both subsets, the frequency of Scl 70 antibody was lower in SPIN compared to EUSTAR (dcsSSc 32% vs 60%; lcSSc 19% vs 23%). RNA Polymerase III was remarkably higher in the SPIN dcSSc subset than EUSTAR (41% vs 5%) and lcSSc subset (5% vs 1%). There were no differences in ANA and centromere positivity.

There was a higher frequency of pitting scars in the SPIN dcSSc subset compared to EUSTAR, and distal pulp ulcers were more frequent in both subsets of SPIN. Abnormal nailfold capillaries, on the other hand, were less frequent in SPIN than CSRG.

Esophageal involvement was more frequent in SPIN compared to EUSTAR. A direct comparison of ILD and PAH could not be made due to methodological differences in measurement of these variables.

Discussion

Overall, the SPIN Cohort has more similarities than differences to the two other cohorts of prevalent SSc patients included in this report. Methodological differences in the definition of organ-specific involvement could explain some of the dissimilarities as well as differences in the underlying rationale for establishing the cohort. The purpose of the SPIN Cohort was to conduct rigorous trials on interventions to improve health-related quality of life and disability. The clinical data that were collected were meant to establish the diagnosis and to provide a disease profile in terms of presence or absence of organ involvement at the time of enrollment. Both the CSRG and the EUSTAR cohorts, however, were developed specifically to follow disease progression over time.

Comparing demographics, there was a high proportion of women and of whites in all cohorts though relative proportions did differ. There was a lower proportion of whites in SPIN compared to EUSTAR and CSRG, which may reflect the multinational recruitment in the SPIN Cohort.

With respect to organ involvement and antibody profiles there were statistical differences between the cohorts but whether the differences are clinically significant or due to differences in methodology is uncertain. There was a high frequency of Raynaud's phenomenon and ANA positivity in all cohorts. The frequency of Scl 70 antibodies was highest in EUSTAR, followed by SPIN, and lowest in CSRG. The Scl 70 antibody has an

established association with lung involvement (32). The difference in frequency was reflected by the higher frequency of ILD in the SPIN dcSSc subgroup compared to the CSRG subgroup; direct comparisons to EUSTAR could not be made due to differences in ILD definition criteria. The frequency of RNA Pol III, also more prevalent in dcSSc and associated with SSc renal crisis, was highest in SPIN and lowest in EUSTAR. Interestingly this was reflected in the higher frequency of SSc renal crisis in SPIN compared to EUSTAR despite the significant missing data (49.9% of the cohort) for the RNA pol III antibody in EUSTAR at the time of the reported data. For the centromere antibody there was no difference between the cohorts.

The frequency of digital pitting/scars was highest in CSRG, followed by SPIN and lowest in EUSTAR. Measures of GI involvement were highest in SPIN but there appear to be heterogeneity in methodology relating to documenting GI disease making direct comparisons problematic. This is also true of PAH where methodology around diagnosis differed; EUSTAR using the 2009 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines, CSRG using echocardiographic measure of PASP of >45 mm Hg, and SPIN using the judgement of the enrolling physician without specific testing criteria.

The present study has limitations that should be considered in interpreting results. First, as both the SPIN Cohort and the CSRG Registry enroll patients from Canada, there is potential overlap between participants in both cohorts. Overall, 26% of SPIN Cohort participants were enrolled from Candian centres, indicating the maximum possible overlap. No data are available to identify the exact overlap between the cohorts. Second, the timeframe of enrolment was somewhat different between the three cohorts. Finally,

the definitions of medical variables were somewhat different between the cohorts, limiting the comparisons that can be made.

Overall, there are remarkable similarities between the SPIN Cohort and the other large recently reported SSc cohorts. Therefore, data emerging from the SPIN Cohort should be generalizable to the broad population of prevalent SSc patients.

