Prevalence, Severity and Clinical Correlates of Pain in Patients with Systemic Sclerosis

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OBJECTIVE: Large descriptive studies of pain in systemic sclerosis (SSc) are lacking. The present study estimated prevalence, severity and associations between SSc clinical variables and pain in all SSc patients and, in limited and diffuse subsets.

METHODS: 585 patients enrolled in a multi-center SSc registry completed a standardized clinical assessment and questionnaires about their physical and psychosocial health, including a pain severity numerical rating scale (NRS range 0-10). Pain prevalence and severity were estimated with descriptive statistics. Crude and adjusted associations between specific SSc clinical variables and pain were estimated with linear regression for the entire group and by SSc subtype.

RESULTS: 484 (83%) patients reported pain (*mild pain* [NRS 1-4], 268 (46%); *moderate pain* [NRS 5-7], 155 (27%); and severe *pain* [NRS 8-10], 61(10%)). More frequent episodes of Raynaud's phenomenon, active ulcers, worse synovitis and gastrointestinal symptoms were associated with pain in multivariate analysis adjusting for demographic variables, depressive symptoms and comorbid conditions. Diffuse cases reported only slightly higher mean (SD) pain than limited cases (*diffuse*: 3.9 (2.8), *limited*: 3.4 (2.7), Hedges's g=0.18, P = 0.05). Regression estimates did not differ significantly between SSc subsets.

CONCLUSION: Pain symptoms were common in the present study of SSc patients and were independently associated with more frequent episodes of Raynaud's phenomenon, active ulcers, worse synovitis and gastrointestinal symptoms. Subsetting by extent of skin involvement was only minimally related to pain severity and did not affect associations with clinical variables. More attention to pain and how to best manage it is needed in SSc.

Systemic sclerosis (SSc) is a multi-system disease characterized by immune system activation, fibrosis and vasculopathy. SSc is highly heterogeneous, although patients are most commonly classified as having either *limited* SSc (skin involvement limited to the face, neck and areas distal to the knees and elbows) or *diffuse* SSc (skin involvement proximal and distal to the knees/ elbows and/or trunk) (1). Patients with diffuse disease typically have more rapidly progressive disease with earlier organ-system involvement and a worse prognosis than patients with limited disease (2). SSc is far more common in women than in men with typical disease onset in the childbearing years (3). SSc is associated with high morbidity and mortality (4), disability (5,6), high healthcare use and productivity losses (7,8) and compromised health-related quality of life (9,10). There is no known cure for SSc; therefore, research aimed at preventing disability and improving patient's quality of life is urgently needed.

Pain is prominent in rheumatic diseases and is associated with more frequent physician consultation, greater disability and diminished quality of life (11). Moreover, patients with rheumatic disease have been shown to prioritize improvements in pain management above any other treatment area (12). Studies in small numbers of SSc patients have reported significant associations between pain and physical, social and emotional health (13-20). An earlier report on 337 SSc patients (21) from our multi-center Canadian SSc registry showed that pain was a strong and significant independent predictor of worse quality of life after adjusting for demographic, clinical and psychosocial variables. Despite these findings, pain has received relatively little attention in SSc and current understandings are based on a small number of studies with relatively small sample sizes.

Only three studies have assessed prevalence of pain in SSc (13,19,20), and each reported that pain was common, occurring in 60-75% of patients. Mean pain in SSc samples has been

suggested to be in the mild range (15,17) and has been found to be similar to other chronic pain and rheumatic disease groups in studies that used the same pain assessment tools for comparison (9,13,22). Several studies have assessed pain in subsets of patients with limited and diffuse SSc (13,18,19,22-24), and all have reported higher pain scores in diffuse cases than in limited cases. Most of these studies have reported small and statistically non-significant differences with the exception of a study by Malcarne et al. (18) that reported a moderate to large and statistically significant effect size. Larger sample sizes are required to obtain robust estimates of the prevalence and the severity of pain in SSc and to determine whether patients with limited and diffuse SSc experience clinically meaningful differences in pain.

