

# Predictors of Hand Contracture in Early Systemic Sclerosis and the Effect on Function: A Prospective Study of the GENISOS Cohort

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**ABSTRACT. Objective.** To identify baseline features that predict progression of hand contractures and to assess the effect of contractures on functional status in the prospective GENISOS cohort.

**Methods.** Rate of decline in hand extension, as an indicator of hand contracture, was the primary outcome. We assessed longitudinal hand extension measurements, modified Health Assessment Questionnaire (MHAQ) score, Medical Outcomes Study Short Form-36 (SF-36) physical function score, and demographic, clinical, and serological variables. Subjects with  $\geq 2$  hand measurements at least 6 months apart were included.

**Results.** A total of 1087 hand measurements for 219 patients were available over an average of  $8.1 \pm 4.8$  years. Hand extension decreased on average by 0.11 cm/year. Antitopoisomerase I antibody (ATA) positivity and higher modified Rodnan Skin Score (mRSS) were predictive of faster decline in hand extension ( $p = 0.009$  and  $p = 0.046$ , respectively). In a subgroup analysis of 62 patients with  $\leq 2$  years from SSc onset, ATA and diffuse disease type were associated with faster decline in hand extension; antientromere positivity was associated with slower rate of decline. Although the rate of decline in patients with disease duration  $\leq 2$  years was numerically higher, the difference was not statistically significant. Hand extension continued to decline in a linear fashion over time and was inversely related to overall functional status.

**Conclusion.** ATA was predictive of contracture development in both early disease ( $\leq 2$  yrs) and in the overall cohort. Hand extension declined linearly over time and was inversely associated with MHAQ and SF-36 scores. ATA positivity and higher baseline mRSS were predictive of faster decline in hand extension. (J Rheumatol First Release June 1 2019; doi:10.3899/jrheum.180093)

## Key Indexing Terms:

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Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular injury, fibrosis of skin and internal organs, and autoantibodies<sup>1</sup>. Although there is considerable individual variation, skin thickening tends to reach a maximum within 3 to 5 years of disease onset<sup>2,3,4</sup> and then can stabilize or improve. The effects of SSc on the hands have been well documented<sup>3,5,6,7,8</sup> and include Raynaud phenomenon (RP), digital ulcerations, joint pain and inflammation, and the development of hand contractures. However, not all patients with SSc develop hand contractures, even after years of disease.

Previous studies have shown that patients with SSc can have significant hand impairment resulting in activity limitations<sup>5,6</sup>. We have previously shown that hand contractures are associated with work disability<sup>9</sup>.

Despite being a well-documented phenomenon, there is a paucity of data regarding the rate of progression or regarding predictors of hand contractures over time.

The aim of our study was to perform a longitudinal analysis to identify the predictors of hand contracture, rate of

progression in SSc, and the association of these contractures with hand function using the modified Health Assessment Questionnaire (MHAQ)<sup>10,11</sup>.

## MATERIALS AND METHODS

Disease characteristics were studied in patients with SSc enrolled in the Genetics versus Environment in Scleroderma Outcomes Study (GENISOS). GENISOS is a prospective study of patients with early SSc<sup>12</sup>. All patients fulfilled either the 1980 American College of Rheumatology (ACR) classification criteria for SSc (for those enrolled 1998–2013)<sup>13</sup> or the 2013 ACR/European League Against Rheumatism criteria<sup>14</sup>. In addition, GENISOS cohort subjects also had to meet the following inclusion criteria: (1) age > 18 years at enrollment; (2) disease onset within 5 years of enrollment (as defined by the date of the first non-RP feature). For the current study, patients with SSc were included from the beginning of study enrollment in January 1998 to October 2014. The GENISOS study is currently conducted at the University of Texas McGovern Medical School in Houston, Texas, USA. However, patients included in our study were also enrolled at the University of Texas at San Antonio and University of Texas Medical Branch in Galveston (1998–2012). Individuals were evaluated with a standard protocol at specified timepoints, which were every 6 months for the first 3 years and then annually. Visit 0 corresponds to study entry at baseline; Visit 5 was at 5 years, and Visit 10 at 10 years from enrollment. To ensure consistency over time, the same group of investigators performed the measurements; training on the skin scoring method as well as the hand extension measurement was done at the annual or (at times) biannual investigator meetings.

This study was approved by our institutional review board (Research Ethics Board IRB number HSC-MS-02-161) and all subjects provided written informed consent.