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Table 1. Baseline SPIN Demographic and Clinical Features

	Combined (n=1125)	**Diffuse (n=460)**	**Limited (n=665)**	**p value (dcSSc vs lcSSc)**
Demographic variables				
Age in years, mean (SD)	55.6 (12.1)	53.0 (12.2) n=457	57.4 (11.7) n=664	p<0.001
Gender (% female)	87.3 (982/1125)	85.9 (395/460)	88.3 (587/665)	p=0.235
Race (% white)	82.0 (922/1124)	75.4 (346/459)	86.6 (576/665)	p<0.001
Body Mass Index, mean (SD)	25.7 (6.0) n=1125	25.3 (6.4) n=460	26.0 (5.8) n=665	p=0.053
Clinical Variables				
Raynaud's phenomenon (% positive)	98.5 (1101/1118)	97.8 (447/457)	98.9 (654/661)	p=0.129
Age at first non-RP, mean (SD)	44.0 (13.4) n=1034	44.0 (13.0) n=431	44.0 (13.7) n=603	p=0.999
Time since first non-RP symptom, mean (SD)	11.6 (8.7) n=1038	9.1 (7.2) n=434	13.4 (9.3) n=604	p<0.001
Time since diagnosis,	9.7 (8)	8.3 (7.0)	10.8 (8.4)	p<0.001

mean (SD)				
SSc-related				
Autoantibodies				
Antinuclear antibody (ANA) by IFA (% positive)	92.9 (953/1026)	91.1 (388/426)	94.2 (565/600)	p=0.058
ANA >1:160 (% positive)	92.1 (832/903)	89.8 (334/372)	93.8 (498/531)	p=0.028
Nucleolar pattern (% positive)	20.0 (225/1125)	24.3 (112/460)	17.0 (113/665)	p=0.002
Centromere by IIF pattern or Immunoassay (% positive)	32.8 (276/841)	9.3 (32/344)	49.1 (244/497)	p<0.001
Scl 70 (% positive)	24.8 (236/951)	32.0 (131/409)	19.4 (105/542)	p<0.001
RNA Polymerase III (% positive)	21.1 (115/545)	41.0 (100/244)	5 (15/301)	p<0.001
Skin Involvement				
mRSS median (IQR)	5 (9)	12 (13.5)	3 (3)	p<0.001
mRSS mean (SD)	7.9 (8.4)	13.3 (10)	4.2 (4.2)	p<0.001
Puffy fingers (% positive)	61.5 (659/1071)	61.1 (267/437)	61.8 (392/634)	p=0.809
Sclerodactyly	85.7	89.1 (407/457)	83.4 (548/657)	p=0.008

(proximal to MCP) (% positive)	(955/1114)			
Digital tip pitting/scar (% positive)	42.1 (463/1101)	50.4 (226/448)	36.3 (237/653)	p<0.001
Distal pulp ulcers (% positive)	35.9 (397/1107)	39.1 (176/450)	33.6 (221/657)	p=0.062
Ulcer anywhere (% positive)	17.7 (191/1082)	26.5 (116/438)	11.6 (75/644)	p<0.001
Telangiectasias (any) (% positive)	73.0 (805/1102)	68.0 (304/447)	76.5 (501/655)	p=0.002
Teleangiectasias (face) (% positive)	81.4 (516/634)	81.1 (189/233)	81.5 (327/401)	p=0.893
Abnormal nailfold Capillaries (% positive)	83.3 (779/935)	85.1 (326/383)	82.1 (453/552)	p=0.218
Abnormal pigment (any) (% positive)	32.9 (344/1047)	51.3 (219/427)	20.2 (125/620)	p<0.001
Abnormal facial pigment (% positive)	52.9 (171/323)	60.4 (116/192)	42.0 (55/131)	p=0.001
Organ Involvement				
Musculoskeletal				
Tendon friction rubs (% positive)	24.6 (248/1008)	41.2 (167/405)	13.4 (81/603)	p<0.001

Joint contractures small (% positive)	25.5 (270/1059)	41.4 (180/435)	14.4 (90/624)	p<0.001
Joint contracture large (% positive)	12.7 (133/1046)	21.7 (93/429)	6.5 (40/617)	p<0.001
Gastrointestinal Involvement				
Esophageal (% positive)	86.9 (971/1,118)	88.5 (406/459)	85.7 (565/659)	p=0.186
Stomach (% positive)	30.6 (334/1092)	37.7 (168/446)	25.7 (166/646)	p<0.001
Intestinal (% positive)	39.5 (435/1100)	43.4 (195/449)	36.9 (240/651)	p=0.029
Pulmonary Involvement				
Interstitial Lung Disease (% positive)	36.2 (398/1099)	48.5 (219/452)	27.7 (179/647)	p<0.001
Pulmonary Arterial Hypertension (% positive)	10.4 (107/1029)	7.5 (31/414)	12.4 (76/615)	p=0.012
History of SSc Renal Crisis (% positive)	4.7 (53/1116)	9.2 (42/457)	1.7 (11/659)	p<0.001

