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ORIGINAL ARTICLE

Association of pain and clinical factors on disability and quality of life in systemic sclerosis: A cross-sectional study from Turkish League Against Rheumatism Network

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ABSTRACT

Objectives: In this study, we aimed to evaluate the factors associated with disability and quality of life (QoL) in Turkish patients with systemic sclerosis (SSc).

Patients and methods: Between January 2018 and January 2019, a total of 256 SSc patients (20 males, 236 females; mean age: 50.9±12.4 years; range, 19 to 87 years) who were diagnosed with SSc were included in the study. Disability and health-related QoL (HRQoL) were evaluated by the Health Assessment Questionnaire (HAQ), scleroderma HAQ (SHAQ), Duruöz Hand Index (DHI), and Short Form-36 (SF-36). Linear regression analysis methods were used to describe factors associated with disability and QoL of the patients.

Results: All disability scores were higher and HRQoL scores were lower in diffuse cutaneous SSc patients compared limited cutaneous SSc, and differentiations were significant (p=0.001 and p=0.007). In multiple regression, pain (VAS) was the strongest predictor for high disability and low QoL scores (p<0.001) as HAQ (β=0.397, 0.386, 0.452), SHAQ (β=0.397, 0.448, 0.372), DHI (β=0.446, 0.536, 0.389), PCS (β=-0.417,-0.499, -0.408) and MCS (β=-0.478, -0.441, -0.370) in combined, lcSSc and dcSSc patients respectively. The factors associated with high disability and low QoL scores were forced vital capacity for HAQ (β=-0.172, p=0.002) and SF-36 PCS (β=0.187, p=0.001); disease duration for HAQ (β=0.208, p<0.001), DHI (β=0.147, p=0.006), and SF-36 PCS (β=-0.134, p=0.014); 6-minute walk test for HAQ (β=-0.161, p=0.005) and SF-36 PCS (β=0.153, p=0.009); and modified Rodnan skin score for SHAQ (β=0.250, p<0.001) and DHI (β=0.233, p<0.001) in SSc patients. Diffusing capacity of the lungs for carbon monoxide for HAQ (β=-0.189, p=0.010) and SHAQ (β=-0.247, p=0.002); erythrocyte sedimentation rate for DHI (β=0.322, p<0.001); age for SF-36 PCS (β=-0.221, p=0.003) and body mass index for SF-36 PCS (β=-0.200, p=0.008) and MCS (β=-0.175, p=0.034) were the other variables associated with high disability or low QoL scores in SSc subsets.

Conclusion: Clinicians should consider the management of the pain and its sources as a key to improve better functional state and quality of daily life in SSc.

Keywords: Disability, pain, quality of life, systemic sclerosis.

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Systemic sclerosis (SSc) is a multisystemic connective tissue disease, characterized by thickening of the skin and fibrosis, often accompanied by organ involvement such as lung, kidney, heart and the gastrointestinal system.[1] Its prevalence rates vary greatly by geographic area from 9.3 to 660 per million, mostly seen in 35 to 55 years of age, with females four to six times more affected than males.[2,3]

Systemic sclerosis is clinically heterogeneous and classified into limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) according to the extent of skin involvement.[4] Limited cutaneous SSc involves extremities distally and face skin with mainly vascular manifestation of disease. Diffuse cutaneous SSc involves whole extremities, face and body skin with fibrotic complication of disease.[5] Disease severity is associated with skin involvement degree of SSc subsets.[6]

Quality of life (QoL) is the dominant method for evaluating the impact of the disease and treatment based on patient perception of daily life.[7] Previous studies have reported poor health-related quality of life (HRQoL) and significant functional disability in SSc.[8-10] Affection of SSc patients daily life similar to the other chronic disorders involve lung, heart and depression.[8] Previously published studies have reported conflicting results regarding factors affecting QoL and functional disability. Different populations and cultures may differ in the degree of impact they associate with what is objectively the same condition.

The Health Assessment Questionnaire (HAQ) is most commonly used disability index in musculoskeletal disorders firstly developed for rheumatoid arthritis and is also used in SSc based on patient-reported outcomes.[11] The HAQ is combined with five scleroderma-related Visual Analog Scales (VASs) into one score to form the scleroderma HAQ (SHAQ), which is more specific for SSc.[12,13]

Duruöz Hand Index (DHI) was developed for assessment of hand functions as self-reported questionnaire and found to be reliable and valid scale for SSc.[14] The Short Form Health Survey (SF-36) is a widely used generic scale to assess QoL in many diseases and also in patients with SSc.[15,16]

Although there are a number of studies carried out on SSc patients to evaluate the QoL and disability, the present study is the first conducted in Türkiye. In this study, we aimed to evaluate the factors associated with disability and QoL in Turkish patients with SSc.

