The Association Between Disease Activity and Duration in Systemic Sclerosis

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ABSTRACT. ***Objective.*** The absence of a standardized disease activity index has been an important barrier in systemic sclerosis (SSc) research. We applied the newly derived Valentini Scleroderma Disease Activity Index (SDAI) among our cohort of patients with SSc to document changes in disease activity over time and to assess possible differences in activity between limited and diffuse disease.

Methods. Cross-sectional study of a national cohort of patients enrolled in the Canadian Scleroderma Research Group Registry. Disease activity was measured using the SDAI. Depression scores were measured using the Centre for Epidemiologic Studies Depression Scale (CES-D).

Results. A total of 326 out of 639 patients had complete datasets at the time of this analysis; 87% were female, of mean age 55.6 years, with mean disease duration 14.1 years. SDAI declined steeply in the first 5 years after disease onset and patients with diffuse disease had 42% higher SDAI scores than patients with limited disease with the same disease duration and depression scores (standardized relative risk 1.42, 95% CI 1.21, 1.65). Patients with higher CES-D scores had higher SDAI scores relative to patients with the same disease duration and disease subset (standardized RR 1.22, 95% CI 1.14, 1.31). Among the 10 components that make up the SDAI, only skin score (standardized OR 0.59, 95% CI 0.43, 0.82) and patient-reported change in skin (standardized OR 0.64, 95% CI 0.45, 0.92) decreased with increasing disease duration. High skin scores (standardized OR 32.2, 95% CI 15.8, 72.0) were more likely and scleredema (standardized OR 0.58, 95% CI 0.37, 0.92) was less likely to be present in patients with diffuse disease. High depression scores were associated with positive responses for patient-reported changes in skin and cardiopulmonary function.

Conclusion. Disease activity declined with time and patients with diffuse disease had consistently higher SDAI scores. Depression was found to be associated with higher patient activity scores and strongly associated with patient self-response questions. The role of depression should be carefully considered in future applications of the SDAI, particularly as several components of the score rely upon patient recall. (J Rheumatol First Release September 1 2010; doi:10.3899/jrheum.090919)

Key Indexing Terms:
SYSTEMIC SCLEROSIS DISEASE ACTIVITY DISEASE DURATION

Systemic sclerosis (SSc) is a multisystem autoimmune disease of unknown etiology. Its clinical manifestations are heterogeneous and reflect 3 major pathogenic events: endothelial dysfunction, fibroblast dysfunction, and dysregulation of the immune system[1]. SSc is divided into 2 subgroups, limited (lSSc) and diffuse cutaneous disease (dSSc). There is controversy regarding the exact division between these 2 groupings although most clinical studies now use the classification proposed by LeRoy and Medsger[2], where lSSc comprises patients with skin thickening extending up to the elbows and knees with or without facial involvement. In contrast, dSSc skin involvement extends proximal to the elbows and knees and may include truncal involvement[2,3]. Some believe that these 2 groups are 2 separate forms of the disease, particularly given differences in outcome[4,5], serology[6], and genetics[7].

An important barrier in the study of SSc continues to be the difficulty in measuring disease activity. Disease activity in SSc has been defined as that aspect of the disease that varies over time and is potentially reversible spontaneously or under treatment[8].

Recently, the Valentini Scleroderma Disease Activity Index (SDAI) was developed using multicenter data from

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290 sequential patients fulfilling criteria for SSc and enrolled through the European Scleroderma Study Group[9]. This index was developed using expert opinion and has since received some measure of internal validation[10]. Criteria were derived and validated in a 3-stage process. First, patient charts were blindly assessed by 3 experts and evaluated according to a semiquantitative score. These data were assessed and then a consensus "gold standard" was reached by 2 investigators. A univariate analysis was undertaken to determine items that correlated with the gold standard of disease activity. Subsequently, multiple linear regression analysis was performed to identify 3 data sets of items that correlated with disease activity in SSc as a whole, as well as dSSc and lSSc separately. Initial validation supported the validity of all 3 indices, but subsequent validation, again using experts as gold standard, supported validation of the index only for the cohort as a whole[9,10]. Subsequently, an amendment was published, recommending that the modified Rodnan skin score be used instead of the Kahaleh skin score initially recommended[11]. To date, this index has not undergone prospective evaluation, nor has it been evaluated in other SSc patient cohorts. Nevertheless, as it stands, it is the first composite measure of disease activity in SSc and represents an important contribution and a useful tool to pursue SSc research.