Since SSc is a complex multi-system disease, pain may have multiple sources. One focus group study (N = 19) (20), reported that participants described joint and musculoskeletal pain, skin pain, pain associated with Raynaud's phenomenon, gastrointestinal and digestive pain, and pain in the distal extremities (tightness, calcinosis and ulcers). Two quantitative studies have examined bivariate associations between specific SSc clinical variables and pain. One study of 82 patients with SSc (22,25) reported higher pain scores in patients with active digital-tip ulcers. Only one published study in SSc (N=114) (18) has examined associations between multiple clinical variables and pain using multivariate analysis. That study examined 28 potential clinical predictor variables, but reported significant multivariate associations only between pain and higher skin score, patient-reported leg swelling and patient-reported joint tenderness. A limitation of that study however, was that significant results from unadjusted analyses were used to screen-in variables for multivariate analysis, and an automated stepwise procedure was used for final variable selection. This is known to lead to model over-fitting, as well as variable selection/exclusion decisions and parameter estimates that often do not generalize to other data

sets (26). No studies have examined whether associations between clinical variables and pain differ between patients with limited and diffuse SSc.

The objectives of the present study were to estimate prevalence, severity and associations of specific clinical variables with pain in all patients with SSc as well as in patients with limited and diffuse SSc separately, using large sample data from a convenience sample of nearly 600 patients enrolled in a multi-center SSc registry.

PATIENTS AND METHODS

Study Design

The present study was a cross-sectional analysis of a convenience sample of SSc patients enrolled in the Canadian Scleroderma Research Group (CSRG) Registry.

Study Patients

The CSRG Registry is an ongoing cohort study of SSc patients from15 Canadian centers. Patients are recruited by participating CSRG rheumatologists who confirm the diagnosis of SSc. Participants must be 18 years or older, fluent in English or French, likely to be compliant with study procedures, and able to give informed consent. Patients meeting criteria for another rheumatic disease in addition to SSc are also eligible to enrol. Registry patients annually undergo a standardized clinical assessment and complete questionnaires assessing demographic information, physical and psychosocial health outcomes. Only patients with a diagnosis of either limited or diffuse SSc were included in the present study.

Study Measures

Independent variables: Information regarding age, sex, race and post-secondary education was obtained from a patient-reported demographic questionnaire. Patients were classified into SSc subsets according to LeRoy's criteria (27). SSc disease duration was defined as the number of years from the date of first non-Raynaud’s manifestation of SSc until the date of first study visit. Skin involvement was assessed with the modified Rodnan Skin Score (MRSS) (28) ranging from 0 to 51. Severity of Raynaud's was assessed with the number of

patient reported episodes in the past week (25,29). Rheumatologists recorded the presence of active digital-tip ulcers, other active ulcers, visible or palpable calcinosis and tendon friction rubs during the clinical assessment. Severity of finger contractures was assessed by recording the fingertip-to-palm (FTP) distance from the tip of the 3rd finger to the distal palmar crease of the more severely affected hand (30). Severity of other joint contractures was measured with the sum of the number of sites (wrists, elbows, hips, knees and/or ankles on both sides of the body) with a total score range of 0-10. The 28-swollen joint count (31) was used as an objective measure of joint swelling. Elevated creatinine kinase (CK), defined according to laboratory cut-offs (Male: 42-396 U/L, Female: 24-240 U/L), was used as an index of muscle involvement. Gastrointestinal symptoms previously reported to be associated with pain in a focus group study of patients with SSc (20) were assessed by summing the number of positive responses to the following 6 patient-reported questions: "I have (or have had) on most days either now or since the onset of my scleroderma: 1) difficulty in swallowing – food or liquids sometimes get stuck behind my breastbone on the way down; 2) food or acid-tasting liquid that comes back up into my mouth or nose (acid reflux); 3) burning feeling rising from my stomach or lower chest up towards my neck (heartburn); 4) constipation; 5) diarrhea; 6) visible swelling of my abdomen or bloating." Using patient reports of GI symptoms is non-invasive and has been shown to be a reliable and valid measure of GI disease (32). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) (33), a 20-item self-report scale for which patients rate the frequency of depressive symptoms in the past week ranging from 0-60. The cut-off for clinically significant depressive symptoms is 16 (33,34). Comorbid conditions known to be associated with pain were defined as the presence of patient-reported osteoarthritis or back pain.

