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Abstract

Objective*:* Systemic sclerosis (SSc) is an autoimmune disease characterized by progressive organ damage, which can be measured using the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI). We aimed to identify whether distinct trajectories of damage accrual exist and determine which variables are associated with different trajectory groups.

Methods: Incident cases of SSc (<2 years) were identified in the Australian Scleroderma Interest Group and Canadian Scleroderma Research Group prospective registries. Group-based trajectory modeling was used to identify SCTC-DI trajectories over the cohort's first 5 annual visits. Baseline variables associated with trajectory membership in a univariate analysis were examined in multivariable models.

Results: 410 patients were included. Three trajectory groups were identified: low (54.6%), medium (36.2%) and high (10.3%) damage. Patients with faster damage accrual had higher baseline SCTC-DI. Older age (OR 1.57, 95% CI 1.18 - 2.10), male sex (OR 2.55, 95% CI 1.10 - 5.88), diffuse disease (OR 6.7, 95% CI 2.57 - 17.48), tendon friction rubs (OR 5.4, 95% CI 1.86 - 15.66), and elevated CRP (OR 1.98, 95% CI 1.49 - 2.63) increased the odds of being in the high damage group versus the reference (low damage), whereas Caucasian ethnicity (OR 0.31, 95% CI 0.12 - 0.75) and anti-centromere antibodies (OR 0.24, 95% CI 0.07 - 0.77) decreased them.

Conclusions: We identified three trajectories of damage accrual in a combined incident SSc cohort. Several characteristics increased the odds of belonging to worse trajectories. These findings may be helpful in recognizing patients in whom early aggressive treatment is necessary.

Significance and Innovations

- Using the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) and group-based trajectory modeling, we studied trajectory patterns of damage accrual in two large prospective scleroderma cohort registries.
- We have identified three distinct trajectories of damage accrual and found that patients with the worst trajectories have already acquired more damage very early (within 2 years of disease onset).
- Older age, male sex, non-Caucasian background, diffuse cutaneous disease, TFRs, and elevated CRP were associated with worse trajectories whereas ACA had a protective association.
- Future studies are needed to explore the impact of different treatment modalities on damage accrual and to investigate ways to practically predict which trajectory an individual patient will fall into.

Introduction

Systemic sclerosis (SSc) is a rare systemic autoimmune disease associated with high mortality. It is characterized by immune dysregulation, vasculopathy and fibroblast dysfunction which ultimately lead to increased deposition of extracellular matrix, fibrosis and irreversible organ damage (1). To measure this damage, the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) was developed and validated in 2019 under the leadership of Australian and Canadian scleroderma experts (2). Previous prognostic studies examined mortality only or used individual organ-specific damage measurements (3, 4). The Medgser Disease Severity Scale, for example, has been used in several studies, but measures both reversible (disease activity) and irreversible (damage) changes (5) and is thus not specific for damage. As the first validated SSc damage measurement, the SCTC-DI may allow us to better study the natural evolution of the disease and be useful in both the clinical and trial design setting.

Group-based trajectory modeling (GBTM) has long been used in psychology and criminology research, but is now increasingly also used in clinical studies (6). GBTM assumes a baseline patient population is heterogenous and composed of clusters of individuals following similar disease courses. It classifies these individuals into groups (or trajectories) based on how they evolve over time and can identify defining characteristics of its members (7, 8).

The evolution of damage accrual over time in SSc patients has not yet been investigated. Describing SSc damage trajectories is important to better understand the evolution of the disease and to potentially help identify patients more likely to have a poor prognosis requiring early aggressive therapy. This study aims to identify if there are distinct trajectories of damage accrual

from early in the course of SSc and to determine which variables are associated with different trajectories.

Methods

Source population

The Canadian Scleroderma Research Group (CSRG) registry, started in 2004, is an ongoing longitudinal study of adult scleroderma patients recruited by rheumatologists from 14 sites across Canada and 1 in Mexico. All sites have the approval of their institutional review boards and patients provide written consent. Data are collected at yearly visits using a standardised data collection protocol which includes clinical (both patient and physician reported) and laboratory data and is recorded in a customized database. The Australian Scleroderma Cohort Study (ASCS) is also an ongoing longitudinal study of SSc patients recruited since 2007 from 12 centers across Australia. Their data collection protocols are similar to the CSRG. Combined, the CSRG and ASCS registries comprise more than 3000 patients. In this study, we included incident SSc cases (disease duration < 2 years) who met 2013 ACR-EULAR SSc classification criteria (9). To be able to determine trajectories, only patients with at least two cohort visits and two SCTC-DI scores were included. The study was approved by the ethics committee at the Jewish General Hospital in Montreal, Canada.

Scleroderma Clinical Trials Consortium - Damage Index (SCTC-DI)

The SCTC-DI measures global irreversible damage in SSc patients and was developed to be highly correlated with mortality and morbidity (measured by Short Form-36) (2). Validated and published in 2019, its development was an international collaboration between 22 experts with input from patient partners using a combined approach of consensus and data driven methods. The index is composed of 23 differently weighted items in several organ systems (musculoskeletal, skin,

vascular, gastrointestinal, respiratory, cardiovascular, and renal). Low, medium, and high SCTC-DI scores are defined as < 5, 6-12 and ≥ 13 respectively, with a maximum score of 55. Definitions of the SCTC-DI items have been published previously (2).

In this study, the SCTC-DI was calculated using registry data, but three items (calcinosis complicated by infection or requiring surgery, GAVE, and right ventricular dysfunction) were removed since they were not collected in the CSRG database, and one item (small joint contractures) was removed due to missing data (>20% of visits). The maximum SCTC-DI score was therefore 42.

Clinical variables

The patients' baseline visit for this study was their first registry visit with a calculable SCTC-DI score which had to be within 2 years of the first non-Raynaud's manifestation. We then extracted baseline variables from the databases. Demographic and lifestyle information (age, sex, ethnicity, postsecondary education, employment, smoking, and environmental exposures) were obtained by patient self-reporting. Environment exposure was defined as exposure to silica, organic solvents, vinyl chloride & epoxy resins. SSc subtype (diffuse or limited), disease duration (years from first non-Raynaud's manifestation), tendon friction rubs (TFR), synovitis, nailfold capillaroscopy abnormalities, and comorbidities (diabetes, atherosclerosis, and non SSc-related lung disease) were determined by study physicians. Nailfold capillary abnormalities were defined as the presence of any abnormality (giant capillaries, dilated capillaries, capillary dropouts). They were assessed using the DermLite dermatoscope, a well validated clinical tool (10). Finally,

baseline inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)) and serologies were recorded.

Serology

Autoantibody serologies for CSRG cohort patients were analyzed in a central laboratory at the University of Calgary. Samples were aliquoted and stored at −80°C until needed. Anti-centromere (ACA) (CENP-A and CENP-B), anti-topoisomerase I antibodies (ATA) and anti-RNA polymerase III (ARNAP) (RP11 and RP155) were assessed using Euroline SSC profile line immunoassay (Euroimmun, Luebeck, Germany) according to the manufacturer's instructions. Serologies for ASCS patients were conducted at local laboratories using local assays and protocols.

Statistical analysis

We performed GBTM to identify SCTC-DI trajectories over 4 years (11). This approach applies a specialized application of finite mixture modeling to identify homogenous clusters of developmental trajectories within a sample population. The number and shape (i.e., linear, quadratic, and cubic) of trajectories were determined by the patterns and distribution of SCTC-DI. We required that trajectory groups each include at least 10% of study participants, allowing the secular patterns of SCTC-DI to be summarized in a parsimonious and meaningful fashion. The final model was evaluated using both Bayesian Information Criterion (BIC) values and the average posterior probability of assignment ($\geq$ 0.70). GBTM handles missing data by using maximum likelihood estimates, assuming that the data is missing at random (i.e. unrelated to the measured outcome), which was a reasonable assumption in this study (12).