Overlapping Autoimmune Disease				
Systemic Lupus Erythematosus (% positive)	3.3 (36/1106)	2.4 (11/452)	3.8 (25/654)	p=0.201
Rheumatoid Arthritis (% positive)	5.8 (64/1103)	6.7 (30/451)	5.2 (34/652)	p=0.316
Sjogren's (% positive)	9.0 (97/1075)	7.5 (33/441)	10.1 (64/634)	p=0.142
Myositis (% positive)	5.8 (64/1100)	8.50 (38/447) 8.5	4.0 (26/653)	p=0.002
Primary Biliary Cirrhosis (% positive)	1.4 (15/1096)	0.90 (4/449) 0.9	1.7 (11/647)	p=0.257
Autoimmune Thyroiditis (% positive)	6.1 (66/1079)	6.1 (27/441)	6.1 (39/638)	p=0.995

NS = not significant

RP = Raynaud’s phenomenon

ANA = antinuclear antibody

IFA = Indirect immunofluorescence assay

IIF = indirect immunofluorescence

mRSS = modified Rodnan skin score

Type tables entirely in double space. Do not include any vertical lines in tables. Include horizontal lines below the title and headings and above the table footnotes only; there should be no horizontal lines separating the individual lines of data in the table body. Limit the width of each table (number of columns) such that it will fit in portrait (not landscape) orientation on a journal column (3¼ inches) or page (7 inches) and will not exceed the height of the page. Refer to current issues of the journal for further guidance regarding table style.

Tables with sections (e.g., Table 1a, Table 1b) are not acceptable and will be handled as two separate tables unless the information can be logically combined into one table with one set of headings.

Provide each table with an explanatory title so that it is intelligible without specific reference to the text. Provide each table column with an appropriate heading. Indicate clearly any units of measure on a table. Lengthy descriptions of methods should appear in the Methods section of the article and not in table footnotes.

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Table 3. Comparison of the SPIN and CSRG Cohort by Subgroups

	SPIN		CSRG			
	Diffuse (n=460)	**Limited (n=665)**	**Diffuse (n=517)**	**Limited (n=873)**	**p value diffuse**	**p value limited**
Demographic variables						
Age in years, mean (SD)	53.0 (12.2) n=457	57.4 (11.7) n=664	53.0 (11.7)	57.1 (12.3)	p=0.991	p=0.678
Gender (% female)	85.9 (395/460)	88.3 (587/665)	78.5 (406)	90.2 (787)	p=0.003	p=0.237
Race (% white)	75.4 (346/459)	86.6 (576/665)	82.6 (427)	91.4 (798)	p=0.006	p=0.003
Clinical Variables						
Raynaud's phenomenon (% positive)	97.8 (447/457)	98.9 (654/661)	96.3 (498)	97.5 (849)	p=0.173	p=0.020
Age at first non-RP, mean (SD)	44.0 (13.0) n=431	44.0 (13.7) n=603	44.0 (13.2)	45.5 (13.9)	p=0.968	p=0.036
Time since first non-RP symptom, mean (SD)	9.1 (7.2) n= 434	13.4 (9.3) n=604	9.0 (8.5)	11.5 (9.9)	p=0.821	p<0.001

SSc-related Autoantibodies						
Antinuclear antibody (ANA) by IFA (% positive)	91.1 (388/426)	94.2 (565/600)	94.6 (489/517)	96.0 (838/873)	p=0.036	p=0.106
Centromere by IIF pattern or Immunoassay (% positive)	9.3 (32/344)	49.1 (244/497)	12.1 (51/422)	47.5 (341/718)	p=0.218	p=0.583
Scl 70 (% positive)	32 (131/409)	19.4 (105/542)	21.8 (92/422)	11.1 (80/718)	p<0.001	p<0.001
RNA Polymerase III (% positive)	41.0 (100/244)	5.0 (15/301)	34.9 (107/307)	7.0 (34/488)	p=0.140	p=0.262
Skin Involvement						
mRSS, mean (SD)	13.3 (10.0) n=364	4.2 (4.2) n=530	18.1 (10.3)	5.1 (4.2)	p<0.001	p<0.001
Sclerodactyly (proximal to MCP) (% positive)	89.1 (407/457)	83.4 (548/657)	96.3 (496)	91.7 (800)	p<0.001	p<0.001
Digital tip pitting/scar (%	50.5 (226/448)	36.3 (237/653)	54.9 (282)	43.6 (380)	p=0.203	p=0.004