We analyzed 1087 longitudinal measures belonging to 219 GENISOS enrollees. Patients were assessed for bilateral hand extension that decreased when/if contractures developed. These measurements were obtained by measuring the distance from the most external point of the thumb tip to the most external point of the fifth digit tip on the palmar side during maximum active effort to extend the fingers, measured in cm using a plastic tape measure pulled taut. This was measured with the first and fifth fingertips aligned in the same plane in the air, not resting or pressing against a flat surface<sup>7</sup>. Those patients with at least 2 hand measurements at least 6 months apart were included in this analysis. The same investigators performed the measurements on their patients (TAM, HTD, JDR, SA, and MDM) and training sessions were held to teach the method. This technique is illustrated in Supplementary Figures 1 and 2 (available with the online version of this article). This measure is a function of skin thickening, flexion contractures of the fingers (related to skin and tendon involvement), and small joint damage.

Baseline demographic and clinical characteristics were assessed for predictive value in hand contracture development. These features included age, sex, race/ethnicity, presence of serum SSc-specific autoantibodies [anti-topoisomerase I (ATA), anticentromere (ACA) and RNA polymerase III (RNAP3) antibodies], SSc disease type [limited cutaneous (lcSSc) or diffuse cutaneous SSc (dcSSc)]<sup>15</sup>, presence of digital ulcers, modified Rodnan skin scores (mRSS)<sup>4,16</sup>, and the presence of small joint arthritis (as determined by the examining investigator). Patients also completed self-reported functional assessments at each visit using the MHAQ as well as the Medical Outcomes Study Short Form-36 (SF-36) physical function (PF) scale<sup>17</sup>. The MHAQ is a patient-reported outcome and was developed for use in patients with rheumatic disease as an assessment of functional status. It has 8 items including (1) dressing and grooming, (2) arising, (3) eating, (4) walking, (5) hygiene, (6) reach, (7) grip, and (8) common daily activities. These items are rated on a 4-point Likert scale where 0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do. Total score is between 0.0 and 3.0 in 0.125 increments, with higher scores indicating worse function and greater disability. The MHAQ has been validated in SSc<sup>11</sup>, as has the SF-36<sup>18,19</sup>.

We also performed a subgroup analysis of 62 patients who were enrolled  $\leq 2$  years from the date of first non-RP and who had 2 hand measurements at least 6 months apart within this 2-year period. This subgroup analysis was done to determine whether the rate of change was more pronounced in this very early disease group or whether predictors were different from the group as a whole.

**Statistical analysis.** Descriptive statistics were calculated for all variables of interest. Separate linear mixed models were used to analyze longitudinal measurements of the right hand, left hand, and their average. The time variable was set as the time of disease onset, defined as the onset date of the first non-RP feature typical of SSc. All models included a random subject intercept and slope to account for the longitudinal aspect of the data. We included these variables as predictors (one at a time) in each model by including a main effect and interaction with time: sex, race, age, autoantibodies (ATA, ACA, RNAP3), disease type (lcSSc or dcSSc), presence of digital ulcers, baseline mRSS scores, and presence of small joint arthritis. A significant interaction would indicate a different rate of change in hand contractures. A multivariable mixed model was conducted for hand average including all main effects and interactions with  $p$  value < 0.10 in the one-at-a-time models. The analyses were repeated in the subgroup of patients with measurements taken  $\leq 2$  years from disease onset, to assess early predictors of contractures.

To evaluate the longitudinal association of mRSS score with average hand extension, we used a linear mixed model including longitudinal mRSS score as a time-varying covariate, time since disease onset, and an indicator variable for disease onset  $\leq 5$  years and its interaction with mRSS score. Presence of an interaction would indicate a different association between mRSS score and average hand extension if disease onset was  $\leq 5$  years. The rate of change corresponds to the  $\beta$  coefficient from linear mixed models.

Pearson correlations between hand extension measurements and the MHAQ score were calculated at each timepoint. A multivariable linear mixed model was used to investigate the association between hand extension measurements and the MHAQ score. The model included as predictors the longitudinal average hand measurement as a time-varying covariate and time since disease onset (and random subject intercept and slope). A similar model was used to evaluate the association of hand extension and SF-36 PF domain score<sup>17</sup>. All analyses were conducted in R software (R Foundation for Statistical Computing).