Outcome variable: Pain severity was assessed with an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (very severe pain) in the last week. The NRS was adapted from the pain visual analogue scale of the Stanford Health Assessment Questionnaire (HAQ-PVAS) which has been validated for use in SSc clinical trials (35). Compared to VAS measures, NRSs are simpler to complete and score and have been shown to be as reliable and responsive as a VAS in patients with ankylosing spondylitis (36) and even more reliable for assessing pain in patients with rheumatoid arthritis (RA) (37). Studies in cancer and musculoskeletal pain groups have recommended NRS cut-offs ≤ 4, 5 to 7 and >7 for mild, moderate and severe pain, respectively (38,39).

Statistical Analysis

Standard descriptive statistics were used to describe the prevalence and severity of pain symptoms in all patients and separately in limited and diffuse subsets. The magnitude of the differences in pain severity between SSc subsets was estimated with their mean difference and 95% confidence interval (CI), as well as with Hedges's g, a measure of standardized effect size (40). Effect sizes were interpreted based on Cohen's operational guidelines for small, medium and large effect sizes (small = 0.2, medium = 0.5, large = 0.8) (41). Separate bivariate linear regressions of each independent variable with pain as the response were performed to calculate unadjusted regression estimates and 95% CIs. Multivariate linear regression including all independent variables simultaneously was used to calculate adjusted regression estimates and 95% CIs. Descriptive analyses were examined to identify variable ranges that were either inconsistent with background knowledge of SSc, or had too much measurement error or too little variability to contribute usefully to multivariate analysis (42). Separate multivariate linear

regressions were then performed in limited and diffuse subsets using the same pre-specified independent variables and were compared by calculating estimated regression coefficient differences and 95% CIs.

Sensitivity Analyses - The association between pain and depression is temporally ambiguous therefore we also performed a separate multivariate analysis adjusting for symptoms of depression. Data on comorbid conditions was not collected for all subjects. Therefore, to include the maximum number of subjects in the present study, multivariate analysis adjusting for comorbid conditions was performed separately in a subgroup with this information. Multivariate Imputation by Chained Equations (43) was also performed to examine potential differences in effect estimates of clinical variables due to missing observations. MICE and MITOOLS packages in R were used to generate 5 complete copies of the data and the MICOMBINE command was used to generate averaged multivariate regression coefficients and adjusted 95% CIs across the 5 data sets.

All statistical procedures were performed using the Statistical Package for the Social Sciences (SPSS) version 13 and R: A Language and Environment for Statistical Computing version 2.8.1.

Ethical Considerations

Ethics committee approval for CSRG registry procedures was obtained at each site and each patient provided written informed consent.

RESULTS

Patient sample

The present study included patients enrolled in the CSRG Registry between September 2004 and November 2008, which included information from 877 patient records. Fifty-one (6%) patient records were excluded because SSc subset status was not recorded (n = 26) or the patient had a diagnosis of sine SSc (n = 25). Of the 826 eligible patient records, 585 (71%) had complete observations for all variables included in the main analyses.