In part because of the heterogeneity of SSc and in part because of its rarity, wide gaps in knowledge on its natural history, including disease activity, remain. We therefore investigated the pattern of disease activity over time in SSc using the SDAI among patients in the Canadian Scleroderma Research Group Registry.

MATERIALS AND METHODS

This was a cross-sectional study of a national cohort of Canadian patients with SSc.

Our objectives were (1) to document disease activity at varying stages of disease in our study population; and (2) to identify possible differences between disease activity in patients with lSSc versus those with dSSc.

Study subjects. The subjects consisted of those enrolled in the Canadian Scleroderma Research Group (CSRG) Registry. Baseline data were used in this study. Patients in the Registry are recruited from 15 centers across Canada. They must have a diagnosis of SSc made by the recruiting rheumatologist, be > 18 years of age, be fluent in English or French, and likely to be compliant with study procedures and visits. The study patients had a baseline visit between August 2004 and April 2008. Patients in the CSRG Registry undergo an extensive standardized evaluation, including a yearly history and physical examination by a rheumatologist and laboratory testing. They also complete several self-report questionnaires, including the Center for Epidemiologic Studies–Depression Scale (CES-D)[12,13] to measure depression.

Outcome measures. Disease activity was measured using the SDAI. It consists of 10 weighted variables: modified Rodnan skin score > 14, scleredema, digital necrosis, arthritis, lung carbon monoxide diffusing capacity (DLCO) < 80%, erythrocyte sedimentation rate (ESR) > 30 mm/h, hypocomplementemia (low C3 and/or C4), and worsening cardiopulmonary, skin and vascular symptoms in the past month as reported by the patient. The final score ranges from 0 (no activity) to 10 (very active).

Patients with dSSc were defined as those with skin sclerosis extending proximal to the elbows and knees with or without truncal involvement. Limited SSc involvement was defined as skin disease distal to the elbows and knees that may or may not involve the face. These criteria are in accord with those proposed by LeRoy and Medsger[2].

Depression was measured using the CES-D[12,13], a 20-item scale designed to measure depression in the general population. It is also useful in clinical and psychiatric settings. It asks an individual to report the frequency with which each of 20 events was experienced during the previous week. The items are graded on a 4-point scale ranging from 0 to 3 and corresponding to the frequency of each symptom in the past week. It yields a summary score, which ranges from 0 to 60, higher scores indicating greater depression. The scale is used as a simple indicator of the degree of depression. If the total is 16 or greater, the patient may have experienced some depression in the past week.

Ethics committee approval was obtained for this study at each site and each patient provided written informed consent to participate.

Statistical analysis. Descriptive statistics were used to summarize patients' baseline characteristics. In all patients, and then in patients with lSSc and dSSc separately, multiple linear regression and generalized linear models were used to assess the association of disease duration with disease activity. Multiple logistic regression was used to assess the association of disease duration with the individual components of the SDAI, controlling for age, sex, and depression, the latter because 3 items in the SDAI are patient-reported and we were concerned that depression could influence how patients would rate their symptoms[14].

Exploratory analyses indicated that a transformation of the duration to log-duration would be more appropriate than using duration itself as a covariate in the model in order to meet the assumption of linearity with the predictor[15].

An initial set of hypotheses determined the original class of regression models considered and the relevant models were selected according to an ensemble of model selection criteria including adjusted R-square[16], Bayesian information criterion[17], and Akaike information criterion[18]. Each of these criteria tries to select models with different objectives and we used several to ensure that our results were not overly sensitive to our choice of criteria.

We chose to fit quasi-likelihood Poisson regression models for the overall disease activity index based upon principles and what was observed in the data. These models are similar to Poisson regression models typically used for count data, but allow for heterogeneity in the error variance that cannot be modeled using standard Poisson regression. Because one can view the SDAI as an unequally weighted sum of binary variables, we believe that an overdispersed Poisson regression model is the most appropriate for the sampling distribution of the SDAI[19]. We used standard linear and generalized linear model residual diagnostics (e.g., Cook's distances, influence measures, standardized residuals, and deviance residuals) to assess fidelity to model assumptions.