PATIENTS AND METHODS

This multi-center, cross-sectional study was conducted at Rheumatology and/or Physical Medicine Departments of twelve hospitals between January 2018 and January 2019. All SSc patients who fulfilled the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for SSc[17] and ≥18 years of age were enrolled with the help of the multi-center Turkish League Against Rheumatism (TLAR) Network in 2018. The TLAR Network is a collaboration platform created to conduct scientific studies in rheumatology by supporting researchers at all stages from the proposal of a scientific project to data collection, control of data, analysis, and creation of publication. Exclusion criteria were as follows: age <18 years, failure to sign informed consent, overlapping and/or comorbid diseases requiring treatment. Finally, a total of 256 SSc patients (20 males, 236 females; mean age: 50.9±12.4 years; range, 19 to 87 years) were included in the study.

The patients were classified as dcSSc or lcSSc according to the most severe skin involvement at the time of the study visit or any prior visit.[18] Demographic and clinical characteristics of patients including age, duration (since the onset of the first non-Raynaud's symptom) and subtype of disease, presence or absence of digital ulcer, telangiectasia, sclerodactyly, calcinosis, arthritis, contracture, tendon friction rubs, dysphagia, dyspnea, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-nuclear antibody (ANA), anticentromere (ACA) and antiScl-70 antibodies, and body mass index (BMI) were recorded. The pulmonary function test was conducted to assess the forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO). High-resolution computed tomography (HRCT) was utilized to evaluate lung fibrosis. Systolic pulmonary

arterial pressure (PAP) measurements were recorded by transthoracic echocardiography.

Measures

HAQ and Scleroderma HAQ (SHAQ)

Global disability in patients with SSc is usually measured by the HAQ, a self-report questionnaire consisting of 20 items divided into eight categories (i.e., dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities), which are averaged into the final HAQ score.[11] Items are rated from 0 (no difficulty) to 3 (unable to do). The sum is, then, divided by 8, making a composite index which, if lower than 1, means no or mild functional limitation and if higher than 1 means moderate to severe functional limitation.[19] The VAS scales in the SHAQ assess daily activities and range from 0 (no limitation) to 100 (very severe limitation). In the original version of the SHAQ, the HAQ and the five VASs were assessed separately.[13] Georges et al.[20] proposed averaging 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. The HAQ and SHAQ are validated outcome measures, and both have been widely applied in studies of SSc.[2,11,21] Numerical rating scales measuring SSc-related functional disability due to the following health problems were also assessed: pain intensity (pain-VAS), severity of Raynaud's symptoms and severity of finger ulcerations, scoring between 0 (no limitation) to 10 (very severe limitation).[22]

Duruöz Hand Index

The DHI is used to assess the degree of hand disability. It corresponds to the sum of 18 questions relating to the difficulty of daily manual activities at the time of assessment. Each individual question is ranked on a Likert scale from 0 (without difficulty) to 5 (impossible to do).[23] The total score is obtained by adding the scores of all items (range 0-90). The reliability and validity of the DHI have been demonstrated in patients with SSc.[14]

The modified Rodnan skin score (mRSS)

The mRSS is a clinical measure of the extent and severity of skin thickening.[24] Skin thickening is assessed in 17 body areas: fingers, hands, forearms, arms, feet, legs, thighs (all bilaterally), face, chest, and abdomen (all singularly). Each area is scored from 0 to 3, with 0 representing normal skin and 3 denoting severe thickening. Cumulatively, it ranges from 0 (no thickening) to 51 (severe thickening in all 17 areas).

Health-related quality of life

The HRQoL was evaluated with the SF-36. It consists of eight health domains as follows: each with a score ranging between 0 and 100, with 100 being the best possible score: physical functioning; role limitations because of physical problems; bodily pain; general health; vitality; social functioning; role limitations because of emotional problems; and mental health. In the present study, we also analyzed two summary scores of SF-36, namely Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.[25]

6-Minute Walk Test (6MWT)

The 6MWT was carried out in accordance with a protocol adapted from the American Thoracic Society (ATS) guidelines,[26] using a straight and 30-m course in an enclosed corridor, performed at room air conditions without additional oxygen.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) for normally distributed variables or in median and interquartile range for skewed data. Categorical variables were expressed in number and frequency. The Shapiro-Wilk test was used for to assess data normality distribution. Differences in frequency were tested using the chi-square and Fisher exact tests. Differences in continuous variables were tested using the t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Multivariable linear regression analysis was used to evaluate associated variables with disability and HRQoL scales. Stepwise backward method was used for regression analysis. The strongest variable detected for model 1, the other associated variables used as model 2. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of all SSc patients are listed in Table 1. Of the

Table 1. Demographic and clinical characteristics of SSc patients

	Limited cutaneous SSc (n=115)				Diffuse cutaneous SSc (n=141)				Total SSc group (n=256)				
	%	Mean±SD	Median	Range	%	Mean±SD	Median	Range	%	Mean±SD	Median	Range	*p*
Age (year)		50.8±12.9				51.5±12.2				50.9±12.4			0.653
Disease duration (year)			8	1-35			10	0-46			9.75	0-46	**0.001**
Time since diagnosis (year)			4	0-24			6.88	0-35			5.00	0-35	**<0.001**
Sex													
Female	92.2				92.1				92.2				1.00
Body mass index (kg/m^2)		28.3±4.7				25.9±5.6				27.0±5.2			**<0.001**
Education													0.275
No formal education	25.2				34				30.1				
Primary school	51.3				45.4				48				
Elementary school	9.6				5.7				7.4				
High school	9.6				7.1				8.2				
University	4.3				7.8				6.3				
Raynaud phenomenon	87.9				90.7				89.5				0.542
Abnormal nail fold capillaries	74.1				80.7				77.7				0.23
Digital ulcers	9.6				29.8				20.7				**<0.001**
Digital pitting	15.8				56				38				**<0.001**
Telangiectasia	38.8				63.6				52.3				**<0.001**
Sclerodactyly	58.6				89.3				75.4				**<0.001**
Calcinosis	7.8				12.1				10.2				0.301
Arthritis	23.3				22.1				22.7				0.88
Contracture	20.7				40.7				31.6				**0.001**
Tendon friction rubs	15.5				26.4				21.5				**0.046**
Modified Rodnan skin score			7	0-23			24.5	9-46			16	0-46	**<0.001**
Dysphagia	31.9				52.9				43.4				**0.001**
Dyspnea	32.8				51.4				43				**0.003**
Lung fibrosis on HRCT	28.1				60.7				46.1				**<0.001**
Pulmonary artery pressure			25	15-80			30	15-65			28	15-80	**0.005**
Forced vital capacity			89.5	26-100			84	37-100			85	26-100	**0.013**
DLCO			84	21-100			80.5	17-100			82	17-100	0.131
Disease activity score			1	0-8.5			2.5	0-10			2	0-10	**<0.001**
6 Minute Walking Distance (m)			435	10-750			392.5	30-640			400	10-750	**<0.001**
ESR (mm/h)			19.5	3-80			19.5	3-74			19.5	3-80	0.482
C-reactive protein (mg/dL)			0.39	0.03-5			0.37	0-5			0.37	0-5	0.96
Anti-nuclear antibody (+)	89.7				86.4				87.9				0.343
Anticentromere (+)	46.6				11.5				27.5				**<0.001**
AntiScl-70 (+)	28.4				51.8				41.2				**0.002**

SSc: Systemic sclerosis; SD: Standard deviation; HRCT: High resolution computed tomography; DLCO: Single breath diffusing capacity for carbon monoxide; ESR: Erythrocyte sedimentation rate.

patients, 44.9 were classified as lcSSc and 55.1% as dcSSc. The disease duration was significantly higher and the BMI was significantly lower in the dcSSc subset.

Arthritis, calcinosis, Raynaud phenomenon (RP), abnormal nail fold capillaries rate, and DLCO were similar in both groups. Characteristics of skin and pulmonary involvement findings were higher in dcSSc patients. The FVC and 6MWT were found to be lower in dcSSc. Patient-reported outcomes of the patients with SSc are shown in Table 2.

Functional disability

The medians of HAQ score were 0.45 in lcSSc and 0.75 in dcSS; and 81.7% of lcSSc patients and 63.8% of the dcSSc patients had 0 to <1 (mild to moderate disability) HAQ scores and 34.8% of the dcSSc and 16.5% of the lcSSc patients were 1 to <2 (moderate to severe disability) HAQ score. Significantly higher HAQ scores were found in dcSSc compared to lcSSc (p=0.001).

The medians of SHAQ score were 0.6 in lcSSc and 1 in dcSSc. A total of 73.9% of lcSSc patients had 0 to <1 (mild to moderate disability), while 51.8% of the dcSSc patients had 1 to <2 (moderate to severe disability) SHAQ score. The SHAQ scores of dcSSc patients were significantly higher compared to lcSSc (p<0.001).

The medians of DHI were 8.5 for lcSSc and 23 for dcSSc subsets, indicating a statistically significant difference (p=0.001).

Health-related quality of life

The medians of SF-36 PCS and MCS were 52.81 and 51.04 for lcSSc, respectively and 40.94 and 38.62 for dcSSc, respectively, indicating a statistically significant difference (p=0.001 and p=0.007).

Predictors of functional disability and QoL

Multivariable linear regression analysis was used to evaluate associated variables with disability and QoL scales. Pain (VAS) was found to be significantly strongly associated with disability and HRQoL scales. Due to the strong relationship between pain and the activities of cutaneous, RP and digital ulcer rated by patients, the VAS outcomes other than pain were excluded as a predictive variable.

The pain (VAS) predicted 25% of HAQ score (β=0.397, p<0.001), 21% of SHAQ score (β=0.397, p<0.001) and 27% of DHI score (β=0.446, p<0.001), 26% of SF-36 PCS (β=-0.417, p<0.001), and 23% of the SF-36 MCS (β=-0.478, p<0.001) in combined SSc considered as model 1.

Disease duration (β=0.208, p<0.001), FVC (β=-0.172, p=0.002), and 6MWT (β=-0.161, p=0.005) were significantly associated with the

Table 2. Patient-reported outcomes in patients with SSc

	Limited cutaneous SSc (n=115)		Diffuse cutaneous SSc (n=141)		Total SSc group (n=256)		
	Median	Range	Median	Range	Median	Range	*p*
Patient rated cutaneous activity (VAS)	3	0-10	7	0-10	5	0-10	<0.001
Patient rated RP activity (VAS)	3	0-10	5	0-10	5	0-10	<0.001
Patient rated digital ulcer activity (VAS)	0	0-10	2	0-8	0	0-10	<0.001
Pain (VAS)	4	0-10	5	0-10	5	0-10	<0.001
HAQ	0.45	0-2.05	0.75	0-2.05	0.55	0-2.05	0.001
SHAQ	0.6	0-2.2	1	0-2.40	0.80	0-2.4	<0.001
DHI total score	8.5	0-62	23	0-72	15	0-72	0.001
SF-36 PCS	52.81	2.5-93.75	40.94	9.37-92.5	47.5	2.5-93.75	0.001
SF-36 MCS	51.04	0-90.5	38.62	6.25-90.75	42.83	0-90.75	0.007

SSc: Systemic sclerosis; VAS: Visual Analog Scale; RP: Raynaud phenomenon; HAQ: Health Assessment Questionnaire; SHAQ: Scleroderma HAQ; DHI: Duruöz Hand Index; SF-36: Short form 36; PCS: Physical Component Score; MCS: Mental Component Score.

HAQ score (model 2) and predicted 11% of the HAQ score, and both models predicted 36% of the HAQ score elevation. The mRSS (β=0.250, p<0.001) had a significant association with SHAQ, which explained 6% of score, and both variables predicted 27% of increasing in the SHAQ score. Furthermore, mRSS (β=0.233, p<0.001) and disease duration (β=0.147, p=0.006) were found to be significantly associated with DHI and predicted 8% of score. Both models predicted 35% of DHI score in the combined SSc group.

Disease duration (β=-0.134, p=0.14), FVC (β=0.187, p=0.001), and 6MWT (β=0.153, p=0.009) were significantly associated variables with SF-36 PCS that predicted 9% of decreased score (model 2). Both models predicted 35% of poorer SF-36 PCS in combined SSc patients (Table 3).

The pain (VAS) predicted 24% both of HAQ (β=0.386, p<0.001) and SHAQ (β=0.448, p<0.001), and 35% of DHI (β=0.536, p<0.001) scores elevation in lcSSc patients (model 1). The FVC (β=-0.271, p=0.001), disease duration (β=0.255, p=0.001), and mRSS (β=0.223, p=0.006) showed a significant association with HAQ score and predicted 18% of elevation (model 2). Both models predicted 42% HAQ scores in lcSSc patients. The FVC predicted 3% (β=-0.173, p=0.042) and both models predicted 27% of elevation in SHAQ score, while ESR predicted 10% (β=0.322, p<0.001) and both models 45% of elevation in DHI score in lcSSc patients.

The pain (VAS) was the strongest predictor (model 1), while FVC and BMI were the other strongly associated variables (model 2) for the

Table 3. Functional disability and QoL predictors in combined SSc patients

	B	SE	β	*p*	95% CI (Factor B)
HAQ					
Pain (VAS)	0.089	0.013	0.397	<0.001	0.064-0.113
Disease duration	0.014	0.004	0.208	<0.001	0.007-0.022
FVC	-0.007	0.002	-0.172	0.002	[-0.012-(-0.003)]
6 Minute Walk Test	-0.001	0.000	-0.161	0.005	-0.001-0.000
		Model 1 R^2=0.25 (p<0.001); Model 2 R^2=0.11 (p<0.001)			
SHAQ					
Pain (VAS)	0.080	0.011	0.397	<0.001	0.057-0.102
mRSS	0.011	0.002	0.250	<0.001	0.006-0.015
		Model 1 R^2=0.21 (p<0.001); Model 2 R^2=0.06 (p<0.001)			
DHI					
Pain (VAS)	3.180	0.381	0.446	<0.001	2.430-3.931
mRSS	0.354	0.082	0.233	<0.001	0.192-0.515
Disease duration	0.322	0.116	0.147	0.006	0.094-0.550
		Model 1 R^2=0.27 (p<0.001); Model 2 R^2=0.08 (p<0.001)			
SF-36 PCS					
Pain (VAS)	-3.783	0.514	-0.417	<0.001	[-4.796-(-2.770)]
FVC	0.314	0.092	0.187	0.001	0.133-0.496
6 Minute Walk Test	0.028	0.010	0.153	0.009	0.007-0.048
Disease duration	-0.379	0.153	-0.134	0.014	[-0.680-(-0.078)]
		Model 1 R^2=0.26 (p<0.001); Model 2 R^2=0.09 (p<0.001)			
SF-36 MCS					
Pain (VAS)	-4.154	0.479	-0.478	<0.001	[-5.097-(-3.212)]
			R^2=0.23 (p<0.001)		

QoL: Quality of life; SSc: Systemic sclerosis; CI: Confidence interval; HAQ: Health Assessment Questionnaire; VAS: Visual Analog Scale; FVC: Forced vital capacity; SHAQ: Scleroderma HAQ; DHI: Duruöz Hand Index; mRSS: Modified Rodnan skin score; SF-36: Short form 36; PCS: Physical Component Score; MCS: Mental Component Score.

both studied SF-36 scores in lcSSc patients. The pain predicted 33% of SF-36 PCS (β=-499, p<0.001) and 25% for MCS (β=-0.441, p<0.001). The FVC and BMI had 9% of prediction for SF-36 PCS and 5% for MCS. Both models predicted 42% of SF-36 PCS, and 30% of MCS decreasing in all (Table 4).

The pain (VAS) predicted 25% of HAQ (β=0.452, p<0.001), 16% of SHAQ (β=0.372, p<0.001) and 18% (β=0.389, p<0.001) of DHI score elevation in dcSSc (model 1). Disease duration (β=0.193, p=0.009) and DLCO (β=-0.189, p=0.010) were significantly associated with HAQ score, and predicted 8% of the HAQ score (model 2). Both models were associated with 33% elevation in HAQ score in dcSSc patients. DLCO (β=-0.247, p=0.002) and predicted 6% of elevation in SHAQ score, and both models estimated 22% of increasing in dcSSc patients. Disease duration (β=0.156, p=0.040) and mRSS (β=0.212, p=0.005) were found to be significantly associated with 7% of increasing in DHI scores (model 2). Both models were associated with 25% of elevation in DHI scores.

The pain (VAS) was the strongest predictor (model 1) of the both SF-36 components in dcSSc patients. Age and FVC were found to be associated with SF-36 PCS (model 2). The pain was predicted 18% (β=-0.408, p<0.001), while age (β=-0.221, p=0.003) and FVC (β=0.195, p=0.010) predicted 9% and both 27% of poorer QoL in SF-36 PCS. The pain was only predictor to be responsible for 14% of decrease (β=-0.370, p<0.001) in the SF-36 MCS (Table 5).

Table 4. Functional disability and QoL predictors in lcSSc patients

	B	SE	β	*p*	95% CI (Factor B)
HAQ					
Pain (VAS)	0.083	0.017	0.386	<0.001	0.048-0.118
FVC	-0.011	0.003	-0.271	0.001	[-0.018-(-0.005)]
Disease duration	0.019	0.006	0.255	0.001	0.007-0.031
mRSS	0.028	0.010	0.223	0.006	0.008-0.048
	Model 1 R^2=0.24 (p<0.001); Model 2 R^2=0.18 (p<0.001)				
SHAQ					
Pain (VAS)	0.086	0.016	0.448	0.000	0.054-0.119
FVC	-0.007	0.003	-0.173	0.042	-0.013-0.000
	Model 1 R^2=0.24 (p<0.001); Model 2 R^2=0.03 (p=0.042)				
DHI					
Pain (VAS)	3.083	0.409	0.536	<0.001	2.273-3.894
ESR	0.341	0.075	0.322	<0.001	0.192-0.490
	Model 1 R^2=0.35 (p<0.001); Model 2 R^2=0.10 (p<0.001)				
SF-36 PCS					
Pain (VAS)	-4.674	0.711	-0.499	0.000	[-6.082-(-3.265)]
FVC	0.487	0.144	0.257	0.001	0.202-0.772
BMI	-1.010	0.377	-0.200	0.008	[-1.757-(-0.263)]
	Model 1 R^2=0.33 (p<0.001); Model 2 R^2=0.09 (p=0.001)				
SF-36 MCS					
Pain (VAS)	-3.793	0.715	-0.441	0.000	[-5.211-(-2.375)]
FVC	0.327	0.145	0.188	0.026	0.040-0.614
BMI	-0.813	0.379	-0.175	0.034	[-1.565-(-0.061)]
	Model 1 R^2=0.25 (p<0.001); Model 2 R^2=0.05 (p=0.018)				

QoL: Quality of life; lcSSc: Limited cutaneous systemic sclerosis; CI: Confidence interval; HAQ: Health Assessment Questionnaire; VAS: Visual Analog Scale; FVC: Forced vital capacity; mRSS: Modified Rodnan skin score; SHAQ: Scleroderma HAQ; DHI: Duruöz Hand Index; SF-36: Short form 36; PCS: Physical Component Score; BMI: Body mass index; MCS: Mental Component Score.

Table 5. Functional disability and QoL predictors in dcSSc patients

	B	SE	β	*p*	95% CI (Factor B)
HAQ					
Pain (VAS)	0.111	0.018	0.452	<0.001	0.076-0.145
Disease duration	0.013	0.005	0.193	0.009	0.003-0.023
DLCO	-0.006	0.002	-0.189	0.010	[-0.011-(-0.001)]
		Model 1 R^2=0.25 (p<0.001); Model 2 R^2=0.08 (p<0.001)			
SHAQ					
Pain (VAS)	0.077	0.016	0.372	<0.001	0.045-0.108
DLCO	-0.007	0.002	-0.247	0.002	[-0.011-(-0.003)]
		Model 1 R^2=0.16 (p<0.001); Model 2 R^2=0.06 (p=0.002)			
DHI					
Pain (VAS)	3.086	0.595	0.389	<0.001	1.910-4.263
mRSS	0.438	0.154	0.212	0.005	0.134-0.742
Disease duration	0.344	0.165	0.156	0.040	0.017-0.671
		Model 1 R^2=0.18 (p<0.001); Model 2 R^2=0.07 (p=0.002)			
SF-36 PCS					
Pain (VAS)	-3.768	0.685	-0.408	0.000	[-5.122-(-2.415)]
Age	-0.400	0.134	-0.221	0.003	[-0.665-(-0.135)]
FVC	0.290	0.111	0.195	0.010	0.071-0.509
		Model 1 R^2=0.18 (p<0.001); Model 2 R^2=0.09 (p<0.001)			
SF-36 MCS					
Pain (VAS)	-2.832	0.608	-0.370	0.000	[-4.035-(-1.629)]
		R^2=0.14 (p<0.001)			

QoL: Quality of life; dcSSc: Diffuse cutaneous systemic sclerosis; CI: Confidence interval; HAQ: Health Assessment Questionnaire; VAS: Visual Analog Scale; DLCO: Diffusing capacity for carbon monoxide; SHAQ: Scleroderma HAQ; DHI: Duruöz Hand Index; mRSS: Modified Rodnan skin score; SF-36: Short form 36; PCS: Physical Component Score; FVC: Forced vital capacity; MCS: Mental Component Score.

DISCUSSION

The approach of physicians to SSc patients and the perception of the disease of SSc patients vary.[27] As physicians tend to focus more on clinical pictures and organ involvement due to the disease, and they pay less attention to pain, which affects the daily lives of patients and is the main source of complaints.[28] Systemic sclerosis affects QoL and daily activities more than other inflammatory autoimmune diseases,[29] although higher pain and similar QoL and functional results reported in rheumatoid arthritis compared to SSc from a single-center study in Türkiye.[30]

However, in recent years, patients' perspective and patient-reported outcomes have become more important. There is an increasing focus on pharmacological and non-pharmacological approach on the management of SSc-related digital ulcer, contractures, and pain which are the main reasons for poorer functional status and HRQoL, as well as unmet clinical needs.[31-33] Our study supports this recent shift in clinical focus by showing that pain is the strongest predictor of greater disability and worse HRQoL in all studied items and disease subsets.

In the present study, we found that pain (VAS) was the most relevant and strongest factor in all aspects of functional status and QoL. Therefore, in the regression analysis, the impact of pain on QoL and functional status was evaluated as the first model and, then, the additional contribution of other significant factors was assessed.

Pain is a common symptom in SSc and affects between 62 to 83% of patients. Localized musculoskeletal aches, joints, Raynaud's phenomenon, gastrointestinal tract, distal extremities (e.g., ulcers), skin thickening, and calcinosis may be the source of in SSc.[34-36]

Previous studies[15,21,37] have reported that pain severity is associated with both functional impairments and worsening HRQoL in SSc, consistent with our results. Hand involvement is important regardless of the type of SSc, due to skin hardening and digital vasculopathy manifesting particularly in this organ. Digital ulcers are painful, disabling, and have a major impact on hand functions, activities of daily living, and QoL. Skin thickening in the hands leads to functional disability due to contractures, while pain reduces grip strength, wrist, and finger motion. Calcinosis is also often painful and disabling and, sometimes, the deposits can become ulcerating to the skin and infected.[14,31,38] More recently, this involvement was also reported in juvenile SSc patients from Türkiye by Dağ et al.[39] The authors reported greater disability and mostly pain in juvenile SSc patients compared to juvenile localized scleroderma and healthy population.

The pain and related patient-rated measurements (RP, digital ulcer, cutaneous) were significantly higher in dcSSc patients. However, pain predicted 25 to 35% poorer disability and HRQoL in total and lcSSc patients, and no more than 20% (except for HAQ) in dcSSc patients. The best prediction for disability was detected for DHI in combined and lcSSc patients as 27% and 35%, respectively, with 16% of prediction in dcSSc. This may be due to different clinical characteristics and involvements of both disease subtypes. Limited cutaneous SSc predominantly involves vasculature and relatively less organ; therefore, pain has predominant impact on disability and HRQoL.

The other important predicting factors of both disability and QoL were FVC, disease duration, and 6MWT. However, mRSS, DLCO, and ESR had an important prediction on disability, but age and BMI on QoL alone.

Lung involvement is the major reason for morbidity and mortality in SSc. Forced vital capacity and DLCO are two measures of lung function which express physiological parameters for SSc pulmonary disease severity. In the current study, FVC was the other significant and common predictive variable for both disability and HRQoL. In our study, the FVC was associated with all studied disability scales except for DHI, while disability and HRQoL in lcSSc patients predicted more than dcSSc subset. Morrisroe et al.[40] reported 22% greater impairment in activities of daily life between moderate and severe interstitial lung disease. Jaeger et al.[12] reported no association between FVC and disability in a large multi-national SSc cohort. Peytrignet et al.[21] reported in the European Scleroderma Observational Study that FVC was associated with HAQ, DHI, and SF-36 PCS in dcSSc patients. However, they only assessed correlation for association, and no prediction for disability and HRQoL was done. In the current study, the FVC was significantly correlated with HAQ and SF-36 PCS, but in the regression analysis, the FVC significantly predicted only SF-36 PCS in dcSSc patients. However, FVC was correlated with all disability and HRQoL indexes used in the study, and predicted all measures (except for DHI) in lcSSc. We found that reduced DLCO predicted increased disability as measured by HAQ and SHAQ only in dcSSc patients, while no significant association was found with the HRQoL in the regression analysis. Peytrignet et al.[21] showed DLCO association with HAQ, DHI, and SF-36 PCS in dcSSc patients, while Jaeger et al.[12] demonstrated no significant association with HAQ and SHAQ in all SSc subsets. Our study suggests that FVC is a better predictor as an indicator of lung involvement for both disability and HRQoL, mainly in lcSSc patients.

Longer disease duration was associated with poorer disability scores as measured by HAQ (in all subsets), DHI (in combined and dcSSc), and impaired physical health (only in combined group) in the current study. Our results are consistent with previous studies,[29,37] suggesting that prolonged disease duration, which increases skin and the internal organs involvement, affects disability and QoL adversely. We found that patient age had a negative impact on PCS of SF-36 scores only in dcSSc patients. A recent studies reported different results in different study populations. Two studies[12,21] demonstrated no association between age and disability and HRQoL, while another study[41] reported a positive correlation between patients age HAQ, although it did not assess HRQoL and predictive value of age on disability.

Decreased 6MWT was associated with the increased HAQ and decreased physical SF-36

scores only in the combined group of patients. The 6MWT was developed for heart failure and lung diseases and, in recent years, it has been used as an outcome measure in clinical trials for SSc. In our study, we found decreased 6MWT results in dcSSc compared lcSSc patients. There is only limited research on the relationship between 6MWT and disability and HRQoL in SSc. Deuschle et al.[42] found a significant association between SHAQ and 6MWT in SSc patients. However, they used multivariate logistic regression for prediction of the 6MWD consisting of SHAQ score, and no any other disability and HRQoL scale evaluated. Therefore, there is a need for further studies to clarify exact association between 6MWT and functional state and QoL in SSc.

The mRSS is the primary outcome measure for evaluating skin involvement rate in SSc. There are different results reported from studies on the relationship between the skin involvement and disability and QoL in SSc. We found mRSS associated with disability, but not with HRQoL. A previously reported significant association between worsening in mRSS and SHAQ disability index, but not the SF-36 measurement, while the improvement in mRSS was not associated with the variables studied.[43] Recently Peytrignet et al.[21] reported that increased mRSS scores were associated with worse levels of disability, as measured by the HAQ and DHI, with decreased hand function. However, Jaeger et al.[12] reported no significant association between mRSS and disability. Park et al.[29] demonstrated that mRSS had a negative impact on both physical and mental scores of SF-36, indicating that extending in skin involvement impaired QoL in SSc patients, while Strickland et al.[44] found no significant association between mRSS and patient-reported outcomes in terms of disability and HRQoL. These different results may reflect different populations, different patient characteristics, and/or sample sizes. Our results demonstrated that mRSS was strongly associated with disability, in addition to pain and disease duration. Skin thickening may progress with disease duration and increase disability, which is also supported by Peytrignet et al.[21]

In the current study, elevated ESR predicted greater disability as measured by DHI in lcSSc patients. There is no more study studies reporting a relationship between ESR and disability or HRQoL in SSc, although two recent studies have shown controversial results. Jaeger et al.[12] reported no association between ESR and disability as measured by HAQ and SHAQ; however, they did not investigate DHI and HRQoL scales in all subsets, while Peytrignet et al.[21] reported a significant correlation between ESR and HAQ, DHI, and SF-36 PCS in dcSSc patients, but regression analysis was not done.

Body mass index has been shown to be lower and positively associated with physical component score of SF-36 in combined SSc patients.[29,45] We demonstrated that the increased BMI predicted poorer HRQoL only in lcSSc patients. Our study population was overweight and lcSSc group had higher BMI values than dcSSc group. Although previously we reported that SSc patients had lower BMI than healthy controls,[45] the mean BMI values in the current study were similar to the normal population of Türkiye.[46] Therefore, there seems to be an inverse association between BMI and HRQoL, similar to the normal studied population.[47]

The strength of the current study are its large sample size, various measurement tools used (i.e., SHAQ and DHI) that are widely used and validated in SSc for ability to demonstrate percentage of variation in the disability and QoL.[19] We could perform subgroup analysis of SSc due to the large sample size to define differentiations between subsets that was previously not reported sufficiently.[15] To the best of our knowledge, this is the first multi-center study in Türkiye to investigate factors associated with functional status and HRQoL in SSc. Although SSc affects disability and HRQoL considerably,[29] patient-reported outcomes are still inadequate to evaluate disease specifically in different cultures with different aspects.[32] In this study, we attempted to analyze clinical and demographic factors associated with disability and HRQoL in SSc patients to contribute to develop management strategies in this devastating disease.

Nevertheless, this study has some limitations. First, our study design is cross-sectional and, therefore, we were able to evaluate associated factors with disability and HRQoL rather than causality. Second, although HAQ and SF-36 were used previously in different musculoskeletal disorders including SSc, they are not

disease-specific tools to assess disease-specific impairment; rather, they are generic instruments providing useful comparison of QoL between normal population and diseases.[15] Third, the study group was enrolled from the Turkish population and the results needs to be confirmed for generalizability to other populations.

In conclusion, this is the first study carried out in Türkiye to identify significant predictors of disability and HRQoL in SSc patients. Pain was found the strongest and best predictor for patient-perceived disability and HRQoL in all subsets of disease. Forced vital capacity, disease duration, and 6MWT also contributed to both disability and QoL. However, mRSS, DLCO, and ESR were significant predictors of disability, while age and BMI were the predictors of QoL. Disability and HRQoL seem to be more affected from pain in lcSSc patients than dcSSc patients. Based on these findings, clinicians should consider patient-perceived outcomes and managing pain and its sources to have a better functional state and QoL in SSc.

Ethics Committee Approval: The study protocol was approved by the Dicle University Hospital Ethics Committee (date, no: 21.12.2017/20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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