Demographic and clinical characteristics for all, limited, and diffuse cases with SSc are presented in Table 1. The mean (SD) age for the total sample was 56 (12) years; 506 (87%) were female; 523 (89%) were white; and 279 (48%) had at least one year of post-secondary education. Five-hundred and thirty-six (92%) patients met ACR criteria for SSc, and median (inter-quartile range) disease duration was 9 (4 to 15) years. Three-hundred and fifty-eight patients had limited SSc (61%) and 227 (39%) had diffuse SSc. Diffuse cases tended to have more skin involvement, digital-tip and other ulcers, finger and other joint contractures, tendon rubs and to score ≥ 16 on the CESD than limited cases. Swollen joints, comorbid osteoarthritis and back pain were more common in limited cases than diffuse cases. There were no significant differences ($P < .05$) observed between partial observations excluded from the present study (n = 241) and complete observations included in the study (n = 585) with respect to demographic characteristics, disease duration, the proportion of patients meeting ACR criteria for SSc or limited/diffuse subset status.

Prevalence and Severity of Pain in Patients with SSc

Four-hundred and eighty-four (83%) patients experienced pain symptoms, with more than a third reporting pain symptoms in the moderate or severe range (*mild:* 268 (46%),

moderate: 155 (27%) and *severe*: 61 (10%)) (Table 2). Mean (SD) pain score for the total sample was 3.6 (2.8), diffuse subset 3.9 (2.8), and limited subset 3.4 (2.7). The mean difference in pain severity between subsets was statistically significant, mean difference = 0.51, 95% CI: 0.06 to 0.97. However, the effect size for this difference (Hedges's g = 0.18, 95% CI: 0.01 to 0.35) was small and distributions of patients reporting mild, moderate and severe pain were similar in both subsets (Table 2).

SSc Clinical Variables and Pain in Patients with SSc

Results of bivariate and multivariate linear regression in all patients with SSc are summarized in Table 3. Crude associations between all clinical variables examined and pain were significant. However, only more frequent episodes of Raynaud's phenomenon, presence of other active ulcers, higher swollen joint count, and more gastrointestinal symptoms were associated with pain in multivariate analyses. Since few (9%) patients had active digital-tip ulcers, its CI was wide and did not reach statistical significance.

Descriptive statistics showed that only 2% of the present sample had an elevated CK indicative of possible muscle involvement which was not enough variability to enter in regression analyses and obtain interpretable regression estimates. Therefore, an index of muscle involvement was not included in regression analyses. The point estimates for calcinosis in crude (unstandardized regression coefficient: -0.139, 95% CI: -0.629 to 0.351) and multivariate linear regression analyses (unstandardized regression coefficient: -0.426, 95% CI: -0.909 to 0.570), were not significant and in the wrong direction. Therefore calcinosis was not retained in regression models.

SSc Clinical Variables and Pain in Limited and Diffuse Sub-sets

Results of bivariate and multivariate linear regression in limited and diffuse subsets are summarized in Table 4. More gastrointestinal symptoms were significantly associated with pain in limited and diffuse subsets. Higher swollen joint count was significantly associated with pain among patients with limited disease while the presence of other active ulcers was significantly associated with pain among patients with diffuse disease. Overall, however, differences in regression effect estimates between patients with limited and diffuse SSc were small, and none were statistically significant (data not shown).

Sensitivity Analysis

The same clinical variables (more frequent episodes of Raynaud's phenomenon, other active ulcers, higher swollen joint count and more gastrointestinal symptoms) remained significant after adjusting for depressive symptoms and comorbid conditions (Table 5). Results were also similar after multiple imputation, with the exception that the effect estimate for active digital-tip ulcers nearly doubled and reached statistical significance (beta: 0.753, 95% CI: 0.110, 1.396) (Table 6).

DISCUSSION

Pain was common (83%) in the present study, and more than 1/3 of patients with SSc reported pain symptoms in the moderate or severe range. After adjusting for demographic variables, depressive symptoms and comorbidities, specific SSc clinical variables associated with pain included more frequent episodes of Raynaud's phenomenon, other active ulcers, worse synovitis and gastrointestinal symptoms. Digital-tip ulcers were significant after multiple imputation. Depressive symptoms and painful comorbidities were also significantly associated with pain symptoms in SSc, but their inclusion in models did not alter the observed relationships with SSc variables. Patients with diffuse disease reported only minimally higher pain levels compared to patients with limited disease, and multivariate regression coefficient differences between subsets were small and were not significant.

