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Validation of the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29) in Scleroderma and Associations with Clinical Characteristics: A Scleroderma Patient-centered Intervention Network (SPIN) Cohort Study

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ABSTRACT

Objective: The Patient-Reported Outcomes Measurement Information System (PROMIS)-29 assesses 7 health-related quality of life (HRQL) domains plus pain intensity. The objective was to examine PROMIS-29v2 validity and explore clinical associations in patients with systemic sclerosis (SSc).

Methods: English-speaking SSc patients in the Scleroderma Patient-centered Intervention Network Cohort from 26 sites in Canada, the United States and the United Kingdom 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 clinical variables and PROMIS-29v2 domain scores. Effect sizes (ES) were labeled 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 disease duration 11.6 years (SD=8.7), 57% with limited cutaneous subtype. Validity indices were consistent with 7 of 9 hypotheses ($|r|$ =0.51-0.87, $p<0.001$) with minor divergence for 2 hypotheses. Gastrointestinal involvement was associated with significantly worse outcomes for all 8 PROMIS-29v2 domains (moderate or moderate to large ES in 6 of 8). Presence of joint contractures was associated with significant decrements in 7 domains (small or small to moderate ES). Skin thickening, diffuse cutaneous subtype, and presence of overlap syndromes were significantly associated (small or small to moderate ES) with 5 domains.

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 HRQL.

KEYWORDS:

Systemic sclerosis; Quality of life; PROMIS; Validation; Clinical

INTRODUCTION

Systemic sclerosis (SSc, or scleroderma) is a rare, chronic, multi-system connective tissue disorder characterized by vascular injury, immune dysfunction, and abnormal fibrotic processes that can affect multiple organ systems including the skin, lungs, gastrointestinal tract and cardiovascular system (1,2). Clinical manifestations of SSc include Raynaud's phenomenon (3), chronic gastrointestinal symptoms (4), and breathlessness due to pulmonary disease (1,2). 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 distressful symptoms and associated disabilities.

The 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 7 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 of 50 and standard deviation (SD) of 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), that included data from 73 and 100 patients from single centers 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.

PATIENTS AND METHODS

Patients and Procedure

The study sample consisted of participants enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort (13) who completed study questionnaires from July 2014 through November 2015. Patients were enrolled at 26 centers from Canada, the United States, and the United Kingdom. To be eligible for the SPIN Cohort, participants must be classified as having SSc according to 2013 ACR/EULAR criteria (14), be ≥ 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 centers 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 enrollment 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 center.

Measures

Sociodemographic and Medical Data. Patients provided demographic data. SPIN

physicians completed all items of the 2013 ACR/EULAR SSc classification criteria (14) and provided time since first non-Raynaud's phenomenon symptoms, onset of Raynaud's phenomenon, and diagnosis; SSc subtype (limited or diffuse cutaneous SSc) (15); modified Rodnan skin score (mRSS) (16); presence of overlap syndromes (systemic lupus erythematosus, rheumatoid arthritis, Sjögrens syndrome, idiopathic inflammatory myositis, primary biliary cirrhosis, and/or autoimmune thyroid disease); and presence of joint contractures (*no/mild (0-25%)* versus *moderate/severe (>25%)* limit in range of motion). Gastrointestinal tract involvement was dichotomized into esophageal, stomach or intestinal involvement versus none. Lung disease was defined as "pulmonary fibrosis seen on high-resolution computed tomography 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 4 items for each of 7 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=50, SD=10).

Legacy Measures. Functional disability was measured using the Disability Index of the Health Assessment Questionnaire (HAQ-DI) (17). The HAQ-DI assesses 8 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 8 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 (CHFS) (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 CHFS 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 were considered present if ≥ 15% of participants reported the worst or best possible score (28). Internal consistency reliability for each domain was calculated using Cronbach's alpha.

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 ($|r| \leq 0.3$), moderate ($0.3 < |r| < 0.5$), or large ($|r| \geq 0.5$) (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. This was the case, for instance, with the PROMIS-29v2 anxiety domain and the BFNE, since the 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% confidence interval (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 labeled 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 time since Raynaud's onset was 14.8 (SD=12.0) years; mean time since first non-Raynaud's symptoms was 11.6 (SD=8.7) years; mean time since diagnosis was 9.7 (SD=8.0) years. Mean PROMIS-29v2 domain scores ranged from 42.6 (SD=8.7) for physical function to 52.8 (SD=8.7) for sleep problems. The mean pain intensity score was 3.7 (SD=2.7). Compared to the US population, the mean PROMIS-29v2 domain scores were 0.7 SD lower (worse) for physical function, 0.6 SD higher (worse) for pain intensity and fatigue, 0.3 SD lower (worse) for social roles, 0.3 SD higher (worse) for sleep problems, and similar for symptoms of depression (0.1 SD higher) and anxiety (0.2 SD 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 alpha 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 ($r = -0.64$, versus hypothesized $0.3<|r|<0.5$), and the correlation between the anxiety domain and BFNE measure was slightly higher than hypothesized ($r=0.51$, versus $0.3<|r|<0.5$). Overall, 7 of 9 hypotheses (78%) were confirmed.

Associations of PROMIS-29v2 domains with clinical characteristics

Among continuous variables, all statistically significant correlations were less than 0.25. 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 Raynaud's phenomenon and lower symptoms of anxiety ($r=-0.12$) and depression ($r=-0.10$), lower fatigue (-0.09), and greater ability to perform roles ($r=0.08$). 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 ($r=0.09$).

Associations of dichotomous clinical characteristics with the PROMIS-29v2 domains are displayed in Tables 3a (function, fatigue, and pain interference domains plus pain intensity item) and 3b (anxiety, depression, sleep, and role domains). There were no statistically significant or

substantive differences between men and women for any domain. Diffuse subtype was significantly associated with lower physical function and less ability to perform social roles (small to moderate ESs), and greater pain interference and symptoms of anxiety and depression (all small ESs). Longer disease duration (>2 year since first non-Raynaud's symptom) was associated with lower fatigue and sleep disturbance (small to moderate ESs), greater depression symptoms and less ability to perform roles (moