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Original article

Performance of the Patient-Reported Outcomes Measurement Information System-29 in scleroderma: a Scleroderma Patient-centered Intervention Network Cohort Study

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Abstract

Objective. The Patient-Reported Outcomes Measurement Information System (PROMIS)-29 assesses seven health-related quality of life domains plus pain intensity. The objective was to examine PROMIS-29v2 validity and explore clinical associations in patients with SSc.

Methods. English-speaking SSc patients in the Scleroderma Patient-centered Intervention Network Cohort from 26 sites in Canada, the USA and the UK completed the PROMIS-29v2 between July 2014 and November 2015. Enrolling physicians provided medical data. To examine convergent validity, hypotheses on the direction and magnitude of correlations with legacy measures were tested. For clinical associations, *t*-tests were conducted for dichotomous variables and PROMIS-29v2 domain scores. Effect sizes (ESs) were labelled as small (<0.25), small to moderate (0.25–0.45), moderate (0.46–0.55), moderate to large (0.56–0.75) and large (>0.75).

Results. There were 696 patients (87% female), mean (S.D.) disease duration 11.6 (8.7) years, 57% with limited cutaneous subtype. Validity indices were consistent with seven of nine hypotheses ($|r|$ =0.51–0.87, $P < 0.001$), with minor divergence for two hypotheses. Gastrointestinal involvement was associated with significantly worse outcomes for all eight PROMIS-29v2 domains (moderate or moderate to large ES in six of eight). Presence of joint contractures was associated with significant decrements in seven domains (small or small to moderate ESs). Skin thickening, diffuse cutaneous subtype and presence of overlap syndromes were significantly associated (small or small to moderate ESs) with five or six domains.

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Conclusion. This study further establishes the validity of the PROMIS-29v2 in SSc and underlines the importance of gastrointestinal symptoms and joint contractures in reduced health-related quality of life.

Key words: systemic sclerosis, quality of life, PROMIS, validation, clinical

Rheumatology key messages

- This study demonstrated the validity of the PROMIS-29v2 in a large international systemic sclerosis sample.
- Gastrointestinal involvement and joint contractures were the disease manifestations most consistently associated with worse outcomes in SSc

Introduction

SSc, or scleroderma is a rare, chronic, multisystem connective tissue disorder characterized by vascular injury, immune dysfunction and abnormal fibrotic processes that can affect multiple organ systems, including the skin, lungs, gastrointestinal (GI) tract and cardiovascular system [1–4]. SSc negatively impacts physical and mental health-related quality of life (HRQL). Limitations in physical mobility and hand function, pain, fatigue, sleep disturbance, depression and body image distress from disfiguring changes in appearance are common [5–9]. There is no proven cure for SSc. Thus a primary goal of care is to improve organ function and maintain HRQL by reducing distressing symptoms and associated disabilities.

The National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) initiative was established to develop, evaluate and standardize item banks for measuring patient-reported outcomes across medical conditions in order to facilitate access to efficient, precise, valid and responsive measures of health and wellbeing [10]. The PROMIS-29 Health Profile includes four items each for seven domains (physical function, anxiety, depression, fatigue, sleep disturbance, pain interference, ability to perform social roles), plus a single pain intensity item. Scores are standardized based on the general US population with a mean (S.D.) of 50 (10). Higher scores represent more of the domain being measured (e.g. greater sleep disturbance, greater ability to perform social roles). The PROMIS-29 is available in multiple languages, and available free-of-charge.

To date, two published studies [11, 12], which included data from 73 and 100 patients from single centres, have evaluated the construct validity and responsiveness of the PROMIS-29 in SSc. The purpose of the present study was to examine the construct validity of the PROMIS-29v2 in SSc patients enrolled in a large multinational study and to explore associations of PROMIS-29v2 domains with clinical variables.

Methods

Patients and procedure

The study sample consisted of participants enrolled in the Scleroderma Patient-centred Intervention Network (SPIN) Cohort [13] who completed study questionnaires from July 2014 through November 2015. Patients were enrolled at 26 centres from Canada, the USA and the UK. To be eligible for the SPIN Cohort, participants must be classified as having SSc according to 2013 ACR/EULAR criteria [14], be $\geqslant$18 years of age, be fluent in English, French or Spanish and be able to respond to questionnaires via the Internet. The SPIN sample is a convenience sample. Eligible participants are invited by attending physicians or supervised nurse coordinators from SPIN centres to participate, and written informed consent is obtained. The local SPIN investigator provides medical data, which triggers an email invitation to participants with instructions for activating their SPIN account and completing SPIN Cohort measures online. Participants complete outcome measures upon enrolment and subsequently every 3 months. Participants who completed all domains of the PROMIS-29v2 at baseline in English were included in the present study. The SPIN Cohort study was approved by the Research Ethics Committee of the Jewish General Hospital, Montréal, Canada and by the research ethics committees of each participating centre. This study had ethical approval from the Research Ethics Committee of the Jewish General Hospital.