## RESULTS

Baseline demographic data and general clinical characteristics of the patients are shown in Table 1. A total of 1087 sets of hand measurements were evaluated over a mean followup period of  $8.1 \pm 4.8$  years [median followup 7.2 yrs; interquartile range (IQR) 4.2–11.6] in 219 patients with SSc; of these 219 patients with 2 or more measurements, 3 subjects had only 2 measurements, 78 had 3, and 138 had 4 or more. The average time interval between measurements was 353 days (0.97 yrs); 186 (85%) were female; 120 (55%) were non-Hispanic whites; 127 (58%) had dcSSc; and mean age was  $48 (\pm 12)$  years. At baseline, mean mRSS was 17 and mean disease duration at cohort entry was  $2.37 \pm 1.50$  years. Mean disease duration from onset to first hand measurement was  $4.1 (\pm 3.2)$  years for all 219 individuals; for the 62 patients with  $\leq 2$  years disease duration, this interval was  $1.1 (\pm 0.6)$  years.

Right hand, left hand, and the average of right and left hand measurements were evaluated. At study enrollment, mean right hand extension was  $17.1 (\pm 2.6)$  cm and mean left hand extension was  $17.5 (\pm 2.5)$  cm with average of both

Table 1. Baseline demographic and clinical data of 219 patients with SS.

Baseline Disease Characteristics	Values
Female sex	186 (85)
Race/ethnicity	
White (non-Hispanic)	120 (55)
Hispanic	48 (22)
African American	40 (18)
Other	11 (5)
Autoantibody	
ACA	27/212 (13)
ATA	40/212 (19)
RNAP3	48/210 (23)
Disease type, dcSSc	127 (58)
Digital ulcers	37/123 (30)
Small joint arthritis	24/123 (20)
Mean age, yrs (SD)	48 (12)
Baseline mRSS	
Mean (SD)	17 (11.2)
Range	2–49
Median (interquartile range)	14.5 (7–26)
Mean disease duration at cohort entry, yrs (SD)	2.37 (1.50)

Values are n (%) unless otherwise specified. SS: systemic sclerosis; ACA: anticentromere antibodies; ATA: antitopoisomerase I antibody; RNAP3: RNA polymerase 3 antibody; dcSSc: diffuse cutaneous SS; mRSS: modified Rodnan skin score.

hands  $17.3 (\pm 2.5)$  cm. Over time the average hand extension decreased by 0.11 cm/year.

Figure 1 is a graphic representation of individual right and left hand measurements over time from first non-RP demonstrating a linear decrease (unadjusted mixed model). Estimates are from a linear mixed model including time as a predictor and random subject intercept and slope. The models included all available observations for each subject.

Table 2 shows the predictive significance of baseline variables (from one-at-a-time models) for faster decline in hand extension. For this analysis, in Table 2 and Table 3, race categories were compressed with the reference category being white (non-Hispanic) and the “other” race category combining Hispanic, African American, and other. The presence of ATA and higher baseline mRSS scores was predictive of accelerated decline in the overall hand extension over time. The average decrease in hand extension in ATA-positive patients was 0.26 cm/year more than in the ATA-negative group (Figure 2). Worse contractures, as defined by decreased hand extension, were found in the ATA-positive patients ( $n = 40$ ) compared to patients without this antibody ( $n = 172$ ;  $p = 0.009$ ). Further, in evaluating baseline mRSS, the following was found: a 1-unit increase