Few studies in SSc include assessments of pain. This may, in part, be related to the fact that pain appears to be assessed and treated less often in SSc compared to other rheumatic diseases (44). This study however confirms that pain is common in SSc. Pain severity in the present sample of patients with SSc was comparable to that reported in a recent study of RA patients (45) seeking specialty care for pain symptoms (*SSc*: mean 3.6, SD 2.8; *RA*: mean 4.3, SD: 2.7). Two smaller studies that compared measures of quality of life in SSc to that in other rheumatic diseases reported consistent findings with the present study. Danieli et al. (9) reported similar SF-36 bodily pain scores (range 0-100) in 76 SSc patients (median 61, interquartile range 41-77) and 118 RA patients (median 51, interquartile range 41-74). Moreover Johnson et al. (22), reported similar HAQ-PVAS scores (range 0-3) in 43 SSc patients (mean 1.4, 95% CI 1.1 to

1.6), 82 psoriatic arthritis patients (mean 1.2, 95% CI 1.0 to 1.4) and 42 RA patients (mean 1.0, 95% CI 0.8 to 1.7) .

Studies describing minimal clinically important differences (MCID) in SSc and other rheumatic diseases suggest that a 10-20% change in pain measures would correspond to a clinically meaningful difference (46,47). Based on regression estimates from multivariate analysis (Tables 3, 6), active ulcers and 2-3 or more gastrointestinal symptoms would likely be considered to have independent clinically meaningful effects on pain. Effects estimates for more Raynaud's episodes and swollen joint count were also statistically significant however patients would need to experience ≥ 30 Raynaud's episodes per week and have ≥ 8 swollen joints to be associated with a 10% increase in pain symptoms, respectively. This suggests that only severe Raynaud's symptoms and moderate to severe synovitis would be associated with significant pain symptoms in SSc. Based on model estimates reported in Table 5, in addition to the SSc symptoms discussed above, painful comorbities and screening positive for depression (CES-D ≥ 16) would both be associated with a clinically meaningful change in pain symptoms.

Two studies (18,20) reported a significant association between skin score and pain that was not observed in the present study after adjusting for all other covariates. Conflicting results may be due to the fact that the other studies did not adjust for the full range of covariates included here. If however, one were to base their judgment on the statistically significant crude point estimate for skin score obtained in the present study (beta: 0.037, CI: 0.014, 0.061), only patients with an MRSS score ≥ 25 would potentially be associated with clinically meaningful pain symptoms.

Diffuse cases reported slightly higher pain than limited cases. However, the effect size for this difference was small (<0.2) and the raw mean difference in pain of 0.51 (95% CI: 0.06 to

0.97) would not meet the MCID threshold as clinically meaningful. Moreover, there were no significant differences in multivariate regression coefficient estimates between SSc subsets.

Future studies should examine associations between specific measures of tender calcinosis, muscle involvement, sicca symptoms, fibromyalgia and dependent oedema and pain that were unavailable in the present study. Longitudinal studies of pain in SSc will also be necessary to examine time varying effects of these clinical covariates in order to begin to identify causal associations. More research clarifying the pathophysiologic mechanisms of pain in SSc as well as psychosocial risk/ protective factors for pain will be needed to develop and implement optimal interventions (48). The role of inflammation in sensitizing pain pathways is an emerging area (49). However, research in pathogenetic processes specific to SSc-related pain is lacking. Multiple psychosocial interventions for pain have been developed and tested primarily in arthritis, including cognitive behavioral therapy, relaxation, biofeedback and meditation (50), but the efficacy of such interventions in patients with SSc remains unknown. Research in patient and physician facilitators/ barriers to pain treatment in SSc will improve health service delivery.