Of note, we do not present models that include age or sex, as these variables were never statistically significant as covariates in any of the models and had little effect on the results. We also fit models to patients with limited and diffuse disease separately, but the model selection criteria indicated that these separate models did not provide significantly better fit than the model considering them together.

All statistical analyses were done using the R statistical package, version 2.5[20], SPSS statistical package (SPSS for Windows, Rel. 14.0, 1999. SPSS Inc., Chicago, IL, USA), and the WinBUGS software package[21].

Multiple imputation and model-fitting. The standard approach using multiple imputation is to include as many variables as possible in order to avoid biasing the imputation procedure. We included in our imputation procedures the following variables: all 10 SDAI variables, a physician global assessment of disease activity, limited/diffuse disease status, disease duration, CES-D score, age, and sex. Using the MICE package in R[22], we conducted runs of 25 independent MCMC chains, sampling the data from an approximation to their joint posterior distribution via alternating full con-

ditional sampling (similar to the IVEware package[23]). The disadvantage of this approach is that it does not guarantee a proper posterior distribution for the imputations generated. However, we found that using other imputation approaches that utilize proper Bayesian procedures, such as the mixed data models proposed by Schafer[24], were intractable due to the large number of categorical variables and the sparsity of their joint contingency table. Nevertheless, because of this possible issue with the MICE package, we also fit a fully Bayesian latent variable model to the 10 binary SDAI indicators using proper priors and the same regressors used in the Frequentist analysis. The results were similar, with 95% credible intervals for all multiple logistic regression coefficients matching closely with the results of the MICE imputation. The interpretation of the fully Bayesian results was similar to that presented for the multiple imputation analysis and thus is not presented here.

RESULTS

The cohort available for this study included 639 patients, of whom 326 had complete datasets (Table 1). Of the whole cohort, 87% were women, mean age was 55.6 years, and mean disease duration since the onset of Raynaud's phenomenon was 14.1 years.

Figures 1 and 2 summarize the crude data for the completely observed subjects in the cohort (N = 326). Figure 1 shows the mean SDAI scores (error bars represent 95% CI for the mean in each group) for patients with limited and diffuse disease in 5 different subsets of disease duration. We note that there is a steep decline in mean SDAI score in the first 5 years, which then levels off after 10 years of duration in both groups. Figures 2A and 2B show the proportion of positive responses for each of the 10 components of the SDAI for patients with limited and diffuse disease, respectively, grouped again according to disease duration. We see that the patterns in duration are similar between limited and diffuse patients, although the overall response probability differs between the 2 groups. On the other hand, unlike the overall mean SDAI scores, not all variables showed decreasing proportions of positive response as disease duration increased.

Association between disease duration and the SDAI. In adjusted analysis, disease activity appeared to decrease with increasing disease duration. Indeed, in the 326 patients with complete data, the standardized coefficient for disease duration in the regression model adjusting for diffuse (versus limited) disease and level of depression was negative, indicating decreasing activity with time (Table 2). The standardized relative risk (RR) for log-duration was 0.88, with 95% confidence interval 0.82, 0.95. Interpreting this interval is difficult due to the transformation of duration and the use of the Poisson model. To simplify matters, this is equivalent to saying that a 3-fold increase in duration yields approximately a 10% decrease in estimated disease activity. Therefore, from the end of the first compared to the end of the fourth year of disease, we would expect a 10% decrease in disease activity, relative to both the level of depression and disease type. In contrast, in the 3-year period between the end of fourth and seventh years of disease, we would estimate only a 5% decrease in disease activity.

The results presented in Table 2 also show a significant difference in disease activity between limited and diffuse patients, patients with diffuse disease having 42% higher SDAI scores than limited patients with the same disease duration and depression scores (standardized RR 1.42, 95% CI 1.21, 1.65). The coefficient for the CES-D was also positive, indicating that patients with higher CES-D scores had

Table 1. Baseline characteristics of patients.

	Whole Cohort, n = 639, mean (SD) or %	N (% missing)	Patients with Complete Information, n = 326, mean (SD) or %
Women, %	87	0	89
Age, yrs	55.6 (12.2)	0	55.6 (12.2)
CES-D (range 0–60)	14.3 (10.5)	17 (3.0)	13.9 (10.3)
Diffuse disease	42	0	41
Disease duration, yrs	14.1 (11.9)	14 (2.2)	14.8 (12.4)
SDAI overall score (range 0–10)	1.9 (1.5)	301 (47)	1.9 (1.5)
SDAI components			
Modified Rodnan skin score > 14	29	16 (3)	29
Scleredema	51	6 (1)	53
Worsening skin	11	52 (8)	9
Digital necrosis	10	8 (1)	10
Worsening vascular symptoms	18	11 (2)	14
Arthritis	11	0	10
Diminished DLCO	63	146 (23)	63
Worsening cardiopulmonary symptoms	8	10 (2)	9
ESR > 30 mm/h	26	142 (22)	24
Hypocomplementemia	12	125 (20)	10

CES-D: Center for Epidemiologic Studies — Depression Scale; SDAI: Scleroderma Disease Activity Index; DLCO: carbon monoxide diffusing capacity; ESR: erythrocyte sedimentation rate.

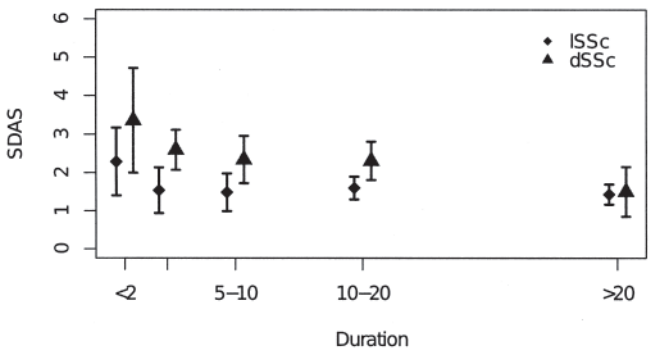

Figure 1. Valentini Scleroderma Disease Activity Index score (SDAS) as a function of disease duration (years) in SSc patients with complete datasets (N = 326; mean score and 95% confidence interval). dSSc: diffuse disease; lSSc: limited disease.

higher SDAI scores relative to patients with the same disease duration and disease subset (standardized RR 1.22, 95% CI 1.14, 1.31).

The results of the multiple imputation procedure were very similar, albeit with narrower confidence intervals (Table 2). Of note, although the estimated fractions of missing data for disease duration and depression were substantial (18%), the effective sample size in this particular analysis was roughly 525, over 60% larger than the sample size of the complete data analysis. The relationship between disease activity and disease duration in the multiple imputation model, adjusted for depression (using a CES-D score of 13, the median value in the cohort, as the reference) is shown in Figure 3. Again, SDAI scores are consistently higher in diffuse compared to limited disease patients, and scores for both subsets decrease with increasing disease duration. Figure 3 also shows model-free estimates of mean activity (with 95% CI) for 5 subsets of disease duration. We note that the fit of the estimated trends seems reasonable given the observed and imputed data.

Effect of disease duration on individual SDAI components. In order to determine which variables, if any, were responsible for the decrease in SDAI with increasing disease duration, we investigated the relationship of the 10 individual SDAI variables and disease duration using multiple logistic regression modeling (Figure 4). With adjustment for diffuse versus limited disease and levels of depression, skin score (standardized OR 0.59, 95% CI 0.43, 0.82) and patient-reported change in skin (standardized OR 0.64, 95% CI 0.45, 0.92) had estimated standardized odds ratios less than 1 and 95% confidence intervals that did not include 1, indicating that the probability of positive response for these 2 variables decreased with increasing disease duration. None of the 8 other variables changed significantly with increasing disease duration. Again, the results of the multiple imputation procedure were very similar for this part of the analysis, albeit with narrower confidence intervals. The only difference in observed statistical significance between the complete and the imputed datasets for duration was that the imputed dataset results indicated that scleredema also decreased significantly as a function of disease duration.

Figure 4 also shows that, with adjustment for disease duration and depression, high skin scores (standardized OR 32.2, 95% CI 15.9, 72.0) were more likely and scleredema (standardized OR 0.58, 95% CI 0.37, 0.92) was less likely to be present in patients with diffuse disease. Similarly, adjusting for disease duration and diffuse versus limited disease, high depression scores were associated with positive responses for the patient-reported variables: i.e., change in skin (standardized OR 1.95, 95% CI 1.39, 2.75) and change in heart/lung symptoms (standardized OR 2.10, 95% CI 1.49, 2.98).