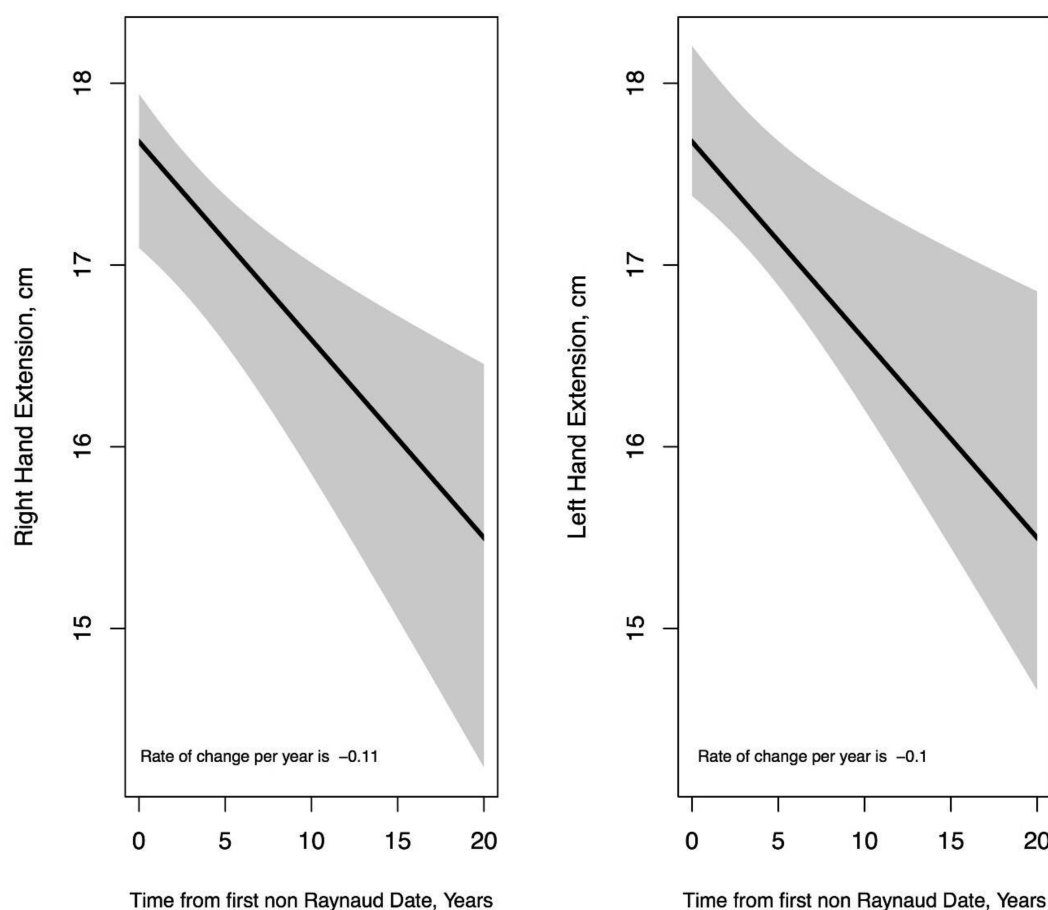


Figure 1. Graphic representation of individual right and left hand measurements (cm) over time from first non-Raynaud phenomenon, demonstrating a linear decrease over time.

Table 2. Predictive significance of baseline demographic and clinical variables for rate of change in hand extension results from mixed models.

Baseline Disease Variables	Right Hand Rate of Change	p*	Left Hand Rate of Change	p*	Average Hand Rate of Change	p*
Female	-0.11	0.70	-0.10	0.77	-0.11	0.99
Race, white (non-Hispanic)	-0.10	0.77	-0.10	0.94	-0.11	0.89
Age	-0.002	0.43	-0.001	0.62	-0.001	0.60
ATA	-0.24	0.03	-0.28	0.002	-0.26	0.009
ACA	-0.03	0.45	-0.03	0.49	-0.02	0.35
RNAP3	-0.11	0.96	-0.08	0.74	-0.10	0.84
dcSSc	-0.12	0.82	-0.12	0.53	-0.12	0.62
Digital ulcers	-0.15	0.41	-0.02	0.68	-0.09	0.71
Small joint arthritis	-0.16	0.43	-0.22	0.15	-0.18	0.28
Baseline mRSS	-0.006	0.04	-0.005	0.08	-0.005	0.046

Units are cm/year. \* P value for interaction between time and variable. dcSSc: diffuse cutaneous systemic sclerosis; ACA: anticentromere antibodies; ATA: antitopoisomerase I antibody; RNAP3: RNA polymerase 3 antibody; mRSS: modified Rodnan skin score.

Table 3. Predictive significance of baseline features for rate of change in hand extension in 62 patients with disease duration < 2 years: results from mixed models.