Measures

Sociodemographic and medical data

Patients provided demographic data. SPIN physicians completed a medical data form including all items of the 2013 ACR/EULAR SSc classification criteria [14], as well as variables that were deemed to be important by SPIN rheumatologists ($\sim$13 experts in the treatment of SSc). Recruiting physicians provided time since first non-RP symptoms, onset of RP and diagnosis; SSc subtype (lcSSc or dcSSc) [15]; modified Rodnan skin score (mRSS) [16]; presence of overlap syndromes (SLE, RA, SS, idiopathic inflammatory myositis, primary biliary cirrhosis and/or autoimmune thyroid disease); and presence of joint contractures [no/mild (0–25%) *vs* moderate/severe ($>$25%) limit in range of motion]. GI tract involvement was dichotomized into oesophageal, stomach or intestinal involvement *vs* none. Lung disease was defined as pulmonary fibrosis seen on high-resolution CT or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of Velcro crackles on auscultation, not due to another cause such as congestive heart failure (yes/no), and pulmonary hypertension was defined as pulmonary arterial hypertension diagnosed by right-sided

heart catheterization according to standard definitions (yes/no).

PROMIS-29

The PROMIS-29 profile version 2.0 (PROMIS-29v2) [10, 11] measures patient-reported health status over the past 7 days, with four items for each of seven domains (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference) plus a single pain intensity item. Items are scored on a 5-point scale (range 1–5), with different response options for different domains. The single pain intensity item is measured on an 11-point rating scale (0 = no pain, 11 = worst imaginable pain). Higher scores represent more of the domain being measured; that is, better physical function and ability to participate in social roles and activities, but higher levels of anxiety, depression, fatigue, sleep disturbance, pain interference and pain intensity. Raw domain scores are obtained by summing item scores for each domain, which are converted into *t*-scores standardized for the general US population [mean (S.D.) 50 (10)]. Compared with PROMIS-29 version 1.0, the Satisfaction with Participation in Social Roles domain is replaced with the Ability to Participate in Social roles and activities domain in version 2.

Legacy measures

Functional disability was measured using the Disability Index of the HAQ (HAQ-DI) [17]. The HAQ-DI assesses eight disability categories over the past 7 days (dressing/grooming, arising, eating, walking, hygiene, reach, grip, common daily activities). Items are rated on a 4-point scale, ranging from 0 (without any difficulty) to 3 (unable to do), with higher scores indicating greater functional disability. The total score is the mean of the highest scores of each of the eight categories, ranging from 0 (no disability) to 3 (severe disability). The HAQ-DI is widely used in rheumatic diseases and has been validated in SSc [18, 19].

Standard numeric rating scales were completed for pain intensity in the past week, ranging from 0 (no pain) to 10 (very severe pain), and for pain interference, also ranging from 0 (pain does not limit activities) to 10 (very severe limitation).

The 18-item Cochin Hand Function Scale [20] was used to measure hand function limitations. Items are scored from 0 (performed without difficulty) to 5 (impossible to do). The total score is the sum of all item scores (range 0–90). The Cochin Hand Function Scale has been validated in SSc [21].

Symptoms of depression were measured using the 8-item Patient Health Questionnaire (PHQ-8) [22]. The PHQ-8 measures depressive symptoms over the last 2 weeks on a 4-point scale (0 = not at all to 3 = nearly every day) with items summed to a total score. The PHQ-8, which omits the ambiguous item 9 of the PHQ-9, performs equivalently to the PHQ-9 [23], which is a valid measure of depressive symptoms in SSc [24].

The 12-item Brief Fear of Negative Evaluation Scale (BFNE-II) [25] assesses the degree to which individuals worry about how they are perceived and evaluated by others. Items are rated on a 5-point scale, ranging from 0 (not characteristic of me at all) to 4 (extremely characteristic of me). Higher scores indicate greater fear. The BFNE-II has strong internal consistency, reliability and validity [25–27].

Statistical analyses

Means and SDs were calculated for PROMIS-29v2 domains. Floor effects are presented as the worst possible score, and ceiling effects as the best possible score (based on the total raw domain score), irrespective of the direction of the scale, and they were considered present if $\geqslant$15% of participants reported the worst or best possible score [28]. Internal consistency reliability for each domain was calculated using Cronbach's α.

To examine convergent validity, hypotheses on the direction and magnitude of Pearson's correlations with other outcome measures of related constructs were formulated *a priori* [29]. Magnitude of correlations was interpreted as small ($|r| \leqslant 0.3$), moderate ($0.3 < |r| < 0.5$) or large ($|r| \geqslant 0.5$) [30]. We expected to obtain large correlations of the PROMIS-29v2 domains with related legacy measures reflecting the same construct (e.g. PROMIS-29v2 physical function domain and HAQ-DI) and moderate correlations for PROMIS-29v2 domains with measures of related, but not fully overlapping, constructs [such as the PROMIS-29v2 anxiety domain and the BFNE (BFNE measures anxiety about being judged negatively, but not general anxiety as measured with PROMIS-29v2)].

For all PROMIS-29v2 domains, *t*-tests were conducted for gender and dichotomous clinical variables. A standardized mean effect size (ES) was calculated with 95% CI to assess the magnitude of differences between groups. Cohen's guidelines for interpreting and communicating ESs are small = 0.20, moderate = 0.50 and large = 0.80 [30]. In the present study, ESs within 0.05 of these guideposts were labelled with that guidepost, whereas other ESs were described as between two guidepost labels (i.e. <0.25 = small; 0.25–0.45 = small to moderate; 0.46–0.55 = moderate; 0.56–0.75 = moderate to large; >0.75 = large). Pearson correlations were calculated for PROMIS-29v2 domain scores with age, disease duration, and mRSS. All statistical analyses were conducted using Stata (Version 13).

Results

Sample characteristics

In total, 696 participants completed the PROMIS-29v2, including 88 men (13%) and 608 women (87%; Table 1). Most patients (73%) were married or living as married. Mean (S.D.) time since Raynaud's onset was 14.8 (12.0) years; mean (S.D.) time since first non-Raynaud's symptoms was 11.6 (8.7) years; mean (S.D.) time since diagnosis was 9.7 (8.0) years. Mean (S.D.) PROMIS-29v2 domain scores ranged from 42.6 (8.7) for physical function to 52.8 (8.7) for sleep problems. The mean (S.D.) pain intensity score was 3.7 (2.7). Compared with the US

Table 1 Demographic characteristics

Variable	Value (n = 696)
Demographic	
Age, mean (SD),[a] years	55.9 (11.8)
Female sex, n (%)	608 (87)
Education, mean (S.D.), years	15.4 (3.2)
Married or living as married, n (%)	505 (73)
Disease characteristics	
Time since onset first non-Raynaud's symptom[b] or sign, mean (S.D.),[b] years	11.6 (8.7)
Time since onset Raynaud's, mean (SD),[c] years	14.8 (12.0)
Time since diagnosis, mean (S.D.),[d] years	9.7 (8.0)
Limited/sine disease subtype, n (%)[e]	394 (57)
Diffuse disease subtype, n (%)[e]	295 (42)
Modified Rodnan Skin Score, mean (S.D.)[f]	8.1 (9.0)
Overlap syndrome, n (%)[g]	155 (23)
PROMIS-29v2 domain scores	
Physical function, mean (S.D.)	42.6 (8.7)
Anxiety, mean (S.D.)[h]	51.5 (9.8)
Depression, mean (S.D.)[h]	50.7 (9.3)
Fatigue, mean (S.D.)[h]	56.1 (11.0)
Sleep, mean (S.D.)[h]	52.8 (8.7)
Roles, mean (S.D)	47.5 (9.6)
Pain interference, mean (S.D.)[h]	56.1 (9.7)
Pain intensity, mean (S.D.)[h]	3.7 (2.7)

n = 696 unless otherwise stated. Due to missing values: [a]$n = 693$, [b]$n = 641$, [c]$n = 644$, [d]$n = 667$, [e]$n = 689$, [f]$n = 558$, [g]$n = 685$. [h]Higher scores reflect worse outcomes.

population, the mean PROMIS-29v2 domain scores were 0.7 S.D. lower (worse) for physical function, 0.6 S.D. higher (worse) for pain intensity and fatigue, 0.3 S.D. lower (worse) for social roles, 0.3 S.D. higher (worse) for sleep problems and similar for symptoms of depression (0.1 S.D. higher) and anxiety (0.2 S.D. higher).

Validity of the PROMIS-29v2

Ceiling effects (best possible outcome) were present for the PROMIS-29v2 anxiety ($n = 242$, 35%), depression ($n = 273$, 39%), pain interference ($n = 159$, 23%) and physical function ($n = 135$, 19%) domains. Additionally, roles ($n = 104$, 14.9%) was just under the 15% threshold for identifying ceiling effects. Cronbach's α was satisfactory for all domains, ranging from 0.86 (sleep) to 0.96 (fatigue).

As hypothesized, large correlations were found for physical function, symptoms of depression, fatigue, sleep and pain interference domains and the pain intensity item with legacy measures (Table 2). A large correlation was found for the social roles domain and the HAQ-DI functional disability measure ($r = -0.64$, *vs* hypothesized $0.3 < |r| < 0.5$), and the correlation between the anxiety domain and the BFNE measure was slightly higher than hypothesized ($r = 0.51$, *vs* $0.3 < |r| < 0.5$). Overall, seven of nine hypotheses (78%) were confirmed.

Associations of PROMIS-29v2 domains with clinical characteristics

Among continuous variables, all statistically significant correlations with PROMIS-29v2 domains were low to very low, $r < 0.25$. Associations of dichotomous clinical characteristics with the PROMIS-29v2 domains are displayed in Table 3 (function, fatigue and pain interference domains plus pain intensity item) and Table 4 (anxiety, depression, sleep and role domains). Only eight patients did not have RP, prohibiting comparisons between patients with and without RP.

Age and disease duration

Older age was statistically significantly associated ($P < 0.05$) with lower symptoms of anxiety ($r = -0.12$) and depression ($r = -0.12$) and lower fatigue ($r = -0.12$). Longer time since first non-Raynaud's symptom was statistically significantly associated with lower symptoms of anxiety ($r = -0.09$) and depression ($r = -0.08$). Similar patterns were found for associations between longer time since onset of RP and lower symptoms of anxiety ($r = -0.12$) and depression ($r = -0.10$), lower fatigue (-0.09) and greater ability to perform roles ($r = 0.08$). Dichotomously, longer disease duration (>2 years since first non-Raynaud's symptom) was associated with four domains: lower fatigue, higher depression, lower sleep and less satisfaction with roles (small to moderate ESs).

Skin involvement

Higher mRSS was associated with lower physical functioning ($r = -0.22$), less ability to perform roles ($r = -0.17$), greater pain interference and severity ($r = 0.14$ and $r = 0.15$, respectively) and higher symptoms of anxiety ($r = 0.09$) and sleep problems ($r = 0.09$). Presence of skin

Table 2 Hypotheses and correlations of PROMIS-29v2 domains and legacy instruments

PROMIS-29v2 domain	*n*	Legacy instrument(s)	Hypothesis for correlation[a]	Pearson correlation (95% CI)	Hypothesis confirmed
Function	690	HAQ-Disability Index (HAQ-DI)	Large, negative	−0.77 (−0.80, −0.74)	Yes
	685	Cochin Hand Function Scale	Large, negative	−0.56 (−0.61, −0.51)	Yes
Anxiety[b]	688	Brief Fear of Negative Evaluation	Moderate, positive	0.51 (0.45, 0.56)	No
Depression[b]	687	Patient Health Questionnaire (PHQ)-8	Large, positive	0.72 (0.68, 0.75)	Yes
Fatigue[b]	689	PHQ-8 item 4 (Feeling tired)	Large, positive	0.78 (0.75, 0.81)	Yes
Sleep disturbance[b]	688	PHQ-8 item 3 (Trouble sleeping)	Large, positive	0.68 (0.64, 0.72)	Yes
Social roles	690	HAQ-DI	Moderate, negative	−0.64 (−0.68, −0.59)	No
Pain interference[b]	688	Pain interference numeric rating scale	Large, positive	0.78 (0.75, 0.81)	Yes
Pain intensity[b]	688	Pain severity numeric rating scale	Large, positive	0.87 (0.87, 0.90)	Yes

[a]The magnitude of the correlations was interpreted as small ($|r| \leqslant 0.3$), moderate ($0.3 < |r| < 0.5$) or large ($|r| \geqslant 0.5$). [b]Higher scores reflect worse outcomes. PHQ: patient health questionnaire; HAQ-DI: disability index of the HAQ; PROMIS-29v2: Patient-Reported Outcomes Measurement Information System-29 version 2.

thickening was associated with greater pain interference (small to moderate ES), worse physical function, greater pain severity, higher symptoms of anxiety and depression and less ability to perform social roles (all small ESs). Patients with diffuse subtype had decrements in five domains (small or small to moderate ESs). The presence of telangiectasias was significantly associated with lower anxiety (small ES).

Organ involvement

Involvement of the GI tract was consistently associated with worse outcomes across all eight PROMIS-29v2 domains, with moderate or moderate to large ESs in six of eight domains. Lung disease, pulmonary hypertension, the presence of digital ulcers (at any time, now or in the past) were significantly associated with one to three domains.

Hand and joint involvement

Joint contractures (in small and/or large joints) were significantly associated with worse outcomes across seven of eight domains (small or small to moderate ESs). Current tendon friction rubs was associated with four domains (small to moderate ESs). The presence of digital ulcers (at any time, now or in the past) was significantly associated with two domains (small ESs).

Overlap syndromes

The presence of at least one overlap syndrome was associated with decrements in five domains (small or small to moderate ESs).

Discussion

The main finding of this study was that indices of convergent validity were generally consistent with study hypotheses, supporting the construct validity of the PROMIS-29v2 in SSc. There were ceiling effects (best possible outcomes) for the anxiety, depression, pain interference, physical function and roles domains. Among disease characteristics, involvement of the GI tract was consistently associated with worse outcomes across domains with moderate to large ESs in six of eight domains. Patients with joint contractures had decrements with small to moderate ESs for seven domains. Other clinical variables with decrements in at least five domains included: skin thickening, diffuse disease and presence of overlap syndromes (all small or small to moderate ESs).

As SSc is a rare disease, there is typically little comparative research available. An important advantage of the PROMIS system is the ability to compare and contextualize the results in relation to general US population scores and across conditions, facilitating the interpretation of research outcomes in SSc [31]. Compared with the US general population, the mean PROMIS-29v2 domain scores reflected between 0.1 and 0.7 S.D. worse physical and mental HRQL in patients with SSc. Consistent with evidence from previous studies, there were substantial decrements in the physical functioning (lower PROMIS-29v2 domain scores), and fatigue and pain interference domains (higher PROMIS-29v2 domain scores) [9, 32, 33]. There were almost no differences for the depression and anxiety domains, however, compared with the general population. This is consistent with findings of a study of 345 SSc patients enrolled in a Canadian registry that reported that prevalence of major depressive disorder for the past 30 days (4%) [34, 35] was higher than in the general population, but not substantially. It is also consistent with findings from a previous study that similarly found that mental health component scores of the SF-36 in 143 SSc patients were only 0.2 S.D. lower than general population scores [32].

Mean domain scores of the present study deviated minimally from the means reported in a previous study by Hinchcliff *et al.* [11] on the PROMIS-29 in 73 SSc patients (differences <1.3 points), except for the physical functioning and fatigue domains, for which patients in the SPIN Cohort on average reported worse outcomes (i.e. lower physical functioning score, higher fatigue score, differences >4 points). This may reflect differences between

Table 3 Mean differences of PROMIS-29v2 function, fatigue and pain domains between subjects with different disease characteristics

Variable	*n*	Function mean (s.d.)	Effect size (95% CI)	Fatigue[a] mean (s.d.)	Effect size (95% CI)	Pain[a] interference mean (s.d.)	Effect size (95% CI)	Pain[a] intensity mean (s.d.)	Effect size (95% CI)
Sex									
Female	608	42.7 (8.7)	0.12 (−0.11, 0.34)	56.3 (11.0)	0.11 (−0.11, 0.34)	56.1 (9.8)	−0.04 (−0.26, 0.19)	3.8 (2.7)	0.03 (−0.19, 0.25)
Male	88	41.7 (8.5)		55.0 (10.8)		56.5 (9.0)		3.7 (2.6)	
Disease subtype									
Limited/Sine	394	43.7 (8.8)	0.31* (0.16, 0.46)	55.7 (11.2)	−0.08 (−0.23, 0.07)	55.4 (9.5)	−0.17* (−0.32, −0.02)	3.6 (2.6)	−0.15 (−0.30, 0.00)
Diffuse	295	41.1 (8.5)		56.6 (10.6)		57.1 (9.8)		4.0 (2.7)	
Disease duration									
Early (⩽2 years)	52	41.2 (9.1)	−0.17 (−0.45, 0.11)	59.1 (10.3)	0.30* (0.01, 0.58)	56.8 (9.9)	0.08 (−0.21, 0.36)	3.9 (2.7)	0.05 (−0.23, 0.33)
Late (>2 years)	644	42.7 (8.7)		55.9 (11.0)		56.1 (9.7)		3.7 (2.7)	
Puffy fingers									
No	227	41.7 (8.5)	−0.12 (−0.28, 0.04)	57.0 (10.5)	0.08 (−0.08, 0.24)	56.5 (9.6)	0.02 (−0.14, 0.18)	3.7 (2.6)	−0.05 (−0.21, 0.11)
Yes	437	42.7 (8.8)		56.1 (11.0)		56.3 (9.7)		3.9 (2.7)	
Sclerodactyly									
No	118	43.2 (8.5)	0.08 (−0.12, 0.27)	56.2 (11.4)	0.01 (−0.19, 0.21)	55.6 (9.8)	−0.07 (−0.27, 0.13)	3.7 (2.7)	−0.02 (−0.22, 0.18]
Yes	574	42.5 (8.8)		56.1 (10.9)		56.3 (9.7)		3.8 (2.7)	
Skin thickening									
No	289	43.5 (8.5)	0.18* (0.03, 0.33)	55.4 (11.6)	−0.12 (−0.27, 0.04)	54.5 (9.8)	−0.30* (−0.45, −0.15)	3.4 (2.7)	−0.24* (−0.39, −0.09)
Yes	399	41.9 (8.8)		56.6 (10.4)		57.4 (9.5)		4.0 (2.7)	
Digital ulcers[b]									
No	422	43.0 (8.6)	0.11 (−0.04, 0.27)	55.9 (11.0)	−0.06 (−0.21, 0.09)	55.5 (9.7)	−0.18* (−0.33, −0.02)	3.5 (2.7)	−0.22* (−0.38, −0.07)
Yes	267	42.0 (9.0)		56.5 (10.9)		57.2 (9.6)		4.1 (2.7)	
Current tendon friction rubs									
No	559	43.1 (8.7)	040* (0.14, 0.65)	55.7 (11.1)	−0.25* (−0.51, 0.00)	55.67 (9.66)	−0.24 (−0.49, 0.01)	3.55 (2.62)	−0.41* (−0.66, −0.15)
Yes	68	39. 7 (8.1)		58.48 (9.5)		57.96 (9.68)		4.62 (2.73)	
Joint contractures[c]									
No	468	43.6 (8.7)	0.42* (0.25, 0.59)	55.7 (10.9)	−0.18* (−0.35, −0.01)	55.1 (9.6)	−0.39* (−0.56, −0.22)	3.4 (2.6)	−0.39* (−0.56, −0.22)
Yes	194	40.0 (8.3)		57.6 (10.6)		58.8 (9.5)		4.5 (2.7)	
Telangiectasias									
No	180	42.9 (8.1)	0.04 (−0.13, 0.21)	56.0 (10.6)	−0.01 (−0.18, 0.16)	55.4 (9.1)	−0.10 (−0.27, 0.07)	3.7 (2.6)	−0.01 (−0.18, 0.16)
Yes	509	42.5 (9.0)		56.1 (11.1)		56.4 (9.9)		3.8 (2.7)	
Overlap syndrome									
No	530	42.9 (8.6)	0.23* (0.05, 0.41)	55.7 (10.7)	−0.26* (−0.44, −0.09)	55.9 (9.5)	−0.20* (−0.38, −0.02)	3.7 (2.6)	−0.22* (−0.40, −0.04]
Yes	155	40.9 (8.7)		58.6 (10.8)		57.8 (9.9)		4.2 (2.8)	
Any GI involvement[d]									
No	79	47.4 (7.8)	0.63* (0.39, 0.87)	49.8 (9.8)	−0.67* (−0.91, −0.43)	51.8 (9.4)	−0.51* (−0.75, −0.27)	2.7 (2.6)	−0.47* (−0.70, −0.23)
Yes	617	42.0 (8.6)		56.9 (10.8)		56.7 (9.6)		3.9 (2.7)	
ILD									
No	426	43.5 (9.0)	0.28* (0.12, 0.44)	55.2 (11.0)	−0.19* (−0.34, −0.03)	55.7 (9.7)	−0.13 (−0.29, 0.02)	3.6 (2.7)	−0.09 (−0.24, 0.07)
Yes	250	41.0 (8.2)		57.3 (10.9)		57.0 (9.6)		3.9 (2.6)	
Pulmonary hypertension									
No	554	42.9 (8.8)	0.50* (0.23, 0.76)	56.1 (11.1)	−0.01 (−0.27, 0.25)	55.9 (9.7)	−0.26 (−0.52, 0.00)	3.7 (2.7)	−0.10 (−0.36, 0.17)
Yes	63	38.5 (8.8)		56.1 (10.5)		58.4 (10.1)		4.0 (2.6)	

[a]Higher scores reflect worse outcomes. [b]At any time, now or in the past. [c]Small and/or large joints. [d]Oesophageal, stomach and/or intestinal involvement. *Statistically significant (P=<0.05). GI: gastrointestinal; PROMIS-29v2: Patient-Reported Outcomes Measurement Information System-29 version 2.

Table 4 Mean differences of PROMIS-29v2 anxiety, depression, sleep and role domains between subjects with different disease characteristics

Variable	*n*	Anxiety[a] mean (S.D.)	Effect size (95% CI)	Depression[a] mean (S.D.)	Effect size (95% CI)	Sleep[a] mean (S.D.)	Effect size (95% CI)	Roles mean (S.D.)	Effect size (95% CI)
Sex									
Female	608	51.6 (9.9)	0.08 (−0.14, 0.30)	50.6 (9.3)	−0.08 (−0.31, 0.14)	52.8 (8.9)	−0.03 (−0.26, 0.19)	47.6 (9.5)	0.06 (−0.17, 0.28)
Male	88	50.8 (9.6)		51.4 (9.3)		53.1 (7.5)		47.1 (10.1)	
Disease subtype									
Limited/Sine	394	50.7 (9.8)	−0.19* (−0.34, −0.04)	49.9 (9.1)	−0.19* (−0.34, −0.04)	52.8 (8.9)	0.01 (−0.14, 0.16)	48.6 (9.7)	0.26* (0.11, 0.41)
Diffuse	295	52.5 (9.8)		51.7 (9.5)		52.8 (8.4)		46.1 (9.2)	
Disease duration									
Early (⩽ years)	52	53.2 (9.8)	0.18 (−0.10, 0.46)	47.0 (7.6)	−0.46* (−0.68, −0.23)	56.1 (9.1)	0.40* (0.12, 0.68)	51.6 (9.1)	0.48* (0.26, 0.71)
Late (> years)	644	51.4 (9.8)		51.2 (9.4)		52.6 (8.7)		47.0 (9.5)	
Puffy fingers									
No	227	51.9 (9.2)	0.02 (−0.14, 0.18)	51.1 (9.2)	0.02 (−0.14, 0.18)	52.3 (8.9)	−0.12 (−0.28, 0.05)	47.3 (9.4)	0.01 (−0.16, 0.16)
Yes	437	51.7 (10.2)		50.8 (9.5)		53.3 (8.8)		47.3 (9.6)	
Sclerodactyly									
No	118	51.8 (10.8)	0.05 (−0.15, 0.24)	51.4 (9.7)	0.09 (−0.11, 0.28)	52.7 (8.8)	−0.02 (−0.22, 0.18)	48.1 (9.4)	0.07 (−0.13, 0.26)
Yes	574	51.4 (9.7)		50.6 (9.3)		52.9 (8.7)		47.4 (9.7)	
Skin thickening									
No	289	50.2 (10.0)	−0.23* (−0.38, −0.08)	49.6 (9.2)	−0.21* (−0.37, −0.06)	52.5 (8.8)	−0.07 (−0.22, 0.08)	48.9 (9.8)	0.24* (0.09, 0.40)
Yes	399	52.5 (9.7)		51.6 (9.4)		53.1 (8.7)		46.6 (9.4)	
Digital ulcers[b]									
No	422	51.4 (9.8)	−0.03 (−0.19, 0.12)	50.5 (9.1)	−0.07 (−0.22, 0.09)	52.9 (8.5)	0.02 (−0.13, 0.18)	47.7 (9.6)	0.03 (−0.12, 0.18)
Yes	267	51.7 (10.0)		51.1 (9.7)		52.7 (9.2)		47.4 (9.8)	
Current tendon friction rubs									
No	559	51.3 (9.9)	−0.05 (−0.3, 0.21)	50.6 (9.4)	−0.10 (−0.35, 0.15)	52.4 (8.6)	−0.16 (−0.41, 0.09)	48.1 (9.6)	0.31* (0.06, 0.56)
Yes	68	51.8 (9.6)		51.5 (8.7)		53.8 (9.5)		45.1 (9.8)	
Joint contractures[c]									
No	468	50.9 (9.8)	−0.21* (−0.38, −0.04)	50.1 (9.0)	−0.26* (−0.43, −0.1)	52.6 (8.4)	−0.09 (−0.25, 0.08)	48.3 (9.5)	0.30* (0.13, 0.47)
Yes	194	53.0 (9.8)		52.5 (9.9)		53.3 (9.4)		45.5 (9.5)	
Telangiectasias									
No	180	52.9 (10.1)	0.19* (0.02, 0.36)	51.7 (9.5)	0.14 (−0.03, 0.31)	53.1 (8.4)	0.04 (−0.13, 0.21)	47.7 (8.6)	0.02 (−0.15, 0.19)
Yes	509	51.0 (9.7)		50.4 (9.2)		52.7 (8.9)		47.5 (9.9)	
Overlap syndrome									
No	530	51.5 (9.5)	−0.08 (−0.26, 0.10)	50.53 (9.1)	−0.14 (−0.32, 0.03)	52.8 (8.5)	−0.09 (−0.27, 0.09)	47.9 (9.4)	0.25* (0.07, 0.43)
Yes	155	52.3 (11.0)		51.88 (9.9)		53.6 (9.3)		45.5 (9.6)	
Any GI involvement[d]									
No	79	47.6 (8.6)	−0.45* (−0.69, −0.22)	46.2 (6.9)	−0.55* (−0.79, −0.32)	50.9 (8.8)	−0.26* (−0.49, −0.02)	52.3 (9.0)	0.57* (0.33, 0.80)
Yes	617	52.0 (9.9)		51.3 (9.4)		53.1 (8.7)		46.9 (9.5)	
ILD									
No	426	51.2 (9.7)	−0.07 (−0.22, 0.09)	50.1 (9.1)	−0.15 (−0.30, 0.01)	52.7 (8.8)	−0.02 (−0.18, 0.13)	48.2 (9.8)	0.19* (0.04, 0.35)
Yes	250	51.9 (10.1)		51.5 (9.7)		52.9 (8.5)		46.4 (9.2)	
Pulmonary hypertension									
No	554	51.6 (10.0)	0.01 (−0.25, 0.27)	50.7 (9.4)	−0.01 (−0.27, 0.25)	52.9 (8.9)	0.04 (−0.22, 0.30)	47.7 (9.6)	0.33* (0.06, 0.59)
Yes	63	51.5 (9.2)		50.8 (8.3)		52.5 (8.8)		44.6 (10.0)	

[a]Higher scores reflect worse outcomes. [b]At any time, now or in the past. [c]Small and/or large joints. [d]Oesophageal, stomach and/or intestinal involvement. *Statistically significant (P=<0.05). GI: gastrointestinal; ILD: interstitial lung disease; PROMIS-29v2: Patient-Reported Outcomes Measurement Information System-29 version 2.

samples, such as the shorter disease duration in the sample in Hinchcliff's study (7.2 years since the onset of the first non-Raynaud's symptom *vs* 11.6 years in the SPIN Cohort), but could also likely be due to sample variability in that study, as only 73 patients were included [11].

The correlations with legacy measures were comparable with the correlations previously reported by Hinchcliff *et al.* [11], although Hinchcliff *et al.* [11] examined only three PROMIS-29 domains. There were a number of domains with ceiling effects in our study. It is not clear, though, to what degree this reflects a true ceiling in which the measure does not capture the full spectrum of symptoms or if there is a proportion of patients that do not experience anxiety or depression, have little or no interference from pain or have good physical functioning and ability and meet their social roles [32]. The ceiling effects in our study were higher for the anxiety, depression and physical functioning domains than in a previous study using Computer Adaptive Test–administered PROMIS item banks [32]. Computer Adaptive Test administration of the PROMIS items banks may better cover the continuum of the concepts measured compared with the fixed format PROMIS-29v2, thereby reducing floor and ceiling effects. Future studies should assess whether these ceiling effects are a measurement artifact or accurately reflect real health status.

The present study has limitations that should be considered when interpreting results. First, the SPIN Cohort is a convenience sample, and participants complete questionnaires online, which may limit the generalizability of findings. Participants may differ from patients without internet access, for instance, in terms of age or education. The Cohort contains a higher than expected proportion of patients with diffuse disease, which may suggest a preponderance of patients with more severe disease or inadvertent sampling bias among study centres. Second, since the study used cross-sectional data, we did not evaluate test–retest reliability or sensitivity to change. Third, we assessed all clinical variables separately using bivariate analyses, but did not conduct multivariate analyses, since the purpose of the study was to assess measurement characteristics and provide a profile of patient characteristics associated with PROMIS-29v2 domains. Future studies should assess the complex interplay of clinical characteristics in more detail, ideally for each of the PROMS-29 domains separately. Fourth, there are no established minimal clinically important differences for the PROMIS-29v2 in SSc, limiting the interpretation of the clinical implications of our results. Finally, the PROMIS-29v2 was developed to measure symptoms and health concepts applicable to a range of chronic conditions, and may not in detail capture SSc-specific symptoms, such as appearance-related distress or hand function problems.

In conclusion, the results of this study support the construct validity of the PROMIS-29v2 in patients with SSc, facilitating its use in SSc and comparison and contextualizing of findings in comparison with the US general population as well as those with other chronic diseases. Data also inform priorities for future patient-centred research, particularly underlining the importance of GI symptoms and joint contractures in reduced HRQL across physical and mental health domains.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Clinical vignette

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A case of vanishing skull: Gorham's disease

Gorham's disease (GD) is a rare form of lymphangiomatosis associated with profound osteolysis. Outcome depends on the site affected. Small limb lesions can cause fractures, while spinal involvement or chylothorax associated with rib lesions can be life threatening. There is no consensus regarding treatment. Surgical resection and/or radiotherapy are most commonly used, but often unsuccessfully [1].

We report the case of an otherwise healthy female who presented at the age of 40 years with a small, painless skull indentation. Over the following 6 years the indentation evolved into an 11 $\times$ 11 cm cranial vault defect. There were no other abnormal findings on examination. Investigations were negative for malignancy, infection, biochemical and immunological abnormalities. CT demonstrated a defect in the occipital region (Fig. 1) but no abnormalities elsewhere in the skeletal system. A skull and dural biopsy confirmed GD.

Radiotherapy proved ineffective. Monthly 5 mg i.v. infusion of zoledronic acid was therefore commenced, with weekly s.c. pegylated IFN-α2b 35 μg. Clinical and radiological follow-up over 3 years demonstrated suppression of the osteolytic process with stabilization of the calvarial defect.

Lymphangiomatoses are non-malignant processes involving abnormal lymphatic proliferation. In GD, an increased number of osteoclasts are often present, which is thought to be promoted by elevated levels of IL-6 [2]. While IFN and bisphosphonate can provide effective therapy, cases with poor response may benefit from trials of anti-cytokine therapy or other biologic modulators in rheumatologic research settings.

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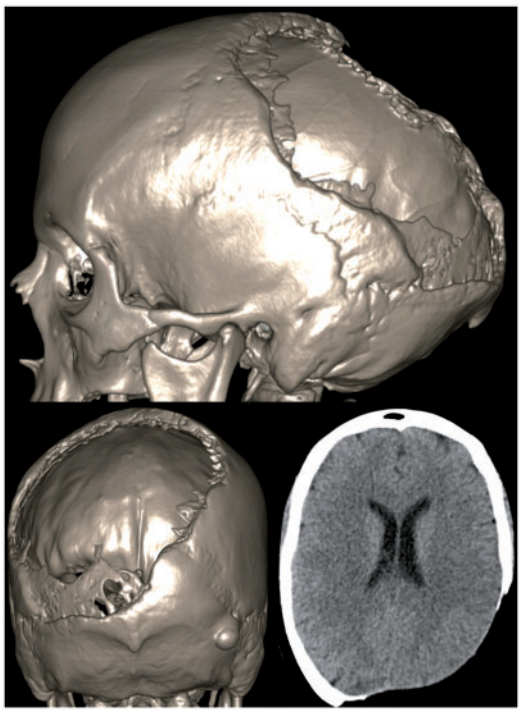
FIG. 1 CT head with 3D rendering of the skull defect



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