The present study was based on a convenience sample of patients with SSc. Therefore, limitations associated with this sampling strategy should be considered. The present sample of SSc patients generally had stable disease (median disease duration 9 years). Patients that are not being cared for by a rheumatologist and patients with very severe SSc that were too sick to participate or that died earlier in their disease course, were not included in the present study. This may have resulted in an over-representation of healthier patients in our SSc sample (survival cohort), and results may therefore not be generalizable to the full spectrum of SSc. Nonetheless, even in this potentially "healthier sample" the prevalence and severity of pain were high. Approximately 29% of the present sample had incomplete observations. Partial respondents

could possibly have differed systematically from full respondents included in the present study. Partial respondents however were similar to full respondents with respect to demographic variables, disease duration, proportion of patients meeting ACR criteria for SSc and proportion classified as limited or diffuse SSc. Moreover, regression estimates from sensitivity analysis that used multiple imputation to fill in missing observations did not differ substantively from regression estimates that deleted missing observations, other than by improving precision of model estimates so that effects for digital-tip ulcers reached statistical significance. Therefore although a certain degree of bias in reported model estimates due to missingness cannot be ruled out from the present study, the rigorous sensitivity analyses performed suggest that this bias, if present, was likely minimal. Only a small proportion of patients were male, non-white and had active ulcers, therefore confidence limits for these variables were wide. This however is consistent with the typical presentation of SSc observed in other research studies. Lastly, measures of gastrointestinal symptoms, episodes of Raynaud's phenomenon, depressive symptoms and comorbidities were patient-reported, so it is possible that there was some misclassification within these measures.

This study also has important strengths. Results from the present study were based on large multi-center data collected using standardized procedures with rigorous data analysis. Therefore, study estimates are likely robust. This study draws attention to the high prevalence of pain symptoms in SSc patients and associations between multiple clinical variables and pain, including episodes of Raynaud's phenomenon, active ulcers, swollen joints and gastrointestinal symptoms. This was the first study to compare associations between SSc clinical variables and pain in patients with limited and diffuse disease, and results of no significant differences in regression estimates suggest that subsetting is not important insofar as pain is concerned.

In summary, current understandings of pain in SSc are based on very few descriptive studies with small samples. Thus, clinicians do not have strong evidence for which to base their understanding of prevalence, severity, and potential sources of pain in these patients. Results from the present large convenience sample of patients with SSc demonstrate that pain is highly prevalent in these patients and is as severe as in other rheumatic diseases. This suggests that more attention to pain and how to best manage it is needed in SSc. Severe Raynaud's, active ulcers, moderate to severe synovitis and gastrointestinal symptoms were associated with pain in the present study and may represent clinical targets for interventions. In addition to SSc symptoms, presence of other painful comorbidites as well as depressive symptoms were associated with pain and may add to the severity of pain symptoms in patients with SSc.

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Table 1. Demographic and Clinical Characteristics of CSRG Sample of Patients with SSc

Variables	*All SSc*	*Limited SSc*	*Diffuse SSc*
n cases	**585**	**358 (61%)**	**227 (39%)**
Age, mean (SD)	56 (12)	57 (12)	53 (11)
Female, n (%)	506 (87%)	321 (90%)	185 (82%)
Race – white, n (%)	523 (89%)	326 (91%)	197 (87%)
Post-secondary education, n (%)	279 (48%)	171 (48%)	108 (48%)
Disease duration years, median (IQR)	9 (4 to 15)	10 (4 to 17)	7 (3 to 14)
Skin score (MRSS 0-51), median (IQR)	7 (4 to 15)	4 (2 to 8)	17 (11 to 25)
Episodes of Raynaud's, median (IQR)	4 (1 to 7)	4 (1 to 7)	3 (1 to 7)
Active digital-tip ulcers, n (%)	52 (9%)	23 (6%)	29 (13%)
Active other ulcers (not digital-tips), n (%)	105 (18%)	40 (11%)	65 (29%)
Calcinosis, n (%)	175 (30%)	109 (30%)	66 (29%)
Finger contractures, (n%)	201 (34%)	81 (23%)	120 (53%)
Other joint contractures, (n%)	108 (19%)	27 (8%)	81 (36%)
Swollen joint count, n (%)	98 (17%)	68 (19%)	30 (13%)
Tendon friction rubs, n (%)	99 (17%)	31 (9%)	68 (30%)
Abnormal creatinine kinase (CK) (n=491), n (%)	16 (3%)	8 (2%)	8 (4%)
Total gastrointestinal symptoms, median (IQR)	2 (1 to 4)	2 (1 to 4)	2 (1 to 4)
Problems swallowing, n (%)	325 (56%)	197 (55%)	128 (56%)
Acid reflux, n (%)	386 (66%)	226 (63%)	160 (71%)
Heartburn, n (%)	258 (44%)	152 (43%)	106 (47%)

Stomach bloating, n (%)	224 (38%)	138 (39%)	86 (38%)
Constipation, n (%)	164 (28%)	95 (27%)	69 (30%)
Diarrhea, n (%)	134 (23%)	77 (22%)	57 (25%)
Depressive Symptoms (CESD 0-60), mean(SD)	14 (10)	13 (10)	15 (10)
Depression Screen Positive (CESD≥16), n (%)	211 (36%)	113 (32%)	98 (43%)
Painful Comorbidities, (n =509), n (%)	218 (43%)	149 (48%)	69 (35%)
Osteoarthritis, n (%)	103 (20%)	81 (26%)	22 (11%)
Back Pain, n (%)	174 (34%)	117 (38%)	57 (29%)

Table 2. Prevalence of Pain in Patients with SSc

Variables	*All SSc (n = 585)*	*Limited SSc (n = 358)*	*Diffuse SSc (n = 227)*
No Pain (NRS 0), n (%)	101 (17%)	67 (19%)	34 (15%)
Mild Pain (NRS 1-4), n (%)	268 (46%)	171 (48%)	97 (43%)
Moderate Pain (NRS 5-7), n (%)	155 (27%)	87 (24%)	68 (30%)
Severe Pain (NRS 8-10), n (%)	61 (10%)	33 (9%)	28 (12%)

Table 3. Crude and Adjusted Linear Regression Coefficients of Clinical Variables with Pain in All Patients with SSc (N=585)

Variables	*Crude Regression coefficients*		*Adjusted Regression coefficients*	
	Beta	95% CI	Beta	95% CI
Skin score (MRSS 0-51)	**0.04**	**(0.01, 0.06)**	0.00	(-0.03, 0.03)
Episodes of Raynaud's	**0.04**	**(0.01, 0.06)**	**0.03**	**(0.01, 0.05)**
Active Digital-tip ulcers	**0.90**	**(0.12, 1.69)**	0.40	(-0.36, 1.16)
Active Other ulcers	**1.21**	**(0.63, 1.78)**	**1.01**	**(0.42, 1.59)**
Finger contractures (FTP)	**0.19**	**(0.08, 0.31)**	0.06	(-0.06, 0.18)
Other joint contractures	**0.25**	**(0.10, 0.41)**	0.12	(-0.06, 0.29)
Swollen joint count (0-28)	**0.12**	**(0.04, 0.21)**	**0.12**	**(0.04, 0.20)**
Tendon friction rubs	**0.81**	**(0.22, 1.41)**	0.34	(-0.25, 0.95)
Total gastrointestinal symptoms	**0.50**	**(0.38, 0.62)**	**0.46**	**(0.34, 0.58)**

Multivariate regression estimates are adjusted for demographic variables (age, sex, race, level of education) and disease duration.

Table 4. Multivariate Linear Regression Coefficients of Clinical Variables with Pain in Limited and Diffuse Subsets

Variables	*Limited SSc (n = 358)*		*Diffuse SSc (n = 227)*	
	Beta	95% CI	Beta	95% CI
Skin score (MRSS 0-51)	0.03	(-0.03, 0.10)	0.01	(-0.05, 0.09)
Episodes of Raynaud's	0.03	(0.00, 0.05)	0.04	(0.00, 0.08)
Active Digital-tip ulcers	0.04	(-1.06, 1.15)	0.82	(-0.29, 1.92)
Active Other ulcers	0.85	(-0.02, 1.71)	**1.16**	**(0.32, 1.99)**
Finger contractures (FTP)	0.07	(-0.10, 0.24)	0.01	(-0.18, 0.19)
Other joint contractures	0.09	(-0.40, 0.58)	0.16	(-0.04, 0.35)
Swollen joint count (0-28)	**0.15**	**(0.04, 0.26)**	0.09	(-0.04, 0.21)
Tendon friction rubs	0.21	(-0.75, 1.16)	0.38	(-0.42, 1.17)
Gastrointestinal symptoms	**0.56**	**(0.41, 0.71)**	**0.30**	**(0.08, 0.52)**

Multivariate regression estimates are adjusted for demographic variables (age, sex, race, level of education) and disease duration.

Table 5. Multivariate Regression Models of Clinical Variables with Pain Adjusting for Depressive Symptoms and Comorbid Conditions in all Patients with SSc

	Adjusting for Depressive Symptoms (N =585)		*Adjusting for Comorbid Conditions (n=508)*	
Variables	Beta	95% CI	Beta	95% CI
Skin score (MRSS 0-51)	0.00	(-0.03, 0.03)	0.01	(-0.02, 0.04)
Episodes of Raynaud's	**0.03**	**(0.00, 0.05)**	**0.03**	**(0.00, 0.05)**
Active Digital-tip ulcers	0.48	(-0.24. 1.21)	0.43	(-0.35, 1.22)
Active Other ulcers	**0.81**	**(0.25, 1.37)**	**1.16**	**(0.54, 1.78)**
Finger contractures (FTP)	0.03	(-0.08, 0.15)	0.02	(-0.10, 0.15)
Other joint contractures	0.07	(-0.09, 0.24)	0.11	(-0.07, 0.29)
Swollen joint count (0-28)	**0.11**	**(0.03, 0.19)**	**0.12**	**(0.04, 0.20)**
Tendon friction rubs	0.30	(-0.27, 0.87)	0.20	(-0.43, 0.82)
Total gastrointestinal symptoms	**0.34**	**(0.22, 0.46)**	**0.44**	**(0.31, 0.58)**
Depressive symptoms (CESD 0-60)	**0.08**	**(0.06, 0.10)**		
Pain Condition (osteoarthritis/ back pain)			**0.69**	**(0.23, 1.15)**

Multivariate regression estimates are adjusted for demographic variables (age, sex, race, level of education) and disease duration.

Table 6. Multivariate Linear Regression Coefficients of Clinical Variables with Pain after Multiple Imputation of Missing Observations in all Patients with SSc (N=826)

Variables	*Multiple Imputation of Cases with Missing Observations*	
	$Beta_{av}$‡	95% CI
Skin score (MRSS 0-51)	0.01	(-0.02, 0.03)
Episodes of Raynaud's	**0.03**	**(0.01, 0.05)**
Active Digital-tip ulcers	**0.75**	**(0.11, 1.40)**
Active Other ulcers	**0.61**	**(0.10, 1.11)**
Finger contractures (FTP)	0.07	(-0.04, 0.18)
Other joint contractures	0.11	(-0.06, 0.27)
Swollen joint count (0-28)	**0.11**	**(0.04, 0.17)**
Tendon friction rubs	0.21	(-0.33, 0.76)
Total gastrointestinal symptoms	**0.42**	**(0.31, 0.52)**

‡ $Beta_{av:}$ Averaged unstandardized regression coefficients across 5 multiple imputed datasets. Multivariate regression estimates are adjusted for demographic variables (age, sex, race, level of education) and disease duration.