We compared the baseline characteristics according to SCTC-DI trajectory groups using Analysis of Variance (ANOVA) or Kruskal-Wallis Test for continuous variables and chi-square test or Fisher's exact test for categorical variables. We examined the relation of baseline socio-demographic and clinical variables to the SCTC-DI trajectory groups using multivariable logistic regression models, adjusting for potential confounders based on clinical knowledge and as guided by causal diagrams (13). Variables were selected for the models based on clinical knowledge and statistical significance ($p < 0.1$ in univariate analysis).

We did not include baseline SCTC-DI as a parameter in the multivariable model because it is part of the outcome variable and could bias the estimates to the null (14). We therefore compared the baseline SCTC-DI, the prevalence of organ-specific damage and mortality between the trajectories in a separate univariate analysis. A survival analysis was performed using a Cox model, which included age and sex. The low damage trajectory group was used as reference. A result was considered statistically significant if the p value was < 0.05 in all our analyses.

Results

Sample population

Of 664 incident SSc patients who met 2013 ACR/EULAR classification criteria, we excluded 254 patients who either had only a baseline visit (n=123), had fewer than 2 SCTC-DI values (n=99) or had their first calculable SCTC-DI after 2 years of disease onset (n=32). Of the remaining 410 patients (219 from ASCS and 191 from CSRG), the mean age was 53 years (SD ± 12.9), 19.5% were men, 85.1% were Caucasian, and 47.8% had diffuse disease (Table 1). The patient characteristics from each database were similar, although the CSRG had fewer Caucasian patients (81.0% vs 88.8%), slightly longer disease duration (1.2 vs 1.0 years), more diffuse patients (53.9% vs 42.2%) and were slightly older (54.3 vs 52.9 years) (supplementary table 1). Year of recruitment and their prevalence in each trajectory group, are described in supplementary table 2.

Trajectory data

We identified three SCTC-DI trajectory groups: low damage (n=224; 54.6%), medium damage (n=144, 36.2%) and high damage (n=42, 10.3%) (Figure 1) over four years (mean length of follow up: 3.0 ± 1.2 years). The shapes of the trajectories were linear (trajectory 1) and quadratic (trajectories 2-3). The average posterior probability of group membership assigned to each group was 0.94, suggesting an excellent fitting model.

Patients in the low damage trajectory group had the lowest mean SCTC-DI at baseline (2.2, SD ± 1.7), then accrued further damage at a constant rate of 0.55/year. Patients in the medium and high damage trajectories started with a mean SCTC-DI of 5.5 (SD ± 2.2), and 10.1 (SD ± 3.3)

respectively. They then accrued further damage following quadratic curves, with overall faster damage accrual rates.

Baseline characteristics and their association with trajectory group membership

Baseline characteristics according to SCTC-DI trajectory groups are shown in Table 1. Variables that were more prevalent in the higher damage trajectories were male sex, diffuse disease, TFRs, and higher inflammatory markers. ACA was more prevalent in lower damage trajectories. Between 1-3% of data were missing for all variables, except ARNAP, for which 13% was missing.

Table 2 presents the association of baseline characteristics with SCTC-DI trajectory groups. Since CRP and ESR are highly correlated, only CRP was included in the multivariable analysis as it is a more consistent measure of inflammation. To minimize bias, age, sex, and ethnicity were controlled for one another only. For example, age was adjusted for sex and ethnicity only and not for the other variables in the model. The remaining variables were controlled for all others except intermediate (CRP) and collinear variables. For example, ARNAP was controlled for all variables except CRP, since it is an intermediate. When compared with the low damage trajectory, older age (per 10 years) (OR 1.57, 95% CI 1.18 - 2.10), male sex (OR 2.55, 95% CI 1.10 - 5.88), diffuse disease (OR 6.7, 95% CI 2.57 - 17.48), TFRs (OR 5.4, 95% CI 1.86 - 15.66), and elevated baseline CRP (OR 1.98, 95% CI 1.49 - 2.63) significantly increased the odds of being in the highest damage trajectory, whereas Caucasian ethnicity (OR 0.31, 95% CI 0.12 - 0.75) and ACA (OR 0.24, 95% CI 0.07 - 0.77) significantly decreased them. No significant association was found for ATA or previous smoking history. Despite a strong trend when comparing prevalence between trajectories, no significant association was identified for ARNAP in the multivariable model.