positive)						
Distal pulp ulcers (% positive)	39.1 (176/450)	33.6 (221/657)	58.4 (302)	48.1 (420)	p<0.001	p<0.001
Telangiectasias (any) (% positive)	68.0 (304/447)	76.5 (501/655)	71.7 (352)	76.4 (654)	p=0.980	p=0.478
Abnormal nailfold Capillaries (% positive)	85.1 (326/383)	82.1 (453/552)	74.4 (384)	74.7 (651)	p<0.001	p=0.001
Organ Involvement						
Gastrointestinal Involvement						
Esophageal (% positive)	88.5 (406/459)	85.7 (565/659)	70.0 (319)	68.9 (557)	p<0.001	p<0.001
Pulmonary Involvement						
Interstitial Lung Disease (% positive)	48.5 (219/452)	27.7 (179/647)	40.3 (203)	25.4 (218)	p=0.004	p=0.237
Pulmonary Arterial Hypertension	7.5 (31/414)	12.4 (76/615)	10.5 (46)	11.1 (82)	p=0.438	p=0.068

(% positive)						
History of SSc Renal Crisis (% positive)	9.2 (42/457)	1.7 (11/659)	7.6 (39)	1.9 (16)	p=0.353	p=0.810
Overlapping Autoimmune Disease						
Systemic Lupus Erythematosus (% positive)	2.4 (11/452)	3.8 (25/654)	3 (15)	3.8 (33)	p=0.653	p=0.966
Rheumatoid Arthritis (% positive)	6.7 (30/451)	5.2 (34/652)	2.8 (14)	4.8 (41)	p=0.003	p=0.643
Sjogren's (% positive)	7.5 (33/441)	10.1 (64/634)	6.3 (32)	8.6 (74)	p=0.428	p=0.282
Myositis (% positive)	8.5 (38/447)	4.0 (26/653)	5.3 (27)	3 (26)	p=0.043	p=0.285

RP = Raynaud’s phenomenon

ANA = antinuclear antibody

IFA = Indirect immunofluorescence assay

IIF = indirect immunofluorescence

mRSS = modified Rodnan skin score

Note: CSRG did not specify n when missing data was less than 10%. Calculations were based on total n when no % missing data was provided.

Table 4. Comparison of the SPIN and EUSTAR Cohort by Subgroups

	SPIN		EUSTAR			
	Diffuse (n=460)	**Limited (n=665)**	**Diffuse (n=2838*)**	**Limited (n=4481*)**	**p value diffuse**	**p value limited**
Demographic variables						
Age in years, mean (SD)	53.0 (12.2) n=457	57.4 (11.7) n=664	51.1 (13.7) n=2787	56.6 (13.4) n=4400	p=0.005	p=0.168
Gender (% female)	85.9 (395/460)	88.3 (587/665)	79.4 (2251/2835)	90.1 (4033/4477)	p=0.001	p=0.149
Race (% white)	75.4 (346/459)	86.6 (576/665)	84.5 (1149/1359)	92.1 (1977/2146)	p<0.001	p<0.001
Body Mass Index, mean (SD)	25.3 (6.4) n=460	26.0 (5.8) n=665	23.5 (4.2) n=1731	24.6 (4.5) n=2733	p<0.001	p<0.001
Clinical Variables						
Raynaud's phenomenon (% positive)	97.8 (447/457)	98.9 (654/661)	96.1 (2703/2812)	96.6 (4290/4441)	p=0.074	p=0.001
Age at first non-RP, mean (SD)	44.0 (13.0) n=431	44.0 (13.7) n=603	44.2 (14.2) n=2543	47.2 (14.1) n=4015	p=0.749	p<0.001
SSc-related Autoantibodies						