DISCUSSION

This study is the first detailed description of patterns of disease activity according to disease duration in SSc. The findings are consistent with previous research that found that the majority of internal organ involvement in diffuse SSc occurs within the first 3 years of disease[25]. It extends those observations to patients with limited SSc and examines the patterns over time of 10 different variables thought to have a large influence on disease activity in SSc. Using the Valentini SDAI as a measure of disease activity, decreases in skin involvement and scleredema have a preponderant effect on overall disease activity in SSc over time, while activity in the other organ systems that were assessed persists over time. Of note, decreased diffusion capacity is an important contributor of disease activity throughout the course of the disease. Although this may in part reflect disease damage, it also reinforces the importance of longterm followup of SSc patients who may develop new cardiopulmonary involvement throughout the course of their disease.

We tested for other variables that may influence disease activity, including age, sex, and disease subset. Age was found not to be a significant indicator of activity, possibly because it may have both negative and positive effects in different organ systems. Gender did not predict activity, although results here should be interpreted with caution due to the relatively small number of men in this study. In so far as skin subsets were concerned, patients with diffuse disease were, not unexpectedly, more likely to have higher skin scores, but the finding of reduced scleredema is surprising and difficult to explain. As diffuse SSc is a more rapidly progressive disease, scleredema may already have advanced to more extensive disease at the time of inclusion into the study, while in limited SSc, these changes may have been slower to progress.

The SDAI is easy to administer and is the first composite disease activity score for SSc. Difficulties inherent to it include the poor level of consensus, even among experts, for what constitutes active disease and the absence of a valid biochemical marker of disease activity. Serum complement