Mortality and organ-specific damage comparison between trajectory groups

The mean baseline damage score and the prevalence of all organ-specific damage increased progressively from lower to higher damage trajectories (Table 3). Most notably, the prevalence of cardiovascular and renal damage was significantly higher in the high damage group (21.4% and 26.2% respectively) compared with the medium (10.4% and 4.9%) and low (1.8% and 0.5%) damage groups. In this 4-year follow-up period, the mortality of patients in low, medium, and high damage trajectories was 6.7%, 18.8%, and 23.8%, respectively. The overall mortality of patients in this study was 12.7%. In a Cox-survival analysis adjusting for age and sex, the hazard ratio for death was 2.97 (1.32, 6.68) in the medium damage group and 3.92 (2.05, 7.51) in the high damage group compared to the low damage trajectory group (table 4).

Discussion

In this international prospective cohort of 410 incident SSc cases, we identified 3 distinct trajectories of damage accrual with approximately half (45.4%) of patients in worse damage trajectories (medium and high damage). Given the high posterior probability of group membership of the model, these trajectory groups are likely truly distinct. Individuals in worse damage trajectories had higher baseline damage and subsequently accrued it more quickly. In addition, patients in medium and high trajectories had a significantly higher mortality (18.8%, and 23.8%) compared to the low damage trajectory (6.7%). The observation that worse trajectories already had significantly more damage at baseline, which was within 2 years of disease onset, highlights that significant damage is accrued very early in the disease and that future rates of damage accrual and even mortality risk may be determined very early.

The concept that damage occurs early in SSc has been suggested previously. A retrospective cohort study of 225 incident SSc patients found that half of diffuse cases developed either serious end-organ complications or died by 3 years of follow-up (3). The mild plateauing of our trajectories at 4 years in the medium and high damage groups suggests disease stabilization or possibly “burn out” though we cannot be certain without longer follow up. Several studies in SSc-ILD and SRC have also suggested that most damage is accrued within the first four years (15-19). This apparent subsequent stabilization, however, may also reflect a survival bias due to higher mortality of patients with more rapidly progressive disease. In a prospective cohort of 171 SSc-ILD patients, for example, Guler et al. found that the plateauing of FVC loss after the first four years was most likely artifactual (20).

The mortality of our cohort was 12.7% with a mean follow up of 3.0 years (SD ± 1.2). This is consistent with other incident cohort studies that have found the 3–5-year mortality to be between 7-32% (4, 21-23). We found progressively higher mortality and prevalence of all types of organ-specific damage from low to high damage trajectories. These findings are consistent with the literature which has identified that baseline visceral organ involvement, particularly gastrointestinal, and higher initial skin scores are associated with a worse prognosis and higher mortality (4, 5, 24, 25).

Our study identified several baseline characteristics that had an association with damage trajectory group membership (Table 2). Older age and male sex increased the odds of being in the worse damage trajectory whereas Caucasian ethnicity decreased them. These findings are in keeping with most studies (4, 22, 23, 25-33). Unsurprisingly, the variable that increased the odds the most for belonging to a higher damage trajectory was diffuse disease, which has consistently been identified as a poor prognostic factor (4, 22, 23, 25, 26, 34, 35). TFRs, highly correlated with diffuse and active disease, were independently associated with higher damage trajectories as well. TFRs, particularly in early disease, have been associated with a poor prognosis in many (26, 36-38), but not all SSc studies (23, 25). In addition, supporting previous studies, our results suggest an association between TFRs and ARNAP antibodies since they were found to be collinear in our analysis (36).