Antinuclear antibody (ANA) by IFA (% positive)	91.1 (388/426)	94.2 (565/600)	93.5 (2595/2776)	93.7 (4106/4382)	p=0.068	p=0.659
Centromere by IIF pattern or Immunoassay (% positive)	9.3 (32/344)	49.1 (244/497)	7.2 (193/2679)	48.2 (2039/4230)	p=0.163	p=0.707
Scl 70 (% positive)	32.0 (131/409)	19.4 (105/542)	59.8 (1607/2688)	23.2 (984/4244)	p<0.001	P=0.046
RNA Polymerase III (% positive)	41.0 (100/244)	5.0 (15/301)	4.7 (67/1422)	1.2 (27/2245)	p<0.001	p<0.001
Skin Involvement						
mRSS median (IQR)	12 (13.5)	3 (3)	16 (14)	6 (6)	**	**
Digital tip pitting/scar (% positive)	50.5 (226/448)	36.3 (237/653)	42.4 (1198/2827)	32.7 (1459/4463)	p=0.001	p=0.068
Distal pulp ulcers (% positive)	39.1 (176/450)	33.6 (221/657)	20.1 (557/2773)	15.5 (679/4378)	p<0.001	p<0.001
Abnormal nailfold	85.1 (326/383)	82.1 (453/552)	92.2 (1070/1161)	90.1 (1651/1833)	p<0.001	p<0.001

Capillaries (% positive)						
Organ Involvement						
Gastrointestinal Involvement						
Esophageal (% positive)	88.5 (406/459)	85.7 (565/659)	69.5 (1966/2829)	66.4 (2966/4468)	p<0.001	p<0.001
Pulmonary Involvement						
Pulmonary Arterial Hypertension (% positive)	7.5 (31/414)	12.4 (76/615)	22.1 (623/2821)	20.7 (922/4454)	p<0.001	p<0.001
History of SSc Renal Crisis (% positive)	9.2 (42/457)	1.7 (11/659)	4 (113/2815)	1 (44/4445)	p<0.001	p=0.115

EUSTAR = European Scleroderma Trials And Research
BMI = body mass index
*Note: Missing Data was reported as a percentage of combined data across subtypes. This table therefore makes the assumption of homogenous missing data percentages across subtypes, used to calculate n for each variable.
**Not possible to assess significance without EUSTAR raw data

Commented [KT1]: Should we alter this or remove it? Because we don't really list MD anywhere, it's just relevant to how we calcualted the N we used

Table 2. Baseline SPIN Patient Reported Outcome Core measures

	Combined (n=1125)	**Diffuse (n=460)**	**Limited (n=665)**	**p value**
Baseline Core Measures	Mean (SD)	Mean (SD)	Mean (SD)	
Cochin Hand Function Scale	13.7 (16.1)	19.2 (18.3)	9.8 (13.0)	p<0.001
HAQ-DI	0.8 (0.7)	1.0 (0.7)	0.6 (0.6)	p<0.001
PHQ-8	6.1 (5.3)	6.4 (5.5)	5.80 (5.1)	p=0.044
PROMIS-29				
Physical Function	43.0 (9.0)	41.4 (8.9)	44.1 (8.8)	p<0.001
Anxiety	51.5 (9.9)	52.6 (9.8)	50.7 (9.9)	p=0.001
Depression	50.9 (9.3)	51.8 (9.5)	50.2 (9.1)	p=0.006
Fatigue	55.3 (11.1)	56.0 (11.0)	54.8 (11.2)	p=0.079
Sleep disturbance	52.3 (8.8)	52.8 (8.8)	52.0 (8.8)	p=0.113
Social roles	48.0 (9.9)	46.7 (9.9)	48.9 (9.8)	p<0.001
Pain interference	55.5 (9.7)	56.6 (9.9)	54.8 (9.5)	p=0.003
SEMCD	6.4 (2.3)	6.2 (2.3)	6.6 (2.3)	p=0.112
SWAP				
Total	31.0 (19.0)	35.3 (19.5)	28.1 (18.1)	p<0.001
Social Impact	9.3 (9.5)	11.6 (10.0)	7.7 (8.7)	p<0.001
Dissatisfaction	21.7 (12.9)	23.6 (12.3)	20.3 (13.2)	p<0.001
Brief-SWAP	14.1 (5.4)	14.2 (5.1)	14.0 (5.6)	p=0.477

HAQ-DI = Health Assessment Questionnaire – Disability Index

PHQ-8 = Patient Health Questionnaire-8

PROMIS-29 = Patient-Reported Outcomes Measurement Information System - 29

SEMCD = Self-Efficacy to Manage Chronic Disease scale

SWAP = Satisfaction With Appearance