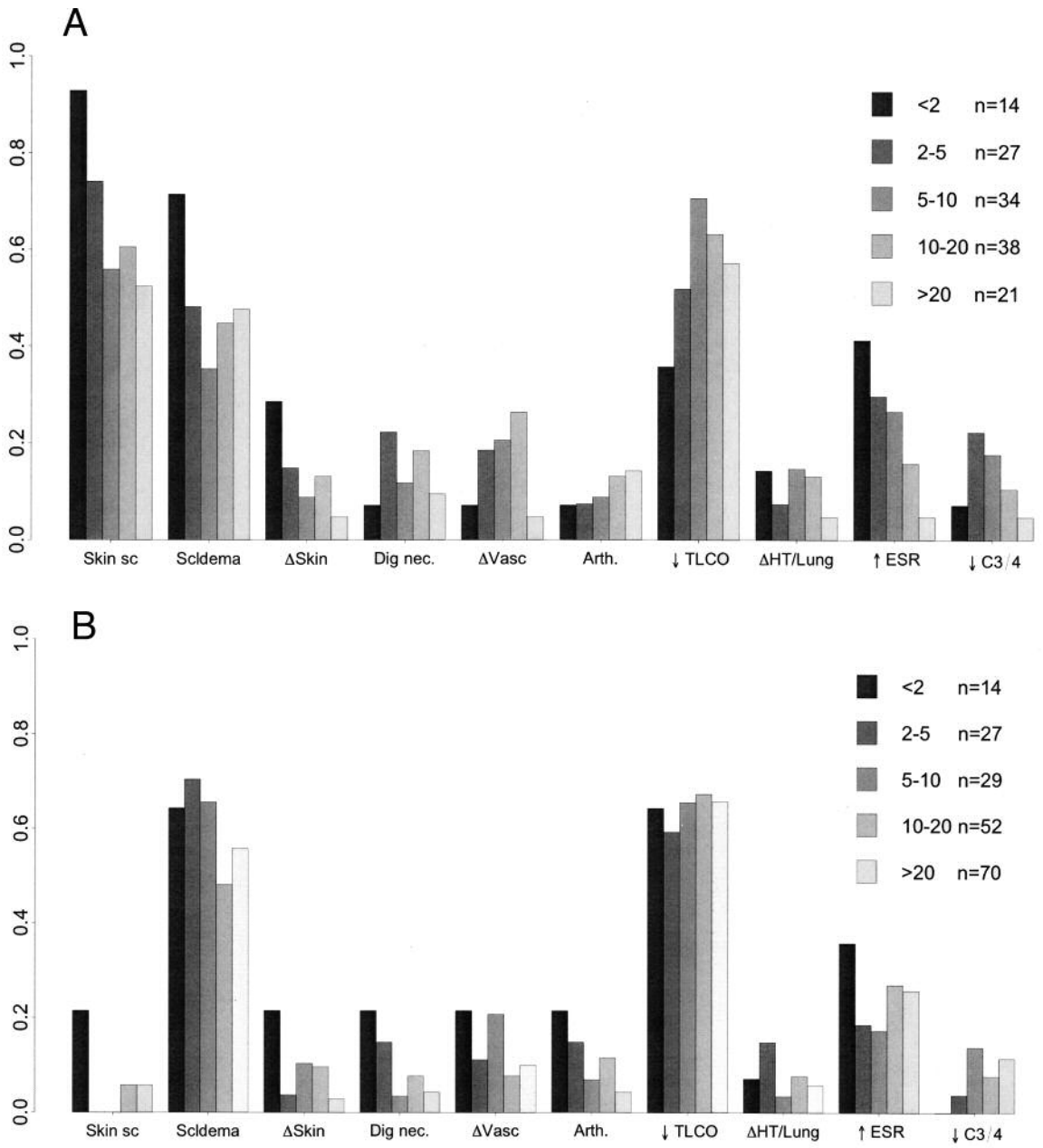

Figure 2. Prevalence of abnormalities in individual Scleroderma Disease Activity Index variables as a function of disease duration. Height of bars indicates proportion of subjects with positive responses for each SDAI component. A. Patients with diffuse disease, dSSc (n = 134). B. Patients with limited disease, lSSc (n = 192). Skin sc: skin score; Scldema: scleredema; Δ Skin: change in skin; Dig nec: digital necrosis; Δ Vasc: change in vascular; Arth: arthritis; TLCO: diffusion capacity; Δ HT/Lung: change in cardiopulmonary; ESR: erythrocyte sedimentation rate; C3/4: hypocomplementemia.

levels, used in the SDAI, have limited efficacy in predicting disease activity. In our own group of Canadian patients, they were found to more accurately reflect overlap disease[26]. Although the patient-recall questions allow easy application of this score, the relatively low representation of objective measures means that it is subject to patient-report bias. Also, to provide a changing view of activity, in 3 questions, patients are asked to recall changes over the last month. This does not allow for constant levels of activity (lasting more than 1 month) and may result in falsely low scores in some patients with active disease. Nevertheless, this index is the first validated composite measure of disease activity in SSc, and represents a valuable tool to understand aspects of the natural history of this rare and complex disease that remain to be described.

The finding that depression influences disease activity is of great interest. Using a cutoff of 16 on the CES-D, others have estimated the prevalence of depression in SSc to be

Table 2. Results of the overdispersed Poisson regression models for the Scleroderma Disease Activity Index. Disease duration was log-transformed for this model. Relative risks are based on standardized covariates (roughly a 2.7-fold increase in raw duration and a 10-point increase in the CES-D score).

	Complete Data n = 326				
	Standardized Coefficients	95% CI	Relative Risk	95% CI	p
Log (disease duration)	–0.13	–0.20, –0.05	0.88	0.82, 0.95	< 0.001
Depression	0.20	0.13, 0.27	1.22	1.14, 1.31	< 0.0001
Diffuse disease	0.35	0.19, 0.50	1.42	1.21, 1.65	< 0.0001

	Multiply Imputed Data n = 639					
	Standardized Coefficients	95% CI	Relative Risk	95% CI	p	Estimated Fraction of Missing Data, %
Log (disease duration)	–0.10	–0.15, –0.05	0.91	0.86, 0.96	< 0.001	18
Depression	0.15	0.09, 0.20	1.16	1.10, 1.22	< 0.0001	16
Diffuse disease	0.35	0.23, 0.47	1.42	1.26, 1.60	< 0.0001	10