Smoking has been associated with poor respiratory, cardiac, gastrointestinal and vascular SSc outcomes (35, 39-41). Although it has been inconsistently associated with SSc mortality (4, 41, 42), studies using validated tools that integrate smoking intensity, duration, and time since cessation, have found decreased survival in these patients (39, 42). We found a trend for more damage in

ex-smokers, but this did not meet statistical significance possibly because we did not have the data necessary to use one of these validated smoking tools. We opted to include past smoking alone in our multivariable model after observing a significantly lower prevalence of active smokers in the highest damage trajectory. We believe this is most likely due to reverse causality whereby sicker patients had stopped smoking (43).

Consistent with previous studies, elevated baseline inflammatory markers is a poor prognostic marker (4, 22, 23, 25, 27, 44, 45). ACA decreased the odds of being in both the medium and high damage trajectories, whereas ATA did not. There was a non-significant trend for ARNAP to be associated with worse trajectories. The association between ACA and improved survival has been well described in the literature (4, 22, 33, 46, 47). On the other hand, results have been mixed concerning the associations of ARNAP and ATA with poor outcomes. Few prognostic studies have included ARNAP (22, 23) and, among those that have, the results are variable (4, 33, 48). In unadjusted analysis there was an increasing prevalence of ARNAP from low to high damage trajectories that was no longer seen in multivariable analysis. This lack of association may be due to lack of power and missing data, since 13% of ARNAP results were missing.

Although ATA is classically recognized as a poor prognostic factor (23, 47), several more recent studies have failed to demonstrate this association (4, 22, 33, 49). Boonstra et al. noted that by using the 2013 ACR/EULAR SSc classification criteria, we are not only identifying ATA+ patients earlier in their disease course, but also newly diagnosing SSc patients who are ATA+ and have a less severe phenotype (50). Combining the data from many of these studies, a 2019 meta-analysis confirmed the protective role of ACA and the deleterious role of ATA, while noting probable publication bias for ATA since few negative small studies were published (4).

Some limitations in this study merit discussion. Given that 85% of our cohort was Caucasian, our trajectories may not be generalizable to other ethnicities. Selection bias is also a consideration as we excluded 254 patients at cohort entry. However, when we compared age, sex, ethnicity, disease duration and cutaneous subtype between included and excluded patients, the only statistically significant difference was that excluded patients were slightly older (53.5 ± 12.9 vs 55.9 ± 12.8; p. 0.22). There were missing data and losses to follow up, which is unfortunately inherent to registry studies. A comparison of patients with 5 visits versus patients with fewer than 5 visits can be found in supplemental table 3. Of note, shorter follow up can be due to many different causes such as deaths, more recent enrollment, or lack of funding/personnel for certain sites to continue data entry. Four items were removed from the SCTC-DI due to missing data (>20%). We could not perform a sensitivity analysis because not enough patients had complete SCTC-DI scores to allow us to compare their trajectories to the rest of the cohort. Despite these missing items, the intent of the SCTC-DI was likely still captured, given the excellent fit of our model and the consistency of our results with previous studies. Of the included variables, only ARNAP had > 3% missing data. In addition, although other less common SSc-specific and related autoantibodies (e.g., fibrillarin, Th/To, PM/Scl) have been linked with disease outcome, they were not included in this study due to insufficient power. Although we found that mortality increased with worse trajectories, this may have been expected because the same patient cohorts were used to develop the SCTC-DI which was specifically designed to predict mortality. In addition, by using a shorter follow up period (4 years rather than 5 or 10), we may have attenuated the strength of the association between damage trajectory groups and mortality, which was, however, already significant. It is important to note that the trajectories we have identified describe the evolution

of SSc patients receiving standard of care at tertiary centers rather than the natural evolution of the disease. In addition, the influence of treatment on damage accrual was not assessed and would be an important topic of future study. Treatment protocols likely differ between country of recruitment (Australia versus North America), as well as between recently versus remotely enrolled patients.

In conclusion, we have identified three distinct trajectories of damage accrual in a large international incident SSc cohort. Patients with the worst trajectories have already acquired more damage very early, i.e., within 2 years of disease onset. Those with more damage within the first 2 years of disease continue to accrue damage at a faster rate in the next 3-4 years. Older age, male sex, non-Caucasian background, diffuse cutaneous disease, TFRs, and elevated CRP were associated with worse trajectories whereas ACA had a protective association.