Baseline Disease Variables	Right Hand Rate of Change	p*	Left Hand Rate of Change	p *	Average	p *
Female	-0.11	0.96	-0.30	0.88	-0.20	0.96
Race, white (non-Hispanic)	-0.16	0.61**	-0.42	0.34**	-0.29	0.41**
Age	0.007	0.71	-0.02	0.39	-0.006	0.74
ATA	-0.50	0.40	-1.53	0.01	-1.01	0.08
ACA	1.29	0.035	1.20	0.02	1.25	0.02
RNAP3	-0.53	0.18	-0.34	0.75	-0.43	0.39
dcSSc	-0.64	0.003	-0.63	0.09	-0.63	0.01
Digital ulcers	0.06	0.66	0.45	0.05	0.26	0.19
Small joint arthritis	-0.46	0.37	-0.68	0.34	-0.56	0.32
mRSS	-0.029	0.09	-0.014	0.45	-0.021	0.19

Units are cm/year. \* P value for interaction between time and variable. \*\* P value for the comparison of other races versus the reference group of white (non-Hispanic). dcSSc: diffuse cutaneous systemic sclerosis; ACA: anticentromere antibodies; ATA: antitopoisomerase I antibody; RNAP3: RNA polymerase 3 antibody; mRSS: modified Rodnan skin score.

in baseline mRSS was predictive of decreased hand extension, on average in both hands, by 0.005 cm/year ( $p = 0.046$ ).

As shown in Table 2, the predictive variables for each hand separately were similar to those of overall hand extension. For example, in the right hand, ATA ( $p = 0.03$ ) and the mRSS were both predictive of faster decline in hand extension ( $p = 0.04$ ). ATA-positive patients showed a decrease in right hand extension by 0.24 cm/year while ATA-negative patients showed a decrease in hand extension by 0.075 cm/year. A similar rate of decline in hand extension was observed in the left hand for ATA-positive patients.

The presence of ACA or anti-RNAP3 antibodies was not associated with rate of change in hand extension.

Although numerically worse contractures were noted in dcSSc than in lcSSc, this was not statistically significant ( $p = 0.62$ ). Similarly, digital ulcers ( $p = 0.71$ ) or small joint arthritis ( $p = 0.28$ ) were not predictive of faster decline in hand extension.

In the multivariable mixed model, both presence of ATA and higher baseline mRSS were significantly associated with faster rates of decline in hand extension.

We then conducted a subgroup analysis of 62 patients who were enrolled  $\leq 2$  years from the date of first non-RP and who had at least 2 hand measurements at least 6 months apart within this 2-year period; 124 hand measurements were included in this subanalysis. Average hand extension decreased by 0.19 cm/year in this group. Predictive significance of baseline variables is described in Table 3. Two disease features were noted to be predictive of faster decline in hand extension in this subgroup analysis: ATA and diffuse disease type. On the other hand, a positive ACA was associated with slower decline in hand extension, but this was based on only 5 patients.

Regarding the ATA-positive early disease group, there was a decline in left hand extension of -1.53 cm, whereas the right hand extension declined by a smaller amount of -0.50 cm (Table 3). The ATA-positive subgroup included only 8



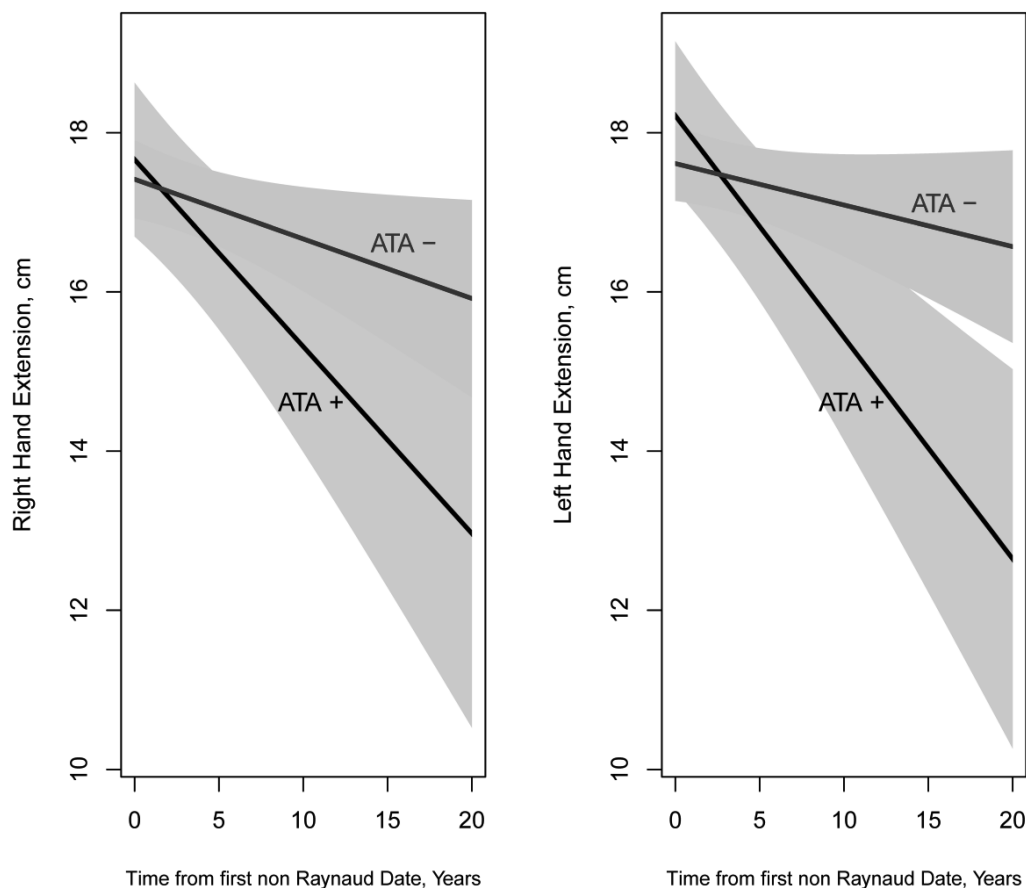


Figure 2. Course of average hand extension over time in ATA-positive and -negative individuals. Fitted extension of hands is shown with 95% CI. ATA: anti-topoisomerase I antibody.

subjects with 22 observations. This discrepancy between right and left hands was not seen in the larger group of 219 subjects.

The longitudinal association between mRSS and average hand extension was found to depend on time from disease onset. For example, in the first 5 years of disease (disease duration  $\leq 5$  yrs), for every increment in mRSS, there was a decline in average hand extension by 0.02 cm/year; whereas after 5 years of disease, the decline in average hand extension was 0.005 cm/year ( $p = 0.05$ ).

Because only patients with  $\geq 2$  hand extension measurements at least 6 months apart were included, we analyzed baseline variables of excluded patients (those with only 1 hand extension measurement) and found that there was no significant difference between these groups in demographic features, disease type, baseline skin scores, disease duration, autoantibodies, or baseline hand measurements.

Because site-specific skin scores (fingers and dorsal hand scores) may have more influence on hand contractures than overall scores, an analysis was done to determine whether finger or dorsum of hand scores were associated with change in hand extension. In the univariate model, both finger scores

and hand scores were predictive of both baseline hand extension (higher scores predicting smaller hand extension) and rate of change (higher scores associated with a more rapid decrease in hand extension). However, in the model adjusting for other covariates, neither finger scores nor dorsal hand scores were predictive of rate of change.

A total of 916 MHAQ scores were collected across all visits from 215 out of the 219 subjects. The MHAQ scores showed a slight decline over time (slope =  $-0.01$ ;  $p = 0.04$ ). The average hand extension was a strong predictor of the MHAQ score because hand extension was inversely associated with the MHAQ score ( $\beta = -0.09$ ;  $p < 0.001$ ; pseudo- $R^2 = 0.19$ ); a decrease of 1 cm in average hand measurement corresponded to a 0.1 increase (worse function) in the MHAQ score. Scatter plots of the average hand measurement and MHAQ score at 3 different timepoints (Figure 3) illustrate this negative association, which was constant across all visits (Pearson correlation ranging from  $-0.36$  to  $-0.63$ ).

Similarly, average hand extension was a significant predictor of the SF-36 PF score ( $p < 0.001$ ), indicating that the larger the hand extension, the higher (better) the SF-36

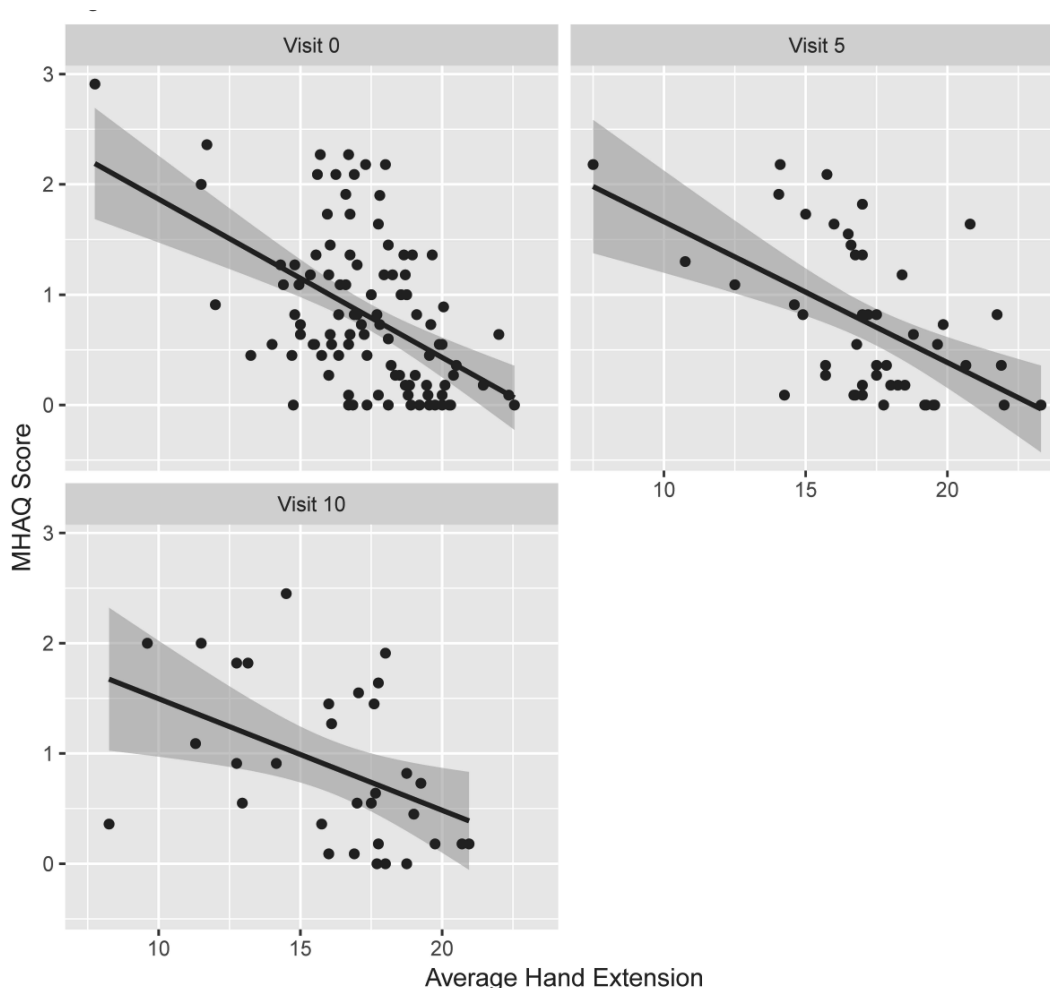


Figure 3. Scatter plots of the MHAQ scores versus the average of right and left hand measurements at 3 different timepoints (baseline at Visit 0, Visit 5 at 5 yrs, and Visit 10 at 10 yrs), illustrating the negative association. MHAQ: modified Health Assessment Questionnaire.

function score. F-36 (the PF domain score of SF-36) paralleled the MHAQ data in that the average hand extension was a significant predictor of the SF-36 PF score ( $p < 0.001$ ), indicating that the greater the hand extension, the higher (better) the SF-36 PF score.

## DISCUSSION

To our knowledge, this is the largest and longest prospective study assessing disease features predictive of hand contractures in patients with SSc. In this prospective observational study of the GENISOS cohort, we investigated predictors of hand contractures in early SSc and the association with clinical, demographic, and serologic features, and MHAQ, and SF-36 functional scores. The presence of ATA and higher mRSS at baseline were predictive of faster decline in hand extension, that is, development of hand contractures. The association with ATA corresponds to the known poorer overall prognosis in this autoantibody group. Further, hand

extension was associated with overall functional status as reflected in MHAQ and SF-36 scores. The minimal clinically important difference (MCID) for the MHAQ is  $-0.22^{20}$ .

Although there is no established MCID for decline in hand extension, the trajectory of decline demonstrated in our data was associated with poorer function, indicating that this has clear relevance for our patients. This is an under-studied but clinically important feature of SSc<sup>21</sup>.

In a previous report of musculoskeletal complications of SSc in the initial Scleroderma Lung Study (SLS-1)<sup>7</sup>, the same hand extension measurement technique was used as in our study. In SLS-1, there were 158 patients with SSc, selected for lung involvement, and randomized to either daily oral cyclophosphamide (CYC) or placebo. At 12 months, mean hand extension increased by 2.8 mm in the CYC group, whereas hand extension decreased by 0.9 mm in the placebo group — a difference that was not statistically significant in this short followup. This finding suggests that the devel-

opment of SSc-related hand contractures may be amenable to therapeutic intervention if more effective therapies are developed.

In another study, Balint, *et al*<sup>22</sup> evaluated both small and large joint contractures in 131 SSc patients with an average disease duration of about 8 years and a mean followup of 4.43 years. Contractures were considered present if there was a limitation in range of motion > 25% of the normal range. Combining both small and large joint contractures, these authors reported no difference at baseline in the number of contractures between those with  $\leq 4$  years disease duration compared to those with > 4 years. This study also reported that more contractures (both large and small joints) were found in dcSSc than in lcSSc and in accordance with our findings, more contractures were seen in ATA-positive than in ATA-negative subjects. They also found that the dominant side was significantly more impaired than the nondominant side. In our study, hand dominance was not recorded so this comparison could not be made. Additional comparisons of our study with that of Balint, *et al*<sup>22</sup> are limited by differences in the definition of contractures, measurement approaches, disease duration, and ethnic makeup.

Surprisingly, we found that hand extension continued to decline with time in a fairly linear fashion over our 8.1-year followup even while the mRSS stabilized and/or improved (data not shown). These divergent trajectories might explain the observed weaker relationship between longitudinal hand extension and mRSS measurements after the first 5 years of disease.

Hand extension was studied in all 219 patients and in patients with recent-onset disease defined as  $\leq 2$  years. In both groups, the presence of ATA was predictive of a decrease in hand extension.

To assess functional status, we used the MHAQ score and SF-36 PF scale. Average hand extension was a strong predictor of the MHAQ score (the greater the hand extension, the lower/better the MHAQ score) and vice versa. Similarly, greater hand extension was positively correlated with a better SF-36 PF score. The average hand extension was found to be a significant predictor of the functional score ( $\beta$  of 2.65;  $p < 0.001$ ), indicating that the greater the hand extension, the higher (better) the SF-36 PF score.

Our present study has some limitations. Hand dominance was not recorded. Therefore, it was not possible for us to assess whether dominance played a role in the development or severity of contractures.

Additionally, although there are more comprehensive measures of hand contractures and function that have been applied in SSc<sup>23</sup>, most of these assessments take longer to perform, or require specialized training or equipment that are not readily available in the rheumatology clinic setting.

Another limitation of our study is the lack of intrarater and interrater reliability data. Additionally, the presence of arthrosis, particularly at the carpometacarpal joint, may affect abduction of the thumbs, and therefore confound the results.

Future study designs should take these issues into consideration. Another potential limitation is the lack of data regarding nonmedical interventions such as occupational and other therapies that were not recorded in our dataset.

The analysis was confined to white non-Hispanic versus others owing to relatively small numbers in the African American and Hispanic individual groups. Therefore, the separate effects of race and ethnicity on severity of hand contractures may have been obscured.

The strength of our study is the large number of subjects ( $n = 219$ ) with early disease, followed prospectively over 8.1 years, with a large number of hand measurements ( $n = 1087$ ) and MHAQ and SF-36 scores ( $n = 916$ ) done at specified intervals. We were also able to analyze 62 patients with  $\leq 2$  years of onset from first non-RP to determine whether there was an accelerated rate of decline in early disease, but this was not the case.

Our study used a simple and straightforward hand extension measurement that can be done quickly during an office visit and can influence decisions on the effectiveness of therapy. We also used a readily available functional measurement (MHAQ) that many clinicians and investigators use routinely. Although this simple measurement was not shown to change significantly with short-term (12-month) CYC therapy in the first SLS<sup>7</sup>, hand contractures may be amenable to improvement with more effective and/or longer-term therapeutic interventions. As these newer therapies become available, this simple hand measurement technique can be incorporated into clinical practice as one gauge of response or lack thereof to these agents.

Hand involvement is a known cause of functional impairment in SSc. To our knowledge, this is the largest study to date assessing for predictors of hand contractures. ATA antibody was associated with hand contracture development in both early disease patients (within 2 yrs from onset) and the overall population (< 5 yrs from SSc onset). The average hand extension was inversely associated with functional status as measured by the MHAQ score and SF-36 functional scale.

Further studies will be needed to assess the reproducibility of these findings particularly in the setting of SSc clinical trials and to correlate this simple and straightforward measure with other hand assessment techniques in SSc.

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## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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