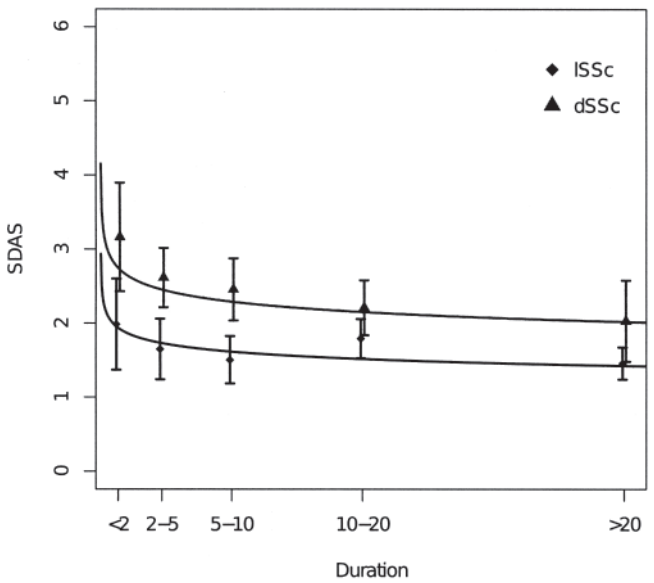

Figure 3. Fitted mean Scleroderma Disease Activity Index curves under the multiple imputation model. Estimated quasi-Poisson regression curves for patients with limited (lSSc) and diffuse (dSSc) disease with CES-D scores of 13 (the median value in the cohort). The points (and 95% confidence interval) result from summarizing mean SDAI across imputed datasets when categorizing subjects according to disease type and duration.

high, ranging from 36% to 50%[27,28]. Three components in the SDAI rely upon self-report and it is likely that subjective perceptions may have influenced SDAI scores. Consistent with this premise, in our data, change in skin and cardiopulmonary symptoms reported by the patients and included in the computation of the overall SDAI score were associated with increased levels of depression in our multiple logistic regression analyses. However, other factors also need consideration. Studies examining depression in SSc have found that depression is linked to gastrointestinal involvement[27]. Gastrointestinal involvement is not assessed in the SDAI. Thus, it is possible that the effects of depression on the self-reported items in the SDAI may in part reflect more severe gastrointestinal involvement.

Our analysis also shows the importance of properly handling missing observations and missing data. By using a multiple imputation approach, we were able to obtain much more precise estimates of model coefficients (as reflected in the narrower confidence intervals). We also were able to assess the effect of the missing data on our conclusions by comparing the multiple imputation analysis with the standard complete data analysis. For example, the difference between patients with limited and diffuse disease would have been underestimated had we used only the complete data or, even worse, had imputed zero (or even mean) values for the missing SDAI indicator variables. Although these methods require additional statistical sophistication and effort, our work shows the importance of such methods when examining composite measurement instruments.

One possible concern with the cross-sectional aspect of our data is "survivor bias"[29]. It is possible that patients with very active disease will die early in the course of their disease, whereas patients with less active disease may be more likely to survive. However, if this were the case, including more patients with early, active disease should result in even higher levels of disease activity than found in this cohort. Thus, a survivor bias in this study could in fact attenuate the estimated effect of duration. We verified the presence of this bias in a subgroup analysis of patients with disease duration less than 5 years. In this subgroup analysis, the effect of duration in both complete data (RR 0.78, 95% CI 0.64, 0.95) and the multiply imputed data (RR 0.84, 95% CI 0.86, 0.96) analyses was indeed slightly more pronounced than that observed in the main analysis on all subjects. Therefore, we believe that, if anything, the results reported in our main analysis are conservative estimates.

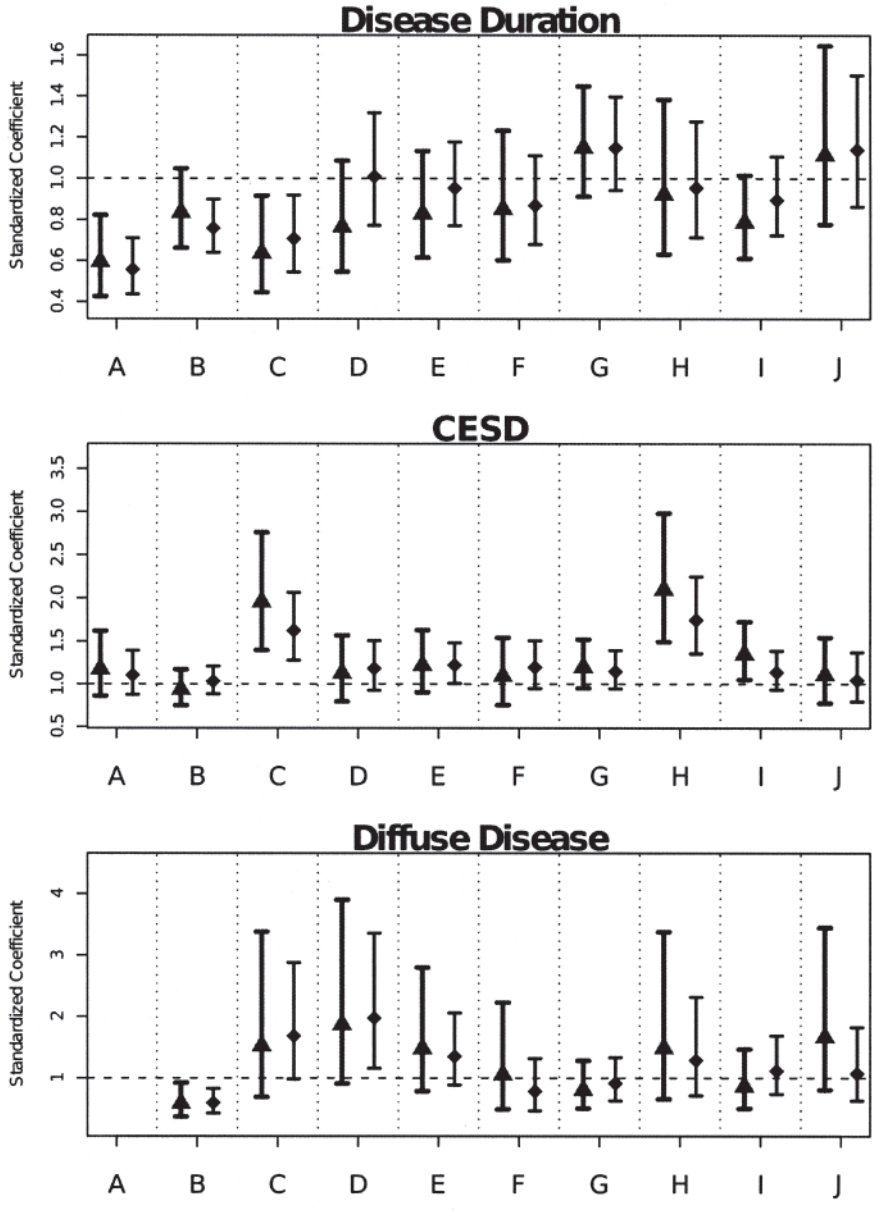

Figure 4. Results of multiple logistic regression analysis for the 10 components of the Scleroderma Disease Activity Index. Points represent standardized odds ratios (error bars cover the 95% confidence interval). Triangles show results of multiple logistic regressions for complete data only; diamonds show the same results for multiply imputed data. The estimate for skin score for patients with diffuse disease ("A"; standardized OR 36.4, 95% CI 20.8, 63.6) was too large to be illustrated. A: Skin score; B: Scleredema; C: Δ Skin; D: Necrosis; E: Δ Vascular; F: Arthritis; G: diminished DLCO; H: Δ Cardiopulmonary; I: elevated ESR; J: Hypocomplementemia.

This was a cross-sectional study using a convenience sample of patients from the Canadian Scleroderma Registry. A prospective study to confirm these results is under way. Another limitation of the study is that, to receive assessment in a CSRG research clinic, patients must be referred to a rheumatologist, meaning that the CSRG may fail to identify patients with milder disease who are not referred or those in whom organ involvement is limited predominantly to one system (for example, gastroenterology). Thus, our results may not be entirely representative of the whole SSc spectrum.

We were able to apply the SDAI with ease among our cohort of Canadian patients with SSc and to demonstrate important patterns of change in SSc disease activity with increasing disease duration. A decline in overall disease activity was mostly driven by changes in skin involvement, while activity persisted in other organ systems we assessed.

Depression was found to be associated with higher patient activity scores and was strongly associated with patient self-response questions. The role of depression should be carefully considered in future applications of the SDAI, particularly as several components of the score rely upon patient recall. Gastrointestinal involvement, a common feature of SSc and a factor found to significantly influence depressive symptoms in SSc, is not well represented in the SDAI and elevated levels of depression among our cohort of patients may partially reflect gastrointestinal involvement. Factors influencing individual components of the SDAI score were variable. Future longitudinal studies will provide more accurate information about changes in disease activity over time.

APPENDIX

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