Short title: Functional disability in systemic sclerosis

Title: Functional disability and its predictors in systemic sclerosis: a study from the DeSScipher project within the EUSTAR group

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ABSTRACT

Objectives: The multisystem manifestations of systemic sclerosis (SSc) can greatly impact the patients' quality of life. The aim of this study was to identify factors associated with disability in SSc

Methods: SSc patients from the prospective DeSScipher cohort who had completed the scleroderma health assessment questionnaire (SHAQ), a disability score that combines the health assessment questionnaire and five visual analogue scales (VAS), were analysed. The effect of factors possibly associated with disability was analysed with multiple linear regressions.

Results: The mean SHAQ and HAQ scores of the 944 patients included were 0.87 (standard deviation [SD] 0.66) and 0.92 (SD 0.78). 59% of patients were in the "mild to moderate difficulty" SHAQ category (score of 0-<1), 34% in the "moderate to severe disability" category (score of 1-<2) and 7% in the "severe to very severe disability" category (score of 2-3). The means of the VAS scores were in order of magnitude: overall disease severity (37mm), Raynaud's phenomenon (31mm), pulmonary symptoms (24mm), gastrointestinal symptoms (20mm) and digital ulcers (DU; 19mm).

In multiple regression, the main factors associated with high SHAQ scores were the presence of dyspnoea (NYHA-class 4 (regression coefficient B=0.62), NYHA 3 (B=0.53) and NYHA 2 (B=0.21; all *vs.* NYHA-class 1), fibromyalgia (B=0.37), muscle weakness (B=0.27), digital ulcers (B=0.20) and gastrointestinal symptoms (oesophageal symptoms, B=0.16; stomach symptoms, B=0.15; intestinal symptoms, B=0.15).

Conclusion: SSc patients perceive dyspnoea, pain, digital ulcers, muscle weakness and gastrointestinal symptoms as the main factors driving their level of disability, unlike physicians who emphasize other measures of disability.

INTRODUCTION

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Systemic sclerosis (SSc) is an uncommon and clinically heterogeneous multisystem disorder which greatly affects the patients' physical and psychological functioning and impairs their ability to participate in work and social activities. Substantial morbidity results from digital ulcers, skeletal muscle weakness, contractures, cardiopulmonary and gastrointestinal involvement [1–3]. One of the most formidable goals of care is to alleviate symptoms and disability and to improve the health-related quality of life (QoL) and functional ability [4].

Whereas physicians tend to emphasize objective measures of disease status, patients may perceive other aspects of their disease as more disabling or burdensome [5]. The evaluation of SSc severity and its impact requires several measures due to multiple organ involvement; single organ outcome measures only provide limited information [6].

The health assessment questionnaire (HAQ) is one of the most commonly used measures of ability/disability in musculoskeletal disorders and was also used in SSc as a simple, inexpensive and practical way to reflect the patient perspective [7–10]. The HAQ is a self-reported questionnaire consisting of twenty questions split across eight domains, addressing, rising, eating, walking, hygiene, reach, grip and usual activities [11]. The HAQ was extended to form the scleroderma HAQ (SHAQ), a more disease-specific disability scale that incorporates the HAQ and five scleroderma related visual analogue scales (VAS) into one score [6]. The five VASs in the SHAQ assess the level of impairment due the complications frequently observed in SSc outside the musculoskeletal system, namely Raynaud's phenomenon, digital ulcers, gastrointestinal symptoms, respiratory symptoms, as well as the overall severity of the disease from the patient's perspective [6]. The SHAQ is a reliable and valid measure of functional disability in SSc [6–8,12,13].

Several studies have assessed the impact of select SSc-specific symptoms on the patients' life [3,14–17], or assessed overall QoL or functional disability and factors associated with it [1,13,18]. However, due to the rarity of the disease, most of these studies have a limited sample size and focus on sub-populations for example only patients with digital ulcers or patients with pulmonary hypertension

[18–21]. Recently, one large internet-based survey assessed the patients' perception on factors impacting on the daily lives, as well as health related quality of life [22]. This study however was a purely patient based survey with no linkage to clinical data.

Our aim was therefore to prospectively analyse functional disability in SSc patients not selected for a particular organ manifestation, and to identify clinical factors contributing to impairment.

METHODS

Study population and design

The DeSScipher ("to decipher the optimal management of systemic sclerosis" [23,24]) project is a multinational, longitudinal study embedded in the European Scleroderma Trials and Research (EUSTAR) group database [25,26]. DeSScipher data were collected prospectively in a multicentre approach following standardised operating procedures. Data quality was additionally enhanced by plausibility checks embedded within the database, monthly data queries sent to the centres as well as onsite monitoring. Data collection for the DeSScipher project started in March 2013. Each DeSScipher centre obtained ethical approval by its local ethics committee; written informed consent was required from each patient prior to enrolment.

All patients had to fulfill either the 1980 American College for Rheumatology (ACR) criteria for SSc, or the 2013 American College for Rheumatology/European League against Rheumatism (ACR/EULAR) criteria and were eligible for this analysis if they were above 18 years of age and had at least one SHAQ available [6,27,28]. Patients were classified as diffuse or limited depending on the most severe skin involvement at the time of the study visit or any prior visit.

The recording of the SHAQ within the DeSScipher database started in October 2014; data were exported for this study in August 2016. The HAQ built into the SHAQ has a recall period of seven days and ranges from 0 to 3 and is categorised into mild to moderate difficulty (score of 0 to <1), moderate to severe disability (score of 1 to <2) and severe to very severe disability (score of 2 to 3) [10,11]. The VAS scales in the SHAQ assess the interference of the disease with daily activities and range from 0 (not limiting activities) to 100 (very severe limitation). In the original version of the SHAQ no combined score was built, instead the HAQ and the five VAS were assessed separately [6]. Georges et al. proposed to average the eight HAQ categories and the five VASs (each downscaled to range from 0 to 3) into a composite SHAQ score ranging from 0 to 3 [29]. For this cross-sectional study, the first SHAQ recorded was analysed.

Statistical analysis

Depending on the categorical or continuous nature of the variables, frequencies and percentages or means and standard deviations (SD) were calculated. For categorical variables, between group comparisons were carried out using X^2-tests or Fisher's exact tests; t-tests were used for continuous variables. Missing data of covariates were imputed using multiple imputations by chained equations [30,31].

After defining possible predictors of functional disability *a priori* (Table 1)*,* predictors of functional disability were identified using univariable and multivariable linear regression analyses. We decided to not include the SSc subset of the patients and sclerodactyly in the multivariable model, as these variables are strongly related to the modified Rodnan skin score (mRSS).

To compare the disability between patients with diffuse SSc and limited SSc we reduced the original model to factors which were strong and clinically significant predictors of functional disability in the overall patient group or were defined *a priori*.

The minimal clinical important difference (MCID) of the HAQ is stated to be ≥0.22 [32]. As the SHAQ is based on the HAQ and has the same range, we applied this threshold also to the SHAQ. We treated a difference of ≥10mm as the MCID for the VAS components [32–34]**.**

All analyses were performed with Stata/IC 13.1 (StataCorp, College Station, Texas, USA).

RESULTS

Patient characteristics

At the time of the data export, 944 (37.9%) of the 2,488 adult DeSScipher patients had a SHAQ score. The demographic and disease characteristics of this study population are listed in Table 2. Of the 944 patients, 115 (12.2%) fulfilled only the 2013 ACR/EULAR criteria but not the 1980 ACR classification criteria for SSc.

Patients included in the study were of similar age and sex distribution than the patients excluded for the lack of a SHAQ. Additionally, both groups had comparable disease durations and an SSc subset distribution (data not shown).

Functional disability

The mean SHAQ score was 0.87 (SD 0.66). 59.5% of the patients were in the lowest SHAQ category (score of 0 to <1), 34.0% had a score of 1 to <2 and 6.5% in the category regarded as "severe to very severe disability" (score of 2 to 3). Patients fulfilling only the 2013 ACR/EULAR criteria but not the 1980 ACR criteria had a lower average SHAQ score (0.55, SD 0.56) than patients fulfilling the 1980 ACR classification criteria (0.91, SD 0.66; $p<0.001$). Patients with diffuse cutaneous SSc had a higher mean SHAQ score (0.96, SD 0.65), than patients with limited SSc (0.83, SD 0.67; $p=0.005$). 46.8% of patients with diffuse SSc had mild to severe disability (score 1 to 3) compared to 37.6% with limited SSc ($p=0.003$).

The mean HAQ score was 0.92 (SD 0.78). 53.8% of patients fell into the "mild to moderate difficulty" category (score <1), 34.1% into the "moderate to severe disability" (score ≥1 to <2) and 12.1% into the "severe to very severe disability" (score ≥2) category. Patients with diffuse SSc had a higher mean HAQ score than patients with limited SSc (1.04, SD 0.77 *vs.* 0.87, SD 0.77; $p=0.002$).

Of the five VAS included in the SHAQ, the highest values were reported on the overall disease severity VAS (mean 37mm, SD 27). Patients with diffuse SSc reported a higher level of limitation due to overall disease severity (mean 40mm, SD 27) than patients with limited SSc (mean 35mm, SD 27; p=0.02).

With respect to RP, the mean VAS impairment reported was 31mm (SD 28). Patients with diffuse SSc reported a higher level of impairment due to RP (mean 34mm, SD 29) than patients with limited SSc (mean 29mm, SD 27; p=0.01).

The average perceived limitation due to pulmonary problems was 24mm (SD 27). Patients with diffuse SSc reported a similar level of impairment due to pulmonary symptoms (mean 24mm, SD 27) as patients with limited SSc (mean 24mm, SD 28; p=0.81). Patients in higher NYHA functional classes perceived a more marked pulmonary limitation than patients in NYHA-class 1 (NYHA-class 4, mean 74mm, SD 24; NYHA-class 3, mean 61mm, SD 24; NYHA-class 2, mean 29mm, SD 26; NYHA-class 1, mean 11mm, SD 19; p<0.001).

With respect to gastrointestinal (GI) problems, patients reported a VAS average of 20mm (SD 26). There was no difference in the perceived impairment due to GI problems between patients with diffuse SSc (mean 18mm, SD 25) and limited SSc (mean 21mm, SD 27; p=0.11). Patients with a higher number of simultaneous gastrointestinal symptoms reported higher average VAS scores than patients with a low number of gastrointestinal symptoms (42mm, SD 31 for patients reporting all of oesophageal, gastric and intestinal symptoms; 26mm, SD 26 for patients reporting symptoms in two gastrointestinal regions; 16mm, SD 23 for patients reporting symptoms in only one gastrointestinal region; *vs.* 7mm, SD 14 for patients reporting no gastrointestinal symptom; respectively; p<0.001).

The VAS assessing the impairment due to the presence of DU had relatively low scores (mean 19mm, SD 28). Patients with diffuse SSc (mean 22mm; SD 30) reported a higher level of impairment than patients with limited SSc (mean 18mm, SD 27; p=0.02). However, patients who had DU prior to enrolment, but not at the time of SHAQ reporting, had a mean DU VAS of 21mm (SD 28), and

patients suffering of DUs at the time of SHAQ completion reported a mean VAS of 53mm (SD 33; p<0.001).

Predictors to functional disability

We first assessed the association of variables with the SHAQ with univariable analysis. The strongest predictor to disability was dyspnoea. In patients with NYHA class 4 the SHAQ score was on average 1.17 units (95%CI 0.80-1.53) higher than in patients with NYHA class 1 (NYHA class 3 - 0.88, 95%CI 0.73-1.04 and NYHA class 2 - 0.40, 95%CI 0.32-0.48 all *vs.* NYHA class 1). Weaker, although still clinically important predictors were (in order of magnitude) muscle weakness (increase of 0.51 units, 95%CI 0.40-0.62), the presence of fibromyalgia (increase of 0.47 units, 95%CI 0.25-0.69) and the three variables referring to gastrointestinal involvement (gastric 0.41 units, 95%CI 0.32-0.50; oesophageal 0.38 units, 95%CI 0.29-0.46 and intestinal symptoms 0.34 units, 95%CI 0.25-9.42).

The multivariable analysis of the SHAQ was in line with the results observed in univariable analysis. Dyspnoea remained the strongest predictor of functional disability. The SHAQ scores reported by patients with NYHA class 4, 3 or 2 were on average 0.62 units, 0.53 units and 0.21 units higher than that of patients with NYHA class 1 (Figure 1). In addition, both, the presence of fibromyalgia as well as muscle weakness were associated with higher levels of disability. Patients with fibromyalgia reported on average a SHAQ value 0.37 units higher than that of patients without fibromyalgia and patients experiencing muscle weakness recorded on average a 0.27 units higher SHAQ (Figure 1). Other factors contributing to disability included the presence of digital ulcers, oesophageal, gastric and/or intestinal symptoms, joint contractures and a more severe skin involvement (Figure 1). Only dyspnoea, fibromyalgia and muscle weakness remained however clinically significant contributors to functional disability when applying the 0.22 threshold for the MCID [32].

Patients experiencing any gastrointestinal involvement (presence of oesophageal, gastric or intestinal symptoms) reported a clinically significant higher SHAQ (0.24 units; 95%CI 0.15-0.32) than patients

reporting no gastrointestinal involvement. In multivariable analysis, patients with multiple simultaneous gastrointestinal symptoms also had higher SHAQ scores than those featuring symptoms in only one or two regions of the gastrointestinal tract (oesophagus, stomach, or intestine). Patients reporting oesophageal, gastric and intestinal symptoms simultaneously had, on average, a SHAQ score of 0.46 units (95% CI 0.34-0.58) higher than patients reporting no gastrointestinal symptoms. Similarly, patients with symptoms in two or one gastrointestinal regions also reported a higher functional disability than patients with no gastrointestinal problems (0.28 units, 95%CI 0.18-0.38 and 0.13 units, 95% CI 0.04-0.22; respectively).

The analysis of the HAQ scores showed impairment similar to the SHAQ. In univariable analysis in patients in NYHA functional class 4 the HAQ was on average 1.32 units higher (95%CI 0.88-1.75) than in patients in NYHA class 1; respective values for patients in NYHA class 3 were 0.96 units (95%CI 0.78-1.14) and in patients in NYHA class 2 0.46 units (95%CI 0.37-0.56 all *vs.* NYHA 1). Other factors associated with higher HAQ scores were (in order of magnitude of the effect measure): the presence of muscle weakness - 0.59 units (95%CI 0.46-0.72), the presence of muscle atrophy - 0.50 units (95%CI 0.30-0.70), the presence of fibromyalgia - 0.42 units (95%CI 0.16-0.67), joint contractures - 0.44 units (95%CI 0.35-0.54), gastrointestinal symptoms (oesophageal - 0.40 units, 95%CI 0.30-0.50; gastric - 0.43 units, 95%CI 0.32-0.54; intestinal - 0.35 units, 95%CI 0.25-0.45) and tendon friction rubs - 0.40 units (95%CI 0.16-0.64).

In multivariable analyses, patients with NYHA functional class 4 had an average HAQ score of 0.70 units higher than patients with NYHA functional class 1 (NYHA class 3 - 0.54 units, NYHA class 2 - 0.23 units all *vs.* NYHA class 1). The presence of fibromyalgia (increase of 0.33 units) as well as of muscle weakness (increase of 0.32 units) were also strong and clinically important predictors of elevated HAQ scores (Figure 1). The presence of any gastrointestinal problems, i.e. either the presence of oesophageal, stomach or intestinal symptoms, led to a clinically important average increase of 0.22 HAQ units (95%CI 0.11-0.31). Similarly, the number of simultaneous gastrointestinal symptoms was a strong predictor of an elevated HAQ; patients reporting each of oesophageal, gastric and intestinal

symptoms, the average HAQ increase was 0.44 units (95%CI 0.30-0.58), for patients reporting symptoms in two gastrointestinal regions the average increase was 0.26 units (95%CI 0.14-0.38) and for patients reporting symptoms in only one gastrointestinal region the HAQ increase was 0.11 units (95%CI 0.002-0.222) compared to patients reporting no gastrointestinal symptom.

Disability in the SSc subsets

In patients with diffuse SSc (n=344), the factors contributing to a clinically meaningful SHAQ increase were similar to those contributing in patients with limited SSc (n=532; Figure 2), namely dyspnoea (NYHA 3/4 *vs.* NYHA 1/2 increase of 0.42 units), muscle weakness (increase of 0.36 units) and gastrointestinal symptoms (Figure 2). Patients with fibromyalgia also had on average a 0.25 units higher SHAQ (Figure 2).

In both SSc subsets, the presence of multiple simultaneous gastrointestinal symptoms also predicted strongly to disability. In patients with diffuse SSc, the SHAQ was on average 0.39 units (95%CI 0.19-0.59) higher in patients simultaneously reporting oesophageal, gastric and intestinal symptoms than in patients not reporting gastrointestinal symptoms. In the group of patients with limited SSc, this difference was even greater (0.60 units (95%CI 0.44-0.78)).

DISCUSSION

The physicians' main attention while caring for SSc patients is often focused on objective measures of function for example pulmonary function tests. These measures may however not reflect the patient's experience with the disease and self-perceived impact on QoL and functional capacity. Our study is by far the largest study linking patients' self-assessed disability with objective clinical data and is also the first study of its size to analyse a comprehensive set of clinical factors contributing to disability in an SSc population not selected for a particular organ manifestation or subset.

The most important factors predicting functional disability in our study were dyspnoea, gastrointestinal symptoms, fibromyalgia, muscle weakness and the presence of DU, in line with the results of smaller studies [5,15,16,20,21,35,36]. Thus, there is a major difference between the factors driving patient perceived levels of disability and those emphasized by physicians (i.e. lung function testing, pulmonary arterial pressure estimates et cetera). Comparing the four specific VASs, the highest patient-rated limitation of daily life was due to RP, followed by pulmonary and gastrointestinal symptoms. A similar finding was observed in two surveys in which SSc patients ranked RP, gastrointestinal complications, musculoskeletal involvements and pain among the symptoms impacting on their daily live the most [22,37]. In contrast to our study, Strickland et al. [18] only found an association between functional disability and gastrointestinal involvement, but not with any other demographic or clinical variable. Similarly, Chow et al. [19] did not detect a correlation between NYHA functional class, the strongest predicting factor in our study, and functional disability in SSc patients with pulmonary arterial hypertension. The most likely reason is the limited sample size of 68 and 41 patients, respectively.

The overall level of disability as identified by the HAQ in our SSc population is more than 4 times higher than that reported in the general French population, and comparable with that reported in other systemic rheumatic diseases [2,38,39]. The HAQ score observed in our cohort is similar to that found in other SSc studies, with about half of patients considering themselves to be mildly to moderately disabled [14,18]. However, the SHAQ scores as well as the VAS encompassed in it are

lower in our study than in a French single-centre study [29]. This discordance might be explained by the lower percentage of diffuse SSc patients in our population.

In patients with diffuse SSc the level of disability was significantly higher than in patients with limited SSc. The differences between SSc subsets in our cohort were however smaller than those reported previously in much smaller studies [13,18,29]. Interestingly, the main factors contributing to disability, namely dyspnoea, gastrointestinal symptoms, muscle weakness, digital ulcers and pain, were similar in SSc subsets. This goes in line with a recent survey by Frantz et al [22] which identified no difference of patient perceived impact of organ involvement on QoL between SSc subsets.

There are limitations of our study. We only had SHAQ data in around 38% of all patients followed in the DeSScipher cohort. A selection bias might have occurred in both directions, i.e. patients with more severe disease may have felt too unwell to fill in the SHAQ questionnaire, or were actually more likely to fill in the questionnaire as they felt more impaired. The demographic characteristics of the patients included in this study were however comparable to the DeSScipher patients without an available SHAQ, as were the disease duration and the distribution of the SSc subsets. One problem often arising in observational studies is the data quality. One big strength of the DeSScipher cohort is that there were various strategies in place to enhance data quality, including on-site data monitoring. Thus, our results are likely to better reflect the bigger SSc community than those of previous studies, particularly due to the multi-centre and multinational nature of this study.

In conclusion, this study demonstrates significantly impaired functional capacity in a large proportion of SSc patients, and demonstrates that dyspnoea, pain, digital ulcers, muscle weakness and gastrointestinal symptoms are the most important contributors perceived by the patients. These results should be taken into account when caring for patients with SSc and when designing clinical trials aimed at improving QoL.

Key messages

- Patients and physicians emphasize different aspects in the evaluation of SSc severity.
- Patients perceive dyspnoea, pain, digital ulcers, weakness and gastrointestinal symptoms as main factors of disability.

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Conflict of interests

None.

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Ethics Approval

Ethics approval according to the Declaration of Helsinki has been obtained from all respective contributing local ethics committees.

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Table 1 Description of possible predictors selected *a priori* for the analysis.

NYHA, New York Heart Association; RP, Raynaud's phenomenon.

Demographics
Age (years)
Sex (female/male)
Disease characteristics
Time since RP onset (years)
Time since first non-RP manifestation (years)
Modified Rodnan skin score (mRSS; range 0 to 51)
Oesophageal symptoms (yes/no; dysphagia, reflux according to patient)
Stomach symptoms (yes/no; early satiety, vomiting according to patient)
Intestinal symptoms (yes/no; diarrhoea, bloating, constipation according to patient)
Any gastrointestinal symptoms (yes/no; any of oesophageal, stomach or intestinal symptoms)
Number of gastrointestinal symptoms (range 0 to 3; oesophageal, stomach and/or intestinal symptoms)
Dyspnoea (NYHA functional class 1 to 4)
Puffy fingers (yes/no; current scleredema)
Digital ulcers (yes/no; current ulcers distal to or at the proximal interphalangeal joint)
Telangiectasia (yes/no)
Joint synovitis (yes/no; by rheumatologist's judgement)
Joint contractures (yes/no; by rheumatologist's judgement)
Muscle weakness (yes/no; by rheumatologist's judgement)
Muscle atrophy (yes/no; by rheumatologist's judgement)
Fibromyalgia (yes/no; by rheumatologist's judgement)
Systolic pulmonary artery pressure (PAPsys, mmHg; as estimated by echocardiography)
Single breath diffusing capacity for carbon monoxide (DLCO, % of predicted)
Forced vital capacity (FVC, % of predicted)
Conduction blocks (yes/no; AV-block, bundle branch blocks)
Diastolic dysfunction (yes/no)
Pericardial effusion (yes/no)
Left ventricular ejection fraction (LVEF)
Laboratory
Anticentromere autoantibodies positivity (ACA; yes/no)
Anti-topoisomerase autoantibodies positivity (Scl-70; yes/no)
Anti-RNA polymerase-III autoantibodies positivity (RNAP-III; yes/no)

Erythrocyte sedimentation rate (ESR; mm/hour)
Serum creatinine kinase elevation (CK; yes/no)

Table 2 Demographic and disease characteristics of the study population at the time of SHAQ assessment (n=944).

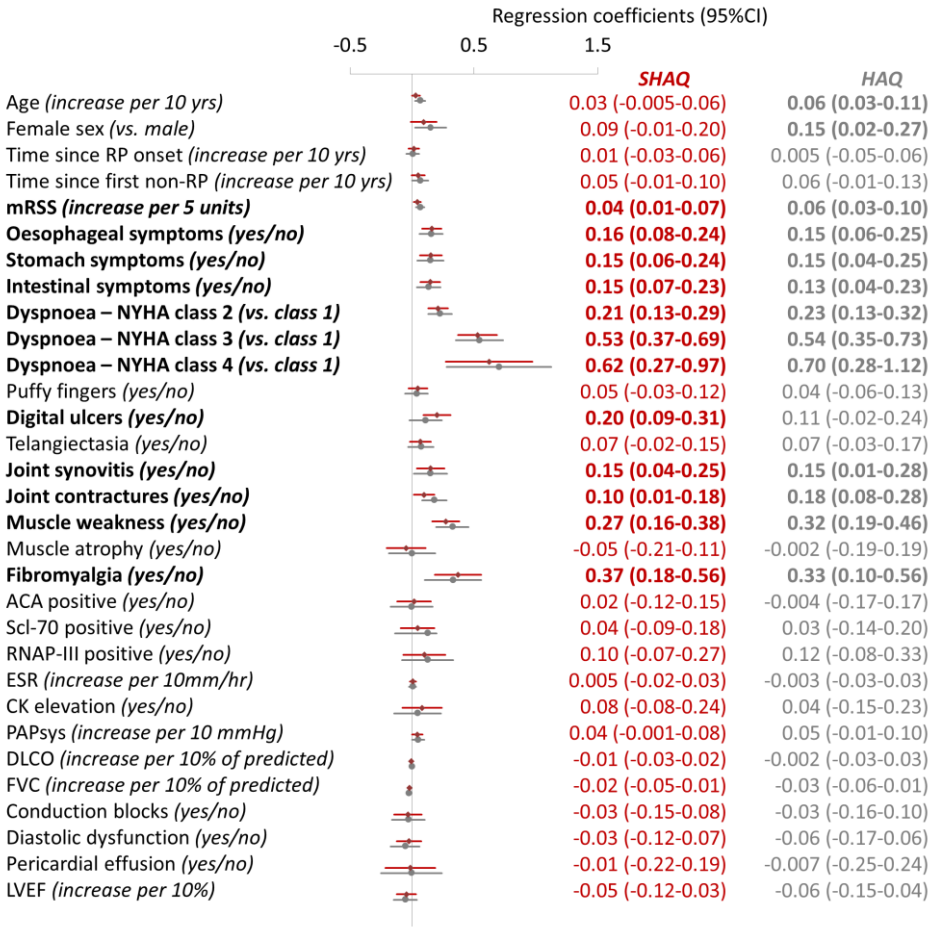
ACA, anticentromere autoantibodies; ANA, anti-nuclear autoantibodies; DLCO, single breath diffusing capacity for carbon monoxide; ESR, Erythrocyte sedimentation rate; FVC, forced vital capacity; IQR, interquartile range; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; NYHA, New York Heart Association; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography; RNAP-III, anti-RNA polymerase-III autoantibodies; RP, Raynaud's phenomenon; Scl-70, anti-topoisomerase autoantibodies.

Characteristics of the study population (N=944)		**% or mean (SD)**
Age; years		56.8 (13.0)
Male sex		15.0
Disease characteristics		
Time since RP onset; years		14.8 (11.9)
Time since first non-RP manifestation; years		11.5 (9.1)
mRSS		6.7 (7.1)
Cutaneous involvement	Sine	6.9
	Limited	56.5
	Diffuse	36.6
Oesophageal symptoms		62.7
Stomach symptoms		26.6
Intestinal symptoms		38.1
Dyspnoea	NYHA functional class 1	44.0
	NYHA functional class 2	47.4
	NYHA functional class 3	7.4
	NYHA functional class 4	1.2
Sclerodactyly		72.5
Puffy fingers		42.8
Digital ulcers		13.2
Telangiectasia		74.9
Joint synovitis		11.4
Joint contractures		50.5
Tendon friction rubs		4.6

Muscle weakness	16.7
Muscle atrophy	6.7
Fibromyalgia	4.0
Conduction blocks	17.7
Diastolic dysfunction	45.2
Pericardial effusion	1.8
LVEF; %	62.2 (5.4)
LVEF <50%	1.3
PAPsys; mmHg	29.8 (12.1)
PAPsys >40mmHg	10.6
DLCO; % of predicted	63.3 (19.3)
FVC; % of predicted	94.8 (21.5)
FVC <80% of predicted	23.3
Laboratory parameters	
ANA positive	98.2
ACA positive	38.7
Scl-70 positive	48.4
RNAP-III positive	6.2
ESR; mm/hr	19.8 (16.0)
Creatinine kinase elevation	6.4

Figure 1 Multivariable regression coefficients with 95% CI for the composite SHAQ and HAQ scores (both ranging from 0 to 3). Regression coefficients and their 95%CI are presented in bold writing if the 95%CIs do not include zero.

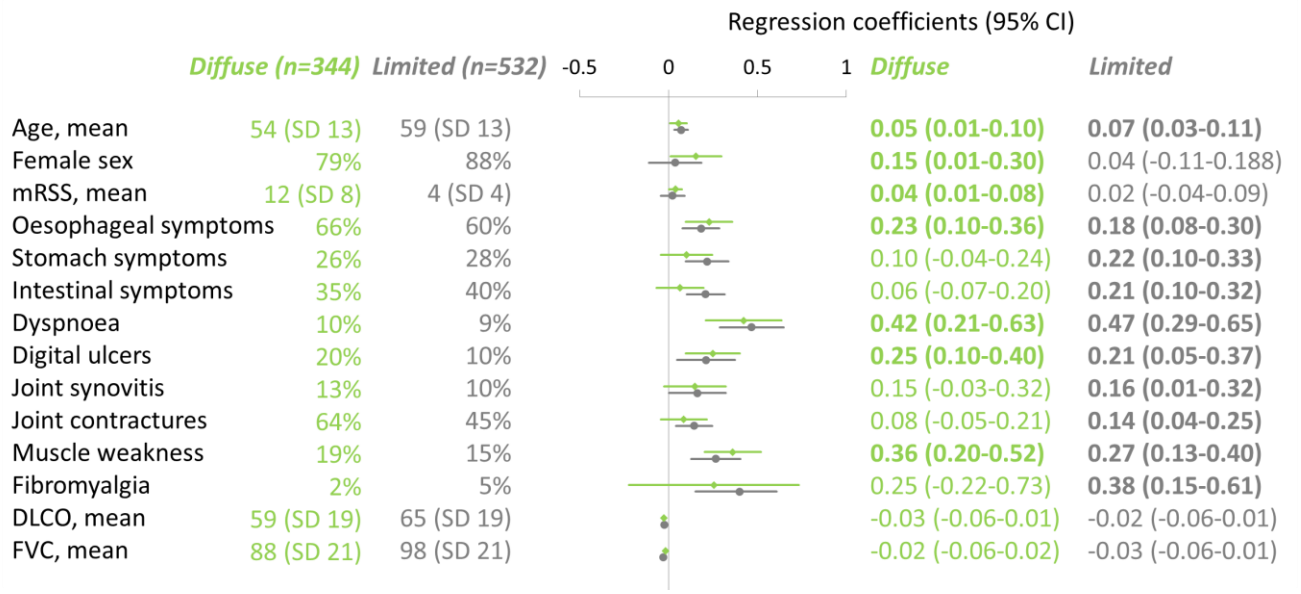
ACA, anticentromere autoantibodies; CI, confidence interval; DLCO, single breath diffusing capacity for monoxide; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; NYHA, New York Heart Association; PAPsys systolic, pulmonary artery pressure as estimated by echocardiography; RP, Raynaud's phenomenon; Scl-70, anti-topoisomerase autoantibodies; yrs, years.



	SHAQ	HAQ
Age *(increase per 10 yrs)*	0.03 (-0.005-0.06)	**0.06 (0.03-0.11)**
Female sex *(vs. male)*	0.09 (-0.01-0.20)	**0.15 (0.02-0.27)**
Time since RP onset *(increase per 10 yrs)*	0.01 (-0.03-0.06)	0.005 (-0.05-0.06)
Time since first non-RP *(increase per 10 yrs)*	0.05 (-0.01-0.10)	0.06 (-0.01-0.13)
mRSS *(increase per 5 units)*	**0.04 (0.01-0.07)**	**0.06 (0.03-0.10)**
Oesophageal symptoms *(yes/no)*	**0.16 (0.08-0.24)**	**0.15 (0.06-0.25)**
Stomach symptoms *(yes/no)*	**0.15 (0.06-0.24)**	**0.15 (0.04-0.25)**
Intestinal symptoms *(yes/no)*	**0.15 (0.07-0.23)**	**0.13 (0.04-0.23)**
Dyspnoea – NYHA class 2 *(vs. class 1)*	**0.21 (0.13-0.29)**	**0.23 (0.13-0.32)**
Dyspnoea – NYHA class 3 *(vs. class 1)*	**0.53 (0.37-0.69)**	**0.54 (0.35-0.73)**
Dyspnoea – NYHA class 4 *(vs. class 1)*	**0.62 (0.27-0.97)**	**0.70 (0.28-1.12)**
Puffy fingers *(yes/no)*	0.05 (-0.03-0.12)	0.04 (-0.06-0.13)
Digital ulcers *(yes/no)*	**0.20 (0.09-0.31)**	0.11 (-0.02-0.24)
Telangiectasia *(yes/no)*	0.07 (-0.02-0.15)	0.07 (-0.03-0.17)
Joint synovitis *(yes/no)*	**0.15 (0.04-0.25)**	**0.15 (0.01-0.28)**
Joint contractures *(yes/no)*	**0.10 (0.01-0.18)**	**0.18 (0.08-0.28)**
Muscle weakness *(yes/no)*	**0.27 (0.16-0.38)**	**0.32 (0.19-0.46)**
Muscle atrophy *(yes/no)*	-0.05 (-0.21-0.11)	-0.002 (-0.19-0.19)
Fibromyalgia *(yes/no)*	**0.37 (0.18-0.56)**	**0.33 (0.10-0.56)**
ACA positive *(yes/no)*	0.02 (-0.12-0.15)	-0.004 (-0.17-0.17)
Scl-70 positive *(yes/no)*	0.04 (-0.09-0.18)	0.03 (-0.14-0.20)
RNAP-III positive *(yes/no)*	0.10 (-0.07-0.27)	0.12 (-0.08-0.33)
ESR *(increase per 10mm/hr)*	0.005 (-0.02-0.03)	-0.003 (-0.03-0.03)
CK elevation *(yes/no)*	0.08 (-0.08-0.24)	0.04 (-0.15-0.23)
PAPsys *(increase per 10 mmHg)*	0.04 (-0.001-0.08)	0.05 (-0.01-0.10)
DLCO *(increase per 10% of predicted)*	-0.01 (-0.03-0.02)	-0.002 (-0.03-0.03)
FVC *(increase per 10% of predicted)*	-0.02 (-0.05-0.01)	-0.03 (-0.06-0.01)
Conduction blocks *(yes/no)*	-0.03 (-0.15-0.08)	-0.03 (-0.16-0.10)
Diastolic dysfunction *(yes/no)*	-0.03 (-0.12-0.07)	-0.06 (-0.17-0.06)
Pericardial effusion *(yes/no)*	-0.01 (-0.22-0.19)	-0.007 (-0.25-0.24)
LVEF *(increase per 10%)*	-0.05 (-0.12-0.03)	-0.06 (-0.15-0.04)

Figure 2 Demographic and disease characteristic as well as multivariable regression coefficients with 95% CI for the composite SHAQ score (range 0 to 3) for patients with diffuse and limited cutaneous SSc. Regression coefficients and their 95%CI are presented in bold writing if the 95%CIs do not include zero. CI, confidence interval; DLCO, single breath diffusing capacity for monoxide; FVC, forced vital capacity; mRSS, modified Rodnan skin score; NYHA, New York Heart Association.

Age, increase per 10 years; DLCO and FVC, increase per 10% of predicted; dyspnoea, NYHA functional class 3/4 *vs.* NYHA functional class 1/2; mRSS, increase per 5 points; all others, yes/no.



	Diffuse (n=344)	*Limited (n=532)*	*Diffuse*	*Limited*
Age, mean	54 (SD 13)	59 (SD 13)	**0.05 (0.01-0.10)**	**0.07 (0.03-0.11)**
Female sex	79%	88%	**0.15 (0.01-0.30)**	0.04 (-0.11-0.188)
mRSS, mean	12 (SD 8)	4 (SD 4)	**0.04 (0.01-0.08)**	0.02 (-0.04-0.09)
Oesophageal symptoms	66%	60%	**0.23 (0.10-0.36)**	**0.18 (0.08-0.30)**
Stomach symptoms	26%	28%	0.10 (-0.04-0.24)	**0.22 (0.10-0.33)**
Intestinal symptoms	35%	40%	0.06 (-0.07-0.20)	**0.21 (0.10-0.32)**
Dyspnoea	10%	9%	**0.42 (0.21-0.63)**	**0.47 (0.29-0.65)**
Digital ulcers	20%	10%	**0.25 (0.10-0.40)**	**0.21 (0.05-0.37)**
Joint synovitis	13%	10%	0.15 (-0.03-0.32)	**0.16 (0.01-0.32)**
Joint contractures	64%	45%	0.08 (-0.05-0.21)	**0.14 (0.04-0.25)**
Muscle weakness	19%	15%	**0.36 (0.20-0.52)**	**0.27 (0.13-0.40)**
Fibromyalgia	2%	5%	0.25 (-0.22-0.73)	**0.38 (0.15-0.61)**
DLCO, mean	59 (SD 19)	65 (SD 19)	-0.03 (-0.06-0.01)	-0.02 (-0.06-0.01)
FVC, mean	88 (SD 21)	98 (SD 21)	-0.02 (-0.06-0.02)	-0.03 (-0.06-0.01)