Given this is the first study to use the SCTC-DI, our findings further validate it as an important tool in research and clinical trials. Future studies are needed to explore the impact of different treatment modalities on damage accrual and to investigate ways to practically predict which trajectory an individual patient will fall into.

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Table 1 – Baseline Characteristics of Trajectory Groups

	All patients (n=410)	Low Damage (n=224)	Medium Damage (n=144)	High Damage (n=42)	p values**
Age, mean ± sd	53.5 ± 12.9	52.8 ± 12.6	53.5 ± 13.5	57.6 ± 11.2	0.079
Male, n (%)	80 (19.5%)	**34 (15.2%)**	**34 (23.6%)**	**12 (28.6%)**	**0.041**
Caucasian, n (%)	343 (85.1%)	193 (88.1%)	118 (83.1%)	32 (76.2%)	0.097
Employed, n (%)		65 (32.5%)	51 (39.2%)	10 (24.4%)	0.176
Smoking status, n (%)					
Current smoking		20 (9.0%)	19 (13.2%)	3 (7.1%)	0.334
Past smoking		94 (42.2%)	64 (44.4%)	24 (57.1%)	0.200
Disease duration, mean ± sd	1.1 ± 0.5	1.1 ± 0.5	1.1 ± 0.5	1.0 ± 0.5	0.300
Diffuse subtype, n (%)	192 (47.8%)	**68 (31.5%)**	**92 (63.9%)**	**32 (76.2%)**	**<.001**
Tendon friction rubs, n (%)		**16 (7.2%)**	**27 (18.8%)**	**16 (38.1%)**	**<.001**
Antibodies, n (%)					
ACA		**78 (36.6%)**	**26 (20.0%)**	**6 (14.6%)**	**<.001**
ATA		48 (22.3%)	29 (22.5%)	7 (17.5%)	0.774
ARNAP		39 (19.9%)	34 (27.9%)	13 (33.3%)	0.097
C-reactive protein, median [IQR]		**4.0 [1.8, 6.4]**	**4.9 [2.7, 10]**	**11.0 [4.7, 38]**	**<.001**

Erythrocyte sedimentation rate, median [IQR]		**14 [7, 28]**	**16 [7, 32]**	**30 [12, 56]**	**0.001**
Synovitis, n (%)		73 (33.5%)	42 (29.6%)	17 (43.6%)	0.253
Environmental exposures*, n (%)		27 (12.7%)	23 (16.7%)	7 (16.7%)	0.535
Nailfold capillaroscopy abnormalities, n (%)		168 (76.0%)	103 (72.5%)	33 (78.6%)	0.648
Other comorbidities, n (%)					
Diabetes		13 (5.9%)	13 (9.0%)	3 (7.1%)	0.514
Atherosclerotic disease		11 (5.0%)	11 (7.6%)	4 (9.5%)	0.400
Non-SSc Lung disease		27 (12.1%)	18 (12.5%)	9 (21.4%)	0.250

* Environment exposure includes silica, organic solvents, vinyl chloride & epoxy resins.

** One way analysis of variance (ANOVA) and Kruskal-Wallis Test were used to compare continuous variables. Chi-square test and Fisher's exact test were used for categorical variables. Significant variables ($p<0.05$) are bolded.

Table 2 - Association of Baseline Variables with Trajectory Group Membership by Multivariable Logistic Regression

	Unadjusted OR* (95% CI)		Adjusted OR* (95% CI)**	
	Medium Damage	High Damage	Medium Damage	High Damage
Age (per 10 years older)	1.05 (0.88, 1.25)	**1.47 (1.10, 1.96)**	1.10 (0.91, 1.33)	**1.57 (1.18, 2.10)**
Male sex	**2.15 (1.19, 3.89)**	**2.45 (1.09, 5.51)**	**2.28 (1.24, 4.16)**	**2.55 (1.10, 5.88)**
Caucasian	0.60 (0.30, 1.18)	**0.38 (0.16, 0.90)**	0.53 (0.26, 1.08)	**0.31 (0.12, 0.75)**
Past smoking	1.11 (0.69, 1.76)	**2.04 (1.01, 4.12)**	1.10 (0.61, 1.97)	2.19 (0.93, 5.16)
Diffuse subtype	**4.25 (2.58, 7.00)**	**7.32 (3.23, 16.60)**	**4.34 (2.44, 7.72)**	**6.70 (2.57, 17.48)**
Tendon friction rubs	**2.86 (1.37, 5.96)**	**9.51 (4.05, 22.31)**	1.87 (0.77, 4.53)	**5.40 (1.86, 15.66)**
ACA	**0.43 (0.24, 0.77)**	**0.27 (0.11, 0.69)**	**0.37 (0.17, 0.81)**	**0.24 (0.07, 0.77)**
ATA	0.92 (0.52, 1.64)	0.72 (0.29, 1.74)	0.70 (0.33, 1.45)	0.67 (0.21, 2.22)
ARNAP	1.51 (0.83, 2.74)	**2.37 (1.09, 5.14)**	0.95 (0.47, 1.93)	1.05 (0.38, 2.93)
CRP (log)	**1.26 (1.08, 1.47)**	**2.01 (1.57, 2.56)**	1.17 (0.97, 1.40)	**1.98 (1.49, 2.63)**
ESR (log)	1.06 (0.96, 1.39)	**1.98 (1.41, 2.77)**	-	-

* Reference group is the low damage group.

** Age, male sex and Caucasian ethnicity were adjusted for each other only (e.g. age adjusted for ethnicity and sex only); all other variables adjusted for all others in the table, except for intermediate variables (CRP) and collinear variables (diffuse disease and antibodies). Significant variables ($p<0.05$) are bolded.

Table 3 – Baseline Damage Characteristics and Mortality of Trajectory Groups

	Low Damage (n=224)	Medium Damage (n=144)	High Damage (n=42)	p values*
SCTC-DI at baseline, mean ± sd	**2.2 ± 1.7**	**5.5 ± 2.2**	**10.1 ± 3.3**	**<.001**
Baseline organ-specific damage				
Musculoskeletal/Skin	**111 (49.6%)**	**111 (77.1%)**	**39 (92.9%)**	**<.001**
Vascular	**15 (6.7%)**	**24 (16.7%)**	**6 (14.3%)**	**0.009**
Gastrointestinal	**52 (23.2%)**	**80 (55.6%)**	**27 (64.3%)**	**<.001**
Respiratory	**22 (9.8%)**	**39 (27.1%)**	**20 (47.6%)**	**<.001**
Cardiovascular	**4 (1.8%)**	**15 (10.4%)**	**9 (21.4%)**	**<.001**
Renal	**1 (0.5%)**	**7 (4.9%)**	**11 (26.2%)**	**<.001**
Death	**15 (6.7%)**	**27 (18.8%)**	**10 (23.8%)**	**<.001**

* One way analysis of variance (ANOVA) and Kruskal-Wallis Test were used to compare continuous variables. Chi-square test and Fisher's exact test were used for categorical variables. Significant variables ($p<0.05$) are bolded.

Table 4 – Cox-Survival Analysis of Trajectory Groups

	Hazard ratio (95% CI)	P values
Male sex	1.57 (0.84, 2.90)	0.155
Age	**1.08 (1.05, 1.11)**	**<.001**
Trajectories		
Medium vs Low Damage	**2.97 (1.32, 6.68)**	**0.009**
High vs Low Damage	**3.92 (2.05, 7.51)**	**<.001**

Figure 1 – Group-Based Trajectory Model of Scleroderma Clinical Trials Consortium – Damage Index at Yearly Visits

ICMJE DISCLOSURE FORM

Date: 1/4/2022

Your Name: Ariane Barbacki

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

Manuscript Number (if known): ACR-21-0760

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Date: 12/15/2021

Your Name: Murray baron

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

Manuscript Number (if known): ACR-21-0760

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9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	Director of the Canadian Scleroderma Research Group until nov 2021. Unpaid position.

