Investigating the trajectory of functional disability in systemic sclerosis: group-based trajectory modelling of the Health Assessment Questionnaire-Disability Index

J.L. Fairley[1,2], D. Hansen[2], M. Baron[3,4], S. Proudman[5,6], J. Sahhar[7,8], G.-S. Ngian[7,8], J. Walker[6], L.V. Host[9], K. Morrisroe[1,2], W. Stevens[2], M. Nikpour[1,2,10,11], L. Ross[1,2]

[1]The University of Melbourne, Victoria, Australia; [2]St. Vincent's Hospital Melbourne, Victoria, Australia; [3]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada; [4]McGill University, Montreal, Canada; [5]University of Adelaide, South Australia, Australia; [6]Royal Adelaide Hospital, Adelaide, South Australia, Australia; [7]Monash Health, Melbourne, Victoria, Australia; [8]Monash University, Melbourne, Victoria, Australia; [9]Fiona Stanley Hospital, Perth, Western Australia, Australia; [10]The University of Sydney School of Public Health, Sydney, New South Wales, Australia; [11]Royal Prince Alfred Hospital Sydney, New South Wales, Australia.

Abstract

Objective

To identify the trajectories and clinical associations of functional disability in systemic sclerosis (SSc).

Methods

Australian Scleroderma Cohort Study (ASCS) participants meeting ACR/EULAR criteria for SSc recruited within 5 years of disease onset, with ≥2 Health Assessment Questionnaire-Disability Index (HAQ-DI) scores were included. Group based trajectory modelling (GBTM) was used to identify the number and shape of HAQ-DI trajectories. Between group comparisons were made using the chi-squared test, two-sample t-test or Wilcoxon rank-sum test as appropriate. Multiple logistic regression was used to identify features associated with trajectory group membership. Survival analyses were performed using Kaplan Meier and Cox proportional hazard modelling.

Results

We identified two HAQ-DI trajectory groups within 426 ASCS participants with incident SSc: low-stable disability (n=221, 52%), and high-increasing disability (n=205, 48%). Participants with high-increasing disability were older at disease onset, more likely to have diffuse SSc (dcSSc), cardiopulmonary disease, multimorbidity, digital ulcers, and gastrointestinal involvement (all p≤0.01), as was use of immunosuppression (p<0.01). Multimorbidity was associated with high-increasing trajectory group membership (OR3.1, 95%CI1.1-8.8, p=0.04); independently, multiple SSc features were also strongly associated including dcSSc (OR2.3, 95%CI1.3-4.2, p<0.01), proximal weakness (OR7.3, 95%CI2.0-27.1, p<0.01) and joint contractures (OR2.7, 95%CI1.3-5.3, p<0.01). High-increasing physical disability was associated with an almost two-fold increased risk of mortality (HR1.9, 95%CI1.0-3.8, p=0.05), and higher symptom burden.

Conclusion

Two trajectories of functional disability in SSc were identified. Those with high-increasing functional disability had a distinct clinical phenotype and worse survival compared to those with low-stable functional disability. These data highlight the pervasive nature of physical disability in SSc, and its prognostic importance.

Key words

systemic sclerosis, physical function, health-related quality of life, survival

Jessica L. Fairley, MBBS FRACP
Dylan Hansen, BSc MBiostatistics
Murray Baron, MD
Susanna Proudman, MBBS MD FRACP
Joanne Sahhar, MBBS FRACP
Gene-Siew Ngian, MBBS FRACP PhD
Jenny Walker, MBBS FRACP PhD
Lauren V. Host, MBBS FRACP
Kathleen Morrisroe, MBBS FRACP PhD
Wendy Stevens, MBBS FRACP
*Mandana Nikpour, MBBS FRACP FRACPA PhD**
*Laura Ross, MBBS FRACP PhD**

**These authors contributed equally to this study.*

Please address correspondence to:
Laura Ross
Department of Rheumatology,
St. Vincent's Hospital,
41 Victoria Parade Fitzroy,
3065 Melbourne, Victoria, Australia.
E-mail: laura.ross@unimelb.edu.au

Received on November 7, 2023; accepted in revised form on January 8, 2024.

Funding: the Australian Scleroderma Cohort Study (ASCS) is supported by Janssen, Boehringer Ingelheim, Scleroderma Australia, Scleroderma Victoria, Arthritis Australia, Musculoskeletal Australia (muscle, bone and joint health), Australian Rheumatology Association and St. Vincent's Hospital Melbourne IT Department and Research Endowment Fund (REF). The Australian Scleroderma Interest Group received research support grants from Actelion.
J.L. Fairley holds a NHMRC Postgraduate Scholarship GNT2013842 and an Australian Government Research Training Program Scholarship.
K. Morrisroe holds NHMRC Investigator Grant GTN1197169.
M. Nikpour holds an NHMRC Investigator Grant (GNT1176538).

Competing interests: page 1588.

Introduction

Up to 70% of people with SSc report functional impairment (1, 2), which can negatively impact health-related quality of life (HRQoL) (3). Digital ulceration (2), pulmonary arterial hypertension (PAH) and gastrointestinal involvement all contribute to impaired physical function(4-6), as can symptoms including dyspnoea, weakness and pain (4). The risk of functional disability and dependency are important concerns to those living with SSc (7). Accordingly, a detailed understanding of the impact of SSc on physical function and disability over the course of the disease is critical to providing person-centred care.

The Health Assessment Questionnaire-Disability Index (HAQ-DI) is a patient-reported measure of function, where a higher score indicates a worse functional status (8). Participants are asked 20 questions about their ability to perform activities of daily living. Each item is rated on a scale from 0-3, where "3" represents being unable to complete the task (8). The HAQ-DI is commonly used as a secondary endpoint in clinical studies, with good retest reliability (9). Data indicate that the HAQ-DI has meaningful sensitivity to change in those with early diffuse SSc (10) and those requiring treatment for digital ulcers (11). However, in other studies only small changes in HAQ-DI have been seen over time, raising questions about its widespread utility as a clinical trial outcome measure (12). This is particularly true in individuals with limited skin involvement or longstanding disease as HAQ-DI is heavily influenced by hand function (12). Furthermore, static joint contractures, chronic digital ulcers or digital amputation may impact the HAQ-DI's sensitivity to change.

Given the spectrum of disease in SSc and variable estimates in mean change in HAQ-DI over time, particularly across SSc subgroups (8, 10, 13), further data are required to better understand the trajectory of physical disability as measured by HAQ-DI over time. Accordingly, we sought to identify trajectories of HAQ-DI scores using group-based trajectory modelling (GBTM) in the Australian Scleroderma Cohort Study (ASCS). We sought to model the long-term trends of HAQ-DI scores within the ASCS and identify clinical associations of functional disability.

Methods

Participants were recruited from the ASCS, a multicentre cohort study of risk and prognostic factors in SSc. The ASCS has been approved by all Human Research Ethics Committees of participating sites. Written informed consent was obtained from all participants at recruitment. We included only those participants recruited to the ASCS within 5 years of onset of the first non-Raynaud's manifestation of SSc, in order to minimise bias introduced by those with longer disease duration having more HAQ-DI scores recorded. All participants met ACR/EULAR criteria for SSc (14) and had a definable disease subclass according to LeRoy criteria (diffuse (dcSSc) or limited (lcSSc)) (15). Participants needed to have at least two HAQ-DI scores recorded within 10 years of SSc onset for inclusion.

Clinical Data

Demographic and disease data, and medication usage were prospectively collected at annual study visits. Disease manifestations were considered present if they were recorded at any time from SSc diagnosis. The presence of co-morbid angina, diabetes, dyslipidaemia, hypertension, smoking and medication use were recorded from patient-reported history and medical record review at each study visit. Ischaemic heart disease (IHD) was defined as abnormal coronary angiography or patient-reported angina/myocardial infarction. Participants were asked to report gastrointestinal symptoms (including reflux, vomiting, sicca symptoms, diarrhoea/constipation) and clinical examination features were recorded by the study physician at each visit (including tendon friction rubs, muscle atrophy, proximal weakness on manual muscle testing (MMT, with weakness defined as scores <5/5) and synovitis. Body mass index was calculated as weight (kilograms) divided by height (metres) squared. All partici-

pants underwent annual transthoracic echocardiography (TTE) and pulmonary function testing (PFT; forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) corrected for haemoglobin) as screening for PAH and interstitial lung disease (ILD). Right heart catheterisation or high-resolution computed tomography (HRCT) were performed if abnormalities were detected on assessment or screening investigations. PAH was defined according to the revised PAH classification criteria(16)(mean pulmonary artery pressure (mPAP) >20 millimetres of mercury (mmHg), pulmonary vascular resistance (PVR) >2 Wood units and a pulmonary arterial wedge pressure (PAWP) ≤15mmHg), or if PVR unavailable, according to previous classification criteria (mPAP ≥25mmHg, PAWP <15mmHg). ILD was diagnosed in the presence of typical radiographic abnormalities on HRCT. Six-minute walk tests (6MWT) were requested at the discretion of the treating physician. Scleroderma renal crisis (SRC) was diagnosed when at least two of three criteria were concurrently present: new-onset hypertension without alternate cause, unexplained rise in serum creatinine, and microangiopathic haemolytic anaemia. Myositis was defined by a positive muscle biopsy. Overlap syndromes were considered present if the physician considered patients also had another connective tissue disease diagnosis in addition to SSc, without mandating that participants fulfilled additional diagnostic criteria. Serological testing was performed according to local laboratory protocols.

The Medsger Severity Score (MSS) was calculated to assess the overall SSc burden at each study visit (17). To measure multimorbidity at each study visit, we calculated a modified Charlson Comorbidity Index (CCI) score (18). A list of included items is provided in Supplementary Table S1; data for some variables (including hemiplegia, HIV/AIDS and dementia) were excluded as these data are not collected as part of the ASCS protocol. A CCI score ≥4 was defined as a multimorbidity (19), with the highest available score being 19.

Physical function and health-related quality of life

Patient-reported outcome measures (PROMs) were recorded at each visit, including the HAQ-DI, Short Form-36 Survey (SF-36), PROM Information System (PROMIS)-29, and the physician-reported World Health Organisation (WHO) Functional Class. Participants were asked to rate their level of breathlessness using the Borg Dyspnoea Scale, on a numerical rating scale from 0-10 where 0=no breathlessness to 10=maximal breathlessness after one flight of stairs. For analysis this was dichotomised into scores of <3/10 (no/slight dyspnoea) or ≥3/10 (moderate/severe dyspnoea).

Statistical analysis

Analyses were performed using STATA 17.0 (Statacorp LP, College Station, TX, USA). Group-based trajectory modelling (GBTM) was performed using the stata plugin *traj* over 10 years from SSc onset (20). GBTM is a specialised approach of finite mixture modelling to identify homogeneous clusters of developmental trajectories within a population (21). Fewer than 10% of participants recorded a HAQ-DI score at SSc-onset as this was before entry into the cohort. The HAQ-DI value was plotted against the time from SSc onset rather than from time in the cohort. HAQ-DI patterns and distribution were used to determine the number and shape (intercept, linear, cubic, quadratic) of trajectories based on statistical criteria balanced with clinical validity. Each trajectory group needed to include at least 10% of participants, and the final model was evaluated using Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), the average posterior probability of assignment (≥0.70) and the odds of correct classification (≥5). GBTM uses maximum likelihood estimates to handle missing data, assuming that the data are missing at random (21). Characteristics of study participants are presented as mean (standard deviation (SD)) for normally distributed continuous variables, median (interquartile range (IQR)) for non-normally distributed continuous variables, and as number (percentage) for discrete variables. Where relevant, if investigation results or other data were not recorded at visit one, the first-recorded value within 5 years of SSc onset was used. Comparisons between demographics and clinical characteristics of patients in different trajectory groups were performed using two sample t-test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables and the chi-squared test for discrete variables. Multiple logistic regression was used to determine associations of high-increasing disability. Included covariates were significant in univariate analyses ($p<0.10$) or deemed clinically important. Kaplan-Meier survival curves and the Wilcoxon test were used to estimate survival from SSc onset in each of the trajectory groups, using the endpoint of all-cause mortality. Multivariable Cox proportional hazards regression analysis was used to determine multivariable associations of all-cause mortality among trajectory groups and using baseline HAQ-DI scores as a continuous outcome. Covariates were chosen for the multivariable analysis if they were either clinically relevant or statistically significant on univariable analysis ($p<0.05$) and did not violate the proportional hazards assumption. Results are reported as hazard ratios (HR) with accompanying 95% confidence intervals (CI).

Results

Of 705 ASCS participants with incident SSc, 426 (60.4%) were identified with ≥2 HAQ-DI scores recorded within 10 years of SSc onset. Those with ≥2 HAQ-DI scores included in the study were less likely to have dcSSc ($p<0.01$) or to have died ($p<0.01$) than those with <2 HAQ-DI scores, with no difference in age at SSc onset, sex or disease duration at recruitment. Those with ≥2 HAQ-DI scores had a longer follow-up duration ($p<0.01$) (Suppl. Table S2).

Of included participants, 272 (63.8%) had 2-5 HAQ-DI scores recorded, while 154 (36.2%) had 5-9 HAQ-DI scores recorded. Median age at SSc onset was 53.0 years (IQR 42.8–60.6

years); 352 (82.6%) were female and 286 (67.1%) had lcSSc. The median baseline HAQ-DI score across the cohort was 0.5 (IQR 0–1.1). Twenty-nine participants (7.1%) reported severe functional disability at study entry (baseline HAQ-DI scores 2–3), 104 (25.5%) reported moderate disability (baseline score 1-<2), and 275 (67.4%) reported mild functional disability (HAQ-DI<1). Of note, 116 participants (28.4%) recorded a baseline HAQ-DI score of 0 and one participant recorded a baseline HAQ-DI score of 3.

Trajectory data

We identified two HAQ-DI trajectory groups: low-stable disability (n=221, 51.9%), and high-increasing disability (n=205, 48.1%) over the first 10 years of SSc (Fig. 1). Median disease duration at enrolment (p=0.24) and follow-up duration (p=0.84) were similar among trajectory groups. The shape of the trajectory was intercept for those with low-stable disability (trajectory 1) and linear for those with high-increasing disability (trajectory 2). The average posterior probability of group membership was 0.87 with odds of correct classification of 6.9 in trajectory 1, with an average posterior probability of group membership of 0.91 and odds of correct classification of 9.8 for trajectory 2, indicating well-fitting models (Supplementary Table S3). Participants in the low-stable disability trajectory group had a baseline HAQ-DI score of 0.22 units which remained stable. Participants in the high-increasing disability group had a baseline HAQ-DI score of 1.18 units, which increased at a constant rate of 0.014 units/year. Peak HAQ-DI score (median) was 1.6 in the high-increasing group, and 0.38 in the low-stable group (p<0.01).

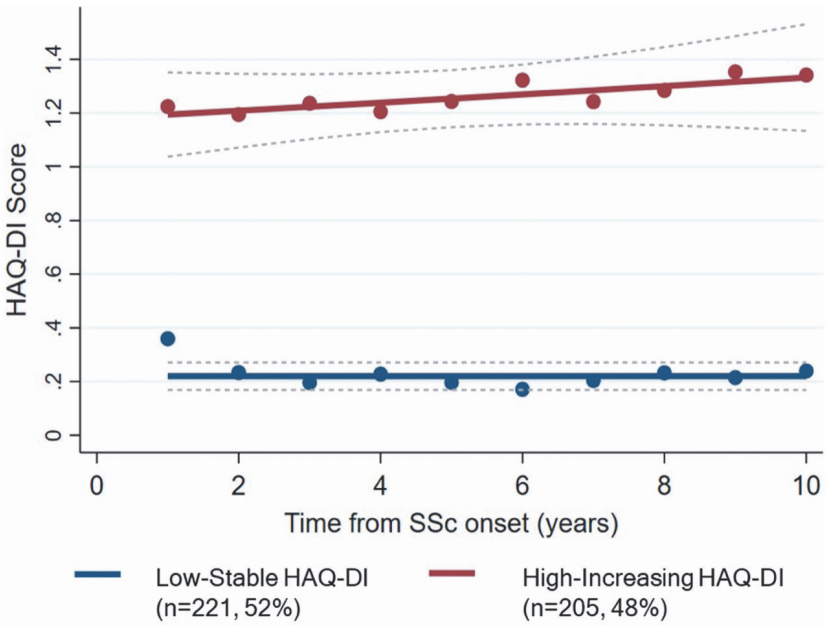

Fig. 1. Trajectory groups based on HAQ-DI scores in SSc.
HAQ-DI: health assessment questionnaire disability index; n: number; SSc: systemic sclerosis.

Baseline characteristics, disease features and association with trajectory group

Participants with high-increasing disability trajectories were older at recruitment (p=0.01), more likely to have dcSSc (p<0.01) with higher peak MRSS (p<0.01) than those with low-stable disability (Table I). Body mass index was marginally higher in those with high-increasing disability (26.6 *vs.* 25.2kg/m^2, p=0.02). Those with high-increasing disability trajectories were less likely to have antinuclear antibody (ANA) centromere positivity (p<0.01), anti-Scl/PM (p=0.01) and anti-RNP antibodies (p=0.05). PAH was more common in those with high-increasing disability (p<0.01), and this group had lower percent-predicted diffusing capacity for carbon monoxide (DLCO; p<0.01) and forced vital capacity (FVC; p<0.01). However, there was no difference in the frequency or severity of radiographic ILD between groups. SRC was more common in those with high-increasing disability although this did not reach statistical significance (p=0.07). Digital ulcers (p<0.01), digital amputation (p=0.01), tendon friction rubs (p<0.01) and synovitis (p<0.01) were all more common in those with high-increasing disability. While there was no difference in peak creatinine kinase or biopsy-proven myositis, proximal muscle weakness (p<0.01) and muscle atrophy (p<0.01) were more common in those with high-increasing disability. Upper (p<0.01) and lower (p<0.01) gastrointestinal symptoms were more common in those with high-increasing disability. There was no increase in overlap syndromes in those with high-increasing disability. Participants with high-increasing HAQ-DI scores had higher levels of multimorbidity than those with low-stable disability (Table I; CCI score ≥4 in 25.9% *vs.* 10.4%, p<0.01). Important co-morbidities such as IHD (p<0.01), hypertension (p<0.00), diabetes (p=0.05), cerebrovascular (p=0.01) and peripheral vascular disease (p<0.01) were more frequent in those with high-increasing disability. In keeping with a higher frequency of cardiovascular disease in this group, use of multiple antihypertensive (p<0.01) and antiplatelet (p=0.02) agents, diuretics (p<0.01) and anticoagulation (p<0.01) were more common. Home oxygen use (p=0.01), opiate analgesia (p<0.01) and use of immunosuppression (p<0.01) including prednisolone (p<0.01) were more common in those with high-increasing disability.

Determinants of trajectory group membership

Using multivariable logistic regression, we assessed baseline characteristics that conferred increased risk of membership in the high-increasing trajectory of functional disability (Table II, Univariable analyses in Suppl. Table S4). dcSSc (OR 2.3, 95%CI 1.3–4.2, p<0.01) and a raised CRP (OR 2.8, 95%CI 1.6–4.9, p<0.01) were associated with a higher trajectory of func-

Table I. Comparison of clinical features and treatments between HAQ-DI trajectory groups in SSc.

	Cohort overall (n=426)	High/Increasing HAQ-DI Score (n=205, 48.1%)	Low/Stable HAQ-DI score (n=221, 51.9%)	*p*-value
Age at SSc onset (years)	53.0 (42.8-60.6)	55.6 (44.0-63.4)	51.7 (41.4-58.9)	<0.01
Female sex	352 (82.6%)	172 (83.9%)	180 (81.4%)	0.50
Diffuse cutaneous SSc	140 (32.9%)	97 (47.3%)	43 (19.5%)	<0.01
Modified Rodnan score (highest)*	8 (4-18)	13 (6-27)	6 (4-11)	<0.01
Deceased	46 (10.8%)	33 (16.1%)	13 (5.9%)	<0.01
Disease duration at enrolment (years)	1.8 (0.9-3.2)	1.7 (0.9-2.9)	1.9 (1.0-3.3)	0.24
Follow-up duration (years)	6.0 (3.5-9.1)	6.1 (3.7-9.0)	5.9 (3.4-9.2)	0.84
Smoker (current or previous)*	231 (54.2%)	112 (54.6%)	119 (53.8%)	0.87
Body mass index (kg/m^2)^	25.7 (22.8-29.7)	26.6 (23.3-30.3)	25.2 (22.4-29.2)	0.02
Multimorbidity (Charlson Comorbidity Index Score ≥4)*	76 (17.8%)	53 (25.9%)	23 (10.4%)	<0.01
Medsger Severity Score (baseline^)	5 (3-7)	6 (4-9)	4 (2-5)	<0.01
Overlap syndrome*	50 (11.7%)	27 (13.2%)	23 (10.4%)	0.50
HAQ-DI Score (baseline^)	0.5 (0.0-1.1)	1.1 (0.8-1.8)	0 (0-0.4)	<0.01
Serology				
ANA centromere	168 (39.7%)	64 (31.5%)	104 (47.3%)	<0.01
RNA polymerase-3	32 (7.6%)	32 (19.8%)	23 (13.5%)	0.12
ENA				
Scl-70	74 (17.6%)	42 (20.9%)	32 (14.5%)	0.09
U1RNP	32 (7.6%)	10 (5.0%)	22 (10.0%)	0.05
Scl/PM	55 (16.5%)	1 (0.5%)	11 (5.0%)	<0.01
Cardiovascular				
Diabetes*	44 (10.4%)	28 (13.7%)	16 (7.2%)	0.05
Dyslipidaemia*	177 (41.6%)	94 (45.9%)	83 (37.6%)	0.10
Hypertension*	211 (49.5%)	126 (61.5%)	85 (38.5%)	<0.01
Stroke/TIA*	29 (6.8%)	21 (10.2%)	8 (3.6%)	0.01
Peripheral vascular disease*	22 (5.8%)	18 (8.8%)	4 (1.8%)	<0.01
IHD[1*]	47 (11.1%)	32 (15.6%)	15 (6.8%)	<0.01
LVH on TTE*	75 (26.3%)	42 (31.6%)	33 (21.7%)	0.06
LVEF (baseline^)	62.6 ± 6.9%	62.7 ± 7.1%	62.5 ± 6.8%	0.65
Left-sided valvular heart disease*	244 (58.2%)	128 (63.4%)	116 (53.5%)	0.04
RV dysfunction *	53 (12.7%)	40 (19.9%)	13 (6.0%)	<0.01
RVSP (baseline^)	29 (25-34)	31 (26-37)	28 (23-32)	<0.01
Respiratory				
PAH*	68 (16.0%)	45 (22.0%)	23 (10.4%)	<0.01
ILD (on HRCT)*	132 (65.4%)	78 (62.9%)	54 (69.2%)	0.36
DLCO (baseline^)	72.5 ± 18.9%	67.4 ± 18.0%	77.1 ± 18.7%	<0.01
FVC (baseline^)	94.2 ± 19.4%	90.1 ± 19.8%	98.1 ± 18.3%	<0.01
Vascular				
SRC*	19 (4.5%)	13 (6.3%)	6 (2.7%)	0.07
Raynaud's phenomenon*	423 (99.3%)	204 (99.5%)	219 (99.1%)	0.61
Digital ulcers*	207 (48.6%)	117 (57.1%)	90 (40.7%)	<0.01
Digital amputation or gangrene*	33 (7.8%)	23 (11.2%)	10 (4.5%)	<0.01
Musculoskeletal				
Myositis (biopsy-proven)*	13 (3.1%)	8 (3.9%)	5 (2.3%)	0.33
Proximal weakness*	106 (24.9%)	75 (36.6%)	31 (14.0%)	<0.01
Proximal muscle atrophy*	88 (20.7%)	64 (31.2%)	24 (10.9%)	<0.01
Synovitis*	207 (48.6%)	118 (57.6%)	89 (40.3%)	<0.01
Tendon friction rub*	56 (13.2%)	44 (21.5%)	12 (5.4%)	<0.01
Joint contracture*	170 (39.9%)	116 (56.6%)	54 (24.4%)	<0.01
Gastrointestinal				
Upper gastrointestinal symptoms*[2]	389 (91.3%)	196 (95.6%)	193 (87.3%)	<0.01
Lower gastrointestinal symptoms*[3]	363 (85.2%)	188 (91.7%)	175 (79.2%)	<0.01
Other				
ESR (peak; mm/hr)*	24.5 (14-38)	30 (16-46)	20 (10-31.5)	<0.01
CRP (peak; IU/L)*	6 (4-14)	9.3 (5-20.6)	5 (2.1-8)	<0.01

*Denotes ever recorded from SSc onset.
^If baseline data not available, earliest data from first 5 years used.
[1]IHD defined by composite endpoint of patient-reported angina or acute myocardial infarction, or abnormal coronary angiogram.
[2]Upper gastrointestinal symptoms include history of Barret's oesophagus, GAVE, oesophageal dysmotility, oesophageal strictures, dysphagia, reflux or vomiting.
[3]Lower gastrointestinal symptoms includes history of bowel dysmotility, pseudo-obstruction, constipation, faecal incontinence, diarrhoea or bloating.
[4]Immunosuppressive treatment defined as ever receiving corticosteroids, synthetic or biologic disease-modifying antirheumatic drugs.
ACE: angiotensin converting enzyme; ANA: antinuclear antibody; CRP: C-reactive protein; dcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing capacity for carbon monoxide; ENA: extractable nuclear antigen; ENA: erythrocyte sedimentation rate; FVC: forced vital capacity; HAQ-DI: health assessment questionnaire disability index; IHD: ischaemic heart disease; ILD: interstitial lung disease; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; n: number; PAH: pulmonary arterial hypertension; RV: right ventricular; RVSP: right ventricular systolic pressure; SSc: systemic sclerosis; SRC: scleroderma renal crisis.

tional disability, although age and sex were not. Multimorbidity at baseline was associated with high-increasing disability (OR 3.1, 95%CI 1.1–8.8, p=0.04), as was DLCO<70% (OR 1.7, 95%CI 1.0-2.8, p=0.03) and gastrointestinal symptoms (OR 2.0, 95%CI 1.1–3.8, p=0.02).Musculoskeletal SSc features including proximal weakness (OR 7.3, 95%CI 2.0–27.1, p<0.01) and joint contractures (OR 2.7, 95%CI 1.3–5.3, p<0.01) were associated with increasing disability, although synovitis and tendon friction rubs did not meet significance in multivariable analyses.

Symptom burden according to trajectory groups

Mental and physical HRQoL were poorer in patients who reported more severe physical disability (SF-36 physical component summary (PCS) and mental component summary (MCS) scores worse, both p<0.01, Table III). The symptom burden from fatigue (PROMIS-29 fatigue p<0.01) and breathlessness (Borg dyspnoea Index score, p<0.01) was greater in those with poor physical function. Increased patient-reported physical disability was associated with physician-assessed functional status (WHO Functional Class, p<0.01) and shortest-recorded 6MWD (p<0.01).

Survival according to functional disability

Those with high-increasing trajectories of physical disability were more likely to have died during follow-up (16.1% *vs*. 5.9%, p<0.01; Fig. 2). In a multivariable model of all cause-mortality from SSc onset including age, sex, dcSSc, PAH, ILD and IHD (Table IV), high-increasing physical disability was associated with reduced survival (HR 2.0, 95%CI1.0–3.9, p=0.05) independent of other significant predictors of poor survival including male sex (HR 2.3, 95%CI1.2–4.5, p=0.02), PAH (HR 5.0, 95%CI2.7–9.3, p<0.01) and older age at SSc onset (HR 1.1, 95%CI1.0–1.1, p<0.01). Univariable analyses are presented in Supplementary Table S5.
We analysed survival in those with a higher baseline HAQ-DI score treated as a continuous variable regardless of trajectory group membership, meas-

Table II. Multiple Logistic Regression Model for SSc HAQ-DI Trajectory Group Membership using baseline[1] characteristics (n=352).

Item (all refer to baseline value[1])	Odds ratio	95% Confidence interval	*p*-value
Age at SSc onset (years)	1.2	0.7-2.0	0.48
dcSSc	2.3	1.3-4.2	<0.01
Multimorbidity[2]	3.1	1.1-8.8	0.04
DLCO<70%	1.7	1.0-2.8	0.03
FVC<80%	0.9	0.5-1.8	0.86
Proximal weakness[3]	7.3	2.0-27.1	<0.01
Joint contractures	2.7	1.3-5.3	<0.01
Synovitis	1.4	0.8-2.4	0.20
Tendon friction rubs	2.0	0.4-9.8	0.37
Gastrointestinal symptoms[4]	2.0	1.1-3.8	0.02
CRP>5IU/L	2.8	1.6-4.9	<0.01

CRP: C-reactive protein; dcSSc: diffuse cutaneous SSc; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; IU/L: international units per litre; n: number; SSc: systemic sclerosis.
[1]Baseline defined as first-recorded value within 5 years of SSc onset.
[2]Multimorbidity at baseline defined as baseline Charlson Comorbidity Index Score ≥4.
[3]Proximal weakness defined as scores <5/5 on manual muscle testing.
[4]Gastrointestinal symptoms defined as either upper (dysphagia, reflux or vomiting) or lower (history of bowel dysmotility, pseudo-obstruction, constipation, faecal incontinence, diarrhoea or bloating) gastrointestinal symptoms.

Table III. Comparison of physical function and HRQoL between HAQ-DI trajectory groups.

	High/Increasing HAQ-DI Trajectory Group	Low/Stable HAQ-DI Trajectory Group	*p*-value
General measures of physical function			
6MWT Performed	145 (70.7%)	162 (73.3%)	0.55
Lowest (shortest) 6MWD (m)*	400 (295-460)	499 (440-555)	<0.01
WHO Functional Class*			<0.01
Class I	36 (17.6%)	112 (51.1%)	
Class II	71 (34.6%)	89 (40.6%)	
Class III	80 (39.0%)	16 (7.3%)	
Class IV	18 (8.8%)	2 (0.9%)	
Patient-reported outcome measures			
SF-36 Physical Component Summary (lowest[1])	25.8 (21.3-30.2)	40.4 (33.5-47.2)	<0.01
SF-36 Mental Component Summary (lowest[1])*	34.1 (27.8-42.3)	43.8 (35.8-51.3)	<0.01
PROMIS-29 anxiety (highest[1])*	61.4 (55.8-65.3)	55.8 (48-61.4)	<0.01
PROMIS-29 depression (highest[1])*	60.5 (55.7-65.7)	53.9 (41-58.9)	<0.01
PROMIS-29 fatigue (highest[1])*	62.7 (57-69)	53.1 (46-58.8)	<0.01
Borg Dyspnoea Index scores of moderate or severe dyspnoea*	152 (76.4%)	90 (41.3%)	<0.01

*Denotes ever recorded from SSc onset.
[1]Patient-reported outcome scale scores presented as lowest scores during SSc course if lower scores indicate more severe symptoms, or highest recorded scores if higher scores indicate more severe symptoms as specified.
6MWT: 6-minute walk test; 6MWD: 6-minute walk distance; HAQ-DI: Health Assessment Questionnaire Disability Index; m: metre; PROMIS: patient-reported outcome measures information system; SF-36: Short Form Survey-36; WHO: world health organisation.

ured using the first reported HAQ-DI score within 5 years of SSc onset. Those with a higher baseline HAQ-DI score had significantly worse survival (HR 1.8, 95%CI1.2–2.6, $p<0.01$; Suppl. Table S5) which remained significant even after adjusting for age, sex, dcSSc, PAH, ILD and IHD (HR 1.8, 95%CI1.2–2.8, $p=0.01$; Table IV).

Discussion

It is possible to identify two distinct trajectories of physical function in individuals with recent-onset SSc: those with high-increasing disability (48%) or low-stable disability (52%). Across the cohort, HAQ-DI scores were either stable or increased slowly (0.014 units/year) which is below the threshold for minimum-clinically important difference for worsening HAQ-DI scores of 0.125 units. Of note, this means participants would take around 10 years to accrue a clinically significant increase in HAQ-DI score. Participants with high-increasing functional disability recorded higher baseline HAQ-DI scores within 5 years of disease onset, suggesting that a significant burden of functional disability occurs early in SSc. High-increasing functional disability was associated with higher likelihood of dcSSc, gastrointestinal symptoms and musculoskeletal disease features including those associated with poorer hand function at baseline, independent of non-SSc multimorbidity. High-increasing functional disability was also associated with worse HRQoL and increased symptom burden. Finally, survival was poorest in those with high-increasing physical disability. These data demonstrate the pervasive nature of functional disability in SSc, and its correlation with a severe SSc phenotype and poorer HRQoL.

Almost half of our incident cohort with SSc had a high and increasing trajectory of functional disability. This highlights the significant burden of functional disability in SSc, and is consistent with data identifying greater work disability in SSc than in rheumatoid arthritis (22). In addition to specific SSc disease features, we identified that patient-reported dyspnoea, fatigue and poorer mental health are associated with a higher burden of functional disability, as well as some novel associations of high-increasing functional disability. While markers of SSc severity have been associated with worse physical function (4, 5), we detected an association of global SSc severity measured by MSS score and functional disability. We identified a large non-SSc comorbidity burden in those with a high-increasing trajectory of functional disability, and a significant association between baseline multimorbidity and increased functional disability. After adjusting for non-SSc comorbidity, important SSc disease features were still strongly associated with functional disability. This relationship between multimorbidity and functional disability has also been seen in general

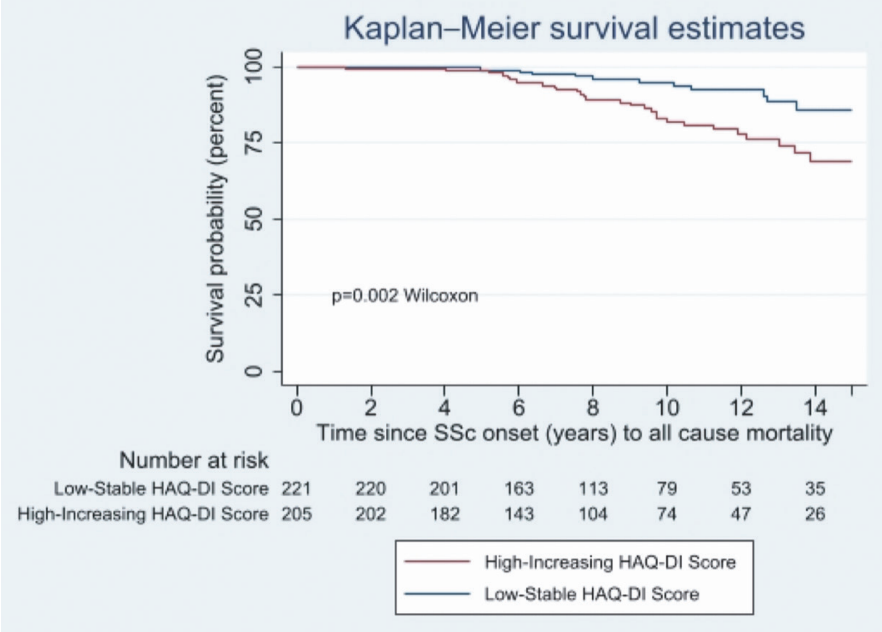

Fig. 2. Kaplan-Meier survival estimates according to HAQ-DI trajectory groups.
HAQ-DI: Health Assessment Questionnaire Disability Index; SSc: systemic sclerosis.

Table IV. Multivariable Cox Proportional Hazard model for all-cause mortality from SSc onset according to both HAQ-DI trajectory group and baseline HAQ-DI score.

	Hazard ratio	95% Confidence interval	*p*-value
Model using HAQ-DI trajectory groups			
High-Increasing HAQ-DI trajectory group	2.0	1.0-3.9	0.05
Age at SSc onset	1.1	1.0-1.1	<0.01
Male sex	2.3	1.2-4.5	0.02
dcSSc*	1.7	0.9-3.3	0.11
PAH*	5.0	2.7-9.3	<0.01
ILD*	1.1	0.6-2.1	0.73
IHD*	1.4	0.7-2.8	0.33
Model using baseline HAQ-DI score			
Baseline HAQ-DI score	1.8	1.2-2.8	0.01
Age at SSc onset	1.1	1.0-1.1	<0.01
Male sex	2.8	1.4-5.8	<0.01
dcSSc*	1.4	0.7-2.8	0.34
PAH*	4.6	2.4-8.8	<0.01
ILD*	1.1	0.6-2.2	0.74
IHD*[1]	1.2	0.6-2.5	0.61

*Denotes ever recorded from SSc onset.
[1]IHD defined by composite endpoint of patient-reported angina or acute myocardial infarction, or abnormal coronary angiogram.
dcSSc: diffuse cutaneous systemic sclerosis; HAQ-DI: Health Assessment Questionnaire Disability Index; IHD: ischaemic heart disease; PAH: pulmonary arterial hypertension; SSc: systemic sclerosis.

populations of older adults (23, 24). Taken together, these data demonstrate that both severity of SSc internal organ involvement and non-SSc comorbidity increase the risk of functional disability in SSc.

Importantly, we demonstrated that functional disability is prognostically important. Survival was significantly worse both in those with a high-increasing trajectory of HAQ-DI scores, and those with higher baseline HAQ-DI scores after adjusting for age, sex, dcSSc, IHD and PAH, consistent with previous reports that have evaluated prognostic markers in SSc (25, 26). In the wider literature, baseline HAQ-DI scores have been shown to predict survival in dcSSc (27, 28), and HAQ scores at one year in rheumatoid arthritis have been associated with all-cause mortality (29). This is in keeping with data demonstrating the prognostic importance of other markers of physical function in SSc, including 6MWD (30) and WHO Functional Class/New York Heart Association Class III/IV dyspnoea (31, 32). These data highlight the important predictive value of physical disability in determining prognosis and confirm baseline self-reported disability as measured by HAQ-DI score as a useful prognostic tool in SSc.

This study demonstrates HRQoL and symptom burden is consistently worse in those with higher levels of functional disability. Participants with an increasing trajectory of functional disability had worse self-reported HRQoL, mental wellbeing and dyspnoea, and worse physical function as measured objectively (6MWD) and by the physician (WHO Functional Class). Dyspnoea (4, 33), pain (34, 35) and fatigue (34) have been identified as determinants of physical function; we identified that patient-reported measures of these symptoms were consistently worse in those with high-increasing disability. Overall, these data demonstrate that higher HAQ-DI scores correlate with other patient-reported outcomes of HRQoL and highlight the importance of patient-reported symptoms as significant correlates of functional disability. Supporting this idea, while mental health as measured by SF-36 MCS has not been associated with SSc subtype or number of clinical manifestations (35), our data show that those with worse functional disability have poorer mental health as measured by SF-36 MCS and PROMIS-29 anxiety and depression scores. Thus, functional disability may be more important than the underlying diagnosis in determining mental health and wellbeing.

The HAQ-DI is a composite score calculated as the mean of 8 categories of physical function, including eating, walking, hygiene and grip. The minimum possible change in HAQ-DI score between tests is ±0.125 units. We identified that HAQ-DI score trajectory was stable for 48% of the cohort and increased slowly (0.014 units/year) in the remainder. This is similar to previous estimates of 0.016 units over a mean of 7.5 months (12), to 0.022

units/year (13). Previous data demonstrating HAQ-DI responsiveness have focussed on cohorts with early dcSSc (10) and treatments affecting hand function (11), as hand function is a major determinant of HAQ-DI scores in SSc (8). Furthermore, we identified that 28% of the cohort recorded a minimum possible baseline HAQ-DI score (0), indicating a significant floor effect of the instrument. A similar floor effect of the HAQ-DI has been identified in gout (36). Together, these points raise concerns about the responsiveness of the HAQ-DI as an outcome measure, particularly in the measurement of change in individual study participants over a short follow-up period. However, physical function, functional disability and dependency are major concerns for patients and remain critically important to quantify (7). Accordingly, further consideration should be given to the most accurate and responsive methods of measuring functional impairment in SSc.

This study has limitations. Our cohort involved participants with <5 years disease duration at ASCS recruitment who had recorded multiple HAQ-DI scores. Ultimately, 60% of our cohort had two or more HAQ-DI scores recorded and were able to be included in GBTM, with lower frequency of dcSSc and mortality in participants recording ≥2 HAQ-DI scores eligible for inclusion. This suggests recording multiple HAQ-DI scores favoured a group with less severe SSc overall, as more unwell patients were less likely to complete and return PROM questionnaires. Additionally, cohort studies like the ASCS are characterised by a degree of "survivor-bias" where those with more severe disease and early mortality are less likely to survive to recruitment. Our cohort is likely to be biased towards a milder and more stable SSc phenotype. However, there is also a degree of selection bias involved in incident SSc cohorts, where those with more severe SSc features (*e.g.* digital ulceration) are more likely to be referred to a specialist centre and thus diagnosed and recruited with SSc within 5 years of disease onset. It is inherent to GBTM that the presented trajectories are those that best fit the data, rather than the actual trajectory of each participant. Furthermore, our cohort includes predominantly Caucasian participants, which limits the generalisability of these data to other ethnic groups. Additionally, some outcomes were rare (*e.g.* SRC or myositis) which limited the power of specific analyses. However, despite these limitations, we identified clinically meaningful trajectories of functional disability in SSc, and important phenotypic, prognostic and symptomatic differences between groups.

Conclusion

We identified two clear trajectories of functional disability as measured by HAQ-DI scores in an incident SSc cohort. Half of the cohort had high-increasing physical disability, while the remainder had low-stable levels of disability. Clear clinical differences were identified in those with a high-increasing trajectory of functional disability, particularly more frequent dcSSc, gastrointestinal and cardiopulmonary involvement independent on non-SSc multimorbidity. Those with a worse trajectory of functional disability clearly present with significant functional impairment within the first 5 years of disease suggesting that rapid deterioration early in disease is an important harbinger of a poor prognosis. Moreover, survival was poorer in those with greater disability, highlighting the prognostic importance of physical function. In addition, those with high-increasing disability reported consistently worse HRQoL, symptom burden and mental wellbeing. These data highlight the pervasive nature of physical disability in SSc, and the importance of physical function in both prognosis and the patient experience.

Competing interests

J.L. Fairley has received conference sponsorship from Pfizer and honoraria from Boehringer-Ingelheim.

S. Proudman has received honoraria from Janssen and Boehringer Ingelheim.

J. Sahhar and J. Walker have received honoraria from Boehringer-Ingelheim Pty Ltd.

L.V. Host has been a paid speaker for the Limbic publication and received honoraria from Abbvie.

W. Stevens has received consultancies from Jansen and Boehringer-Ingelheim.

M. Nikpour has received honoraria or consultancies from Janssen, AstraZeneca, GlaxoSmithKlein, Boehringer-Ingelheim and Bristol-Myers Squibb.

The other authors have declared no competing interests.

References

1. ZAGHLOL RS, DAWA GA, MAKARM WK: Functional disability among systemic sclerosis patients: relation to disease characteristics and quality of life parameters. *Curr Rheumatol Rev* 2022; 18(3): 257-65. https://doi.org/10.2174/1573397117666211130150241
2. GUILLEVIN L, HUNSCHE E, DENTON CP *et al.*: Functional impairment of systemic scleroderma patients with digital ulcerations: results from the DUO Registry. *Clin Exp Rheumatol* 2013; 31 (Suppl. 76): S71-80.
3. HOSSAIN S, CHOUDHURY MR, HAQUE MM, YEASMIN S, HOSSAIN F, ZAMAN MM: Functional disability and health-related quality of life among systemic sclerosis patients in Bangladesh. *BMC Rheumatol* 2022; 6(1): 60. https://doi.org/10.1186/s41927-022-00291-x
4. JAEGER VK, DISTLER O, MAURER B *et al.*: Functional disability and its predictors in systemic sclerosis: a study from the DeSScipher project within the EUSTAR group. *Rheumatology* (Oxford) 2018; 57(3): 441-50. https://doi.org/10.1093/rheumatology/kex182
5. VAN LEEUWEN NM, CIAFFI J, LIEM SIE, HUIZINGA TWJ, DE VRIES-BOUWSTRA JK: Health-related quality of life in patients with systemic sclerosis: evolution over time and main determinants. *Rheumatology* (Oxford) 2021; 60(8): 3646-55. https://doi.org/10.1093/rheumatology/keaa827
6. ROSS L, COSTELLO B, LINDQVIST A *et al.*: Disease specific determinants of cardiopulmonary fitness in systemic sclerosis. *Semin Arthritis Rheum* 2023; 58: 152137. https://doi.org/10.1016/j.semarthrit.2022.152137
7. SUAREZ-ALMAZOR ME, KALLEN MA, ROUNDTREE AK, MAYES M: Disease and symptom burden in systemic sclerosis: a patient perspective. *J Rheumatol* 2007; 34(8): 1718-26.
8. POPE J: Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). *Arthritis Care Res* (Hoboken) 2011; 63 Suppl. 11: S98-111. https://doi.org/10.1002/acr.205989.
9. STEEN VD, MEDSGER TA, JR.: The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate

change in systemic sclerosis patients over time. *Arthritis Rheum* 1997;40(11):1984-91. https://doi.org/10.1002/art.1780401110
10. KHANNA D, FURST DE, CLEMENTS PJ *et al*.: Responsiveness of the SF-36 and the Health Assessment Questionnaire Disability Index in a systemic sclerosis clinical trial. *J Rheumatol* 2005; 32(5): 832-40.
11. ZELENIETZ C, POPE J: Differences in disability as measured by the Health Assessment Questionnaire between patients with and without digital ulcers in systemic sclerosis: a post hoc analysis of pooled data from two randomised controlled trials in digital ulcers using bosentan. *Ann Rheum Dis* 2010; 69(11): 2055-56. https://doi.org/10.1136/ard.2009.122960
12. SEKHON S, POPE J, CANADIAN SCLERODERMA RESEARCH G, BARON M: The minimally important difference in clinical practice for patient-centered outcomes including health assessment questionnaire, fatigue, pain, sleep, global visual analog scale, and SF-36 in scleroderma. *J Rheumatol* 2010; 37(3): 591-98. https://doi.org/10.3899/jrheum.090375
13. SCHNITZER M, HUDSON M, BARON M *et al*.: Disability in systemic sclerosis -- a longitudinal observational study. *J Rheumatol* 2011; 38(4): 685-92. https://doi.org/10.3899/jrheum.100635
14. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al*.: 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72(11): 1747-55. https://doi.org/10.1136/annrheumdis-2013-204424
15. LEROY EC, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15(2): 202-5.
16. HUMBERT M, KOVACS G, HOEPER MM *et al*.: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; 61(1): 2200879. https://doi.org/10.1183/13993003.00879-2022
17. MEDSGER TA JR, BOMBARDIERI S, CZIRJAK L, SCORZA R, DELLA ROSSA A, BENCIVELLI W: Assessment of disease severity and prognosis. *Clin Exp Rheumatol* 2003; 21 (Suppl. 29): S42-46.
18. CHARLSON ME, POMPEI P, ALES KL, MACKENZIE CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5): 373-83. https://doi.org/10.1016/0021-9681(87)90171-8
19. CHARLSON M, WELLS MT, ULLMAN R, KING F, SHMUKLER C: The Charlson comorbidity index can be used prospectively to identify patients who will incur high future costs. *PLoS One* 2014; 9(12): e112479. https://doi.org/10.1371/journal.pone.0112479
20. JONES BN, NAGIN DS: A note on a Stata Plugin for estimating group-based trajectory models. *Sociological Methods Research* 2013; 42(4): 608-13. https://doi.org/10.1177/0049124113503141
21. NAGIN DS, ODGERS CL: Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010; 6: 109-38. https://doi.org/10.1146/annurev.clinpsy.121208.131413
22. OUIMET JM, POPE JE, GUTMANIS I, KOVAL J: Work disability in scleroderma is greater than in rheumatoid arthritis and is predicted by high HAQ scores. *Open Rheumatol J* 2008; 2: 44-52. https://doi.org/10.2174/1874312900802010044
23. MOEN K, ORMSTAD H, WANG-HANSEN MS, BROVOLD T: Physical function of elderly patients with multimorbidity upon acute hospital admission versus 3 weeks post-discharge. *Disabil Rehabil* 2018; 40(11): 1280-87. https://doi.org/10.1080/09638288.2017.1294211
24. WEI MY, KABETO MU, LANGA KM, MUKAMAL KJ: Multimorbidity and physical and cognitive function: performance of a new Multimorbidity-Weighted Index. *J Gerontol A Biol Sci Med Sci* 2018; 73(2): 225-32. https://doi.org/10.1093/gerona/glx114
25. POKEERBUX MR, GIOVANNELLI J, DAUCHET L *et al*.: Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. *Arthritis Res Ther* 2019; 21(1): 86. https://doi.org/10.1186/s13075-019-1867-1
26. HAO Y, HUDSON M, BARON M *et al*.: Early mortality in a multinational systemic sclerosis inception cohort. *Arthritis Rheumatol* 2017; 69(5): 1067-77. https://doi.org/10.1002/art.40027
27. ALLANORE Y, BOZZI S, TERLINDEN A *et al*.: Health Assessment Questionnaire-Disability Index (HAQ-DI) use in modelling disease progression in diffuse cutaneous systemic sclerosis: an analysis from the EUSTAR database. *Arthritis Res Ther* 2020; 22(1): 257. https://doi.org/10.1186/s13075-020-02329-2
28. CLEMENTS PJ, WONG WK, HURWITZ EL *et al*.: The Disability Index of the Health Assessment Questionnaire is a predictor and correlate of outcome in the high-dose versus low-dose penicillamine in systemic sclerosis trial. *Arthritis Rheum* 2001; 44(3): 653-61. https://doi.org/10.1002/1529-0131(200103)44:3%3C653::aid-anr114%3E3.0.co;2-q
29. FATIMA S, SCHIEIR O, VALOIS MF *et al*.: Health assessment questionnaire at one year predicts all-cause mortality in patients with early rheumatoid arthritis. *Arthritis Rheumatol* 2021; 73(2): 197-202. https://doi.org/10.1002/art.41513
30. PUGNET G, MARJANOVIC Z, DELIGNY C *et al*.: Reproducibility and utility of the 6-minute walk test in systemic sclerosis. *J Rheumatol* 2018; 45(9): 1273-80. https://doi.org/10.3899/jrheum.170994
31. TYNDALL AJ, BANNERT B, VONK M *et al*.: Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; 69(10): 1809-15. https://doi.org/10.1136/ard.2009.114264
32. FOOCHAROEN C, THINKHAMROP W, CHAICHAYA N, MAHAKKANUKRAUH A, SUWANNAROJ S, THINKHAMROP B: Development and validation of machine learning for early mortality in systemic sclerosis. *Sci Rep* 2022; 12(1): 17178. https://doi.org/10.1038/s41598-022-22161-9
33. BARON M, SUTTON E, HUDSON M *et al*.: The relationship of dyspnoea to function and quality of life in systemic sclerosis. *Ann Rheum Dis* 2008; 67(5): 644-50. https://doi.org/10.1136/ard.2007.075721
34. SANDUSKY SB, MCGUIRE L, SMITH MT, WIGLEY FM, HAYTHORNTHWAITE JA: Fatigue: an overlooked determinant of physical function in scleroderma. *Rheumatology* (Oxford) 2009; 48(2): 165-69. https://doi.org/10.1093/rheumatology/ken455
35. GEORGES C, CHASSANY O, TOLEDANO C *et al*.: Impact of pain in health-related quality of life of patients with systemic sclerosis. *Rheumatology* (Oxford) 2006; 45(10): 1298-302. https://doi.org/10.1093/rheumatology/kel189
36. TAYLOR WJ, COLVINE K, GREGORY K, COLLIS J, MCQUEEN FM, DALBETH N: The Health Assessment Questionnaire Disability Index is a valid measure of physical function in gout. *Clin Exp Rheumatol* 2008; 26(4): 620-26.