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Date: 12/15/2021

Your Name: Mianbo Wang

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

Manuscript Number (if known): ACR-21-0760

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Date: 1/5/2022

Your Name: Susanna Proudman

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

Manuscript Number (if known): ACR-21-0760

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9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	Medical Director Arthritis Australia

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Date: 12/15/2021

Your Name: Wendy Stevens

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

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Your Name: Yuqing Zhang

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

Manuscript Number (if known): ACR-21-0760

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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Date: 8/19/2021

Your Name: Assoc Prof Joanne Sahhar

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

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Date: 1/5/2022

Your Name: Mandana Nikpour

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

Manuscript Number (if known): ACR-21-0760

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1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ **None**	
		NHMRC Emerging Leadership Investigator Grant (GNT1176538)	
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		Research grant support from Astra Zeneca, BMS, GSK, Janssen, UCB	
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		Astra Zeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Pfizer, UCB	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		GSK, Janssen, Pfizer, UCB	
6	Payment for expert testimony	☒ **None**	
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Date: 1/4/2022

Your Name: Ada Man

Manuscript Title: Damage Trajectories in Systemic Sclerosis Using Group-Based Trajectory Modeling

Manuscript Number (if known): ACR-21-0760

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		Boehringer Ingelheim	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
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7	Support for attending meetings and/or travel	☒ **None**	
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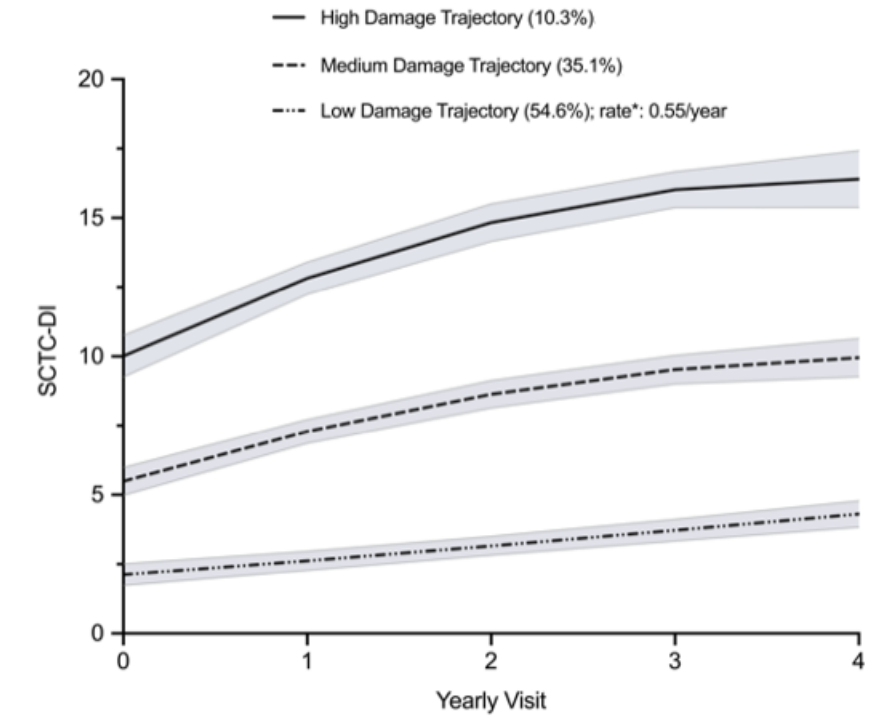

High Damage (N = 42)	38	29	28	22
Medium Damage (N = 144)	130	102	85	68
Low Damage (N = 224)	195	173	148	119

* Mean rise of SCTC-DI from baseline to the last visit.
Shaded area represents 95% CIs

ACR_24873_Figure 1 - GBTM of SCTC-DI at yearly visits._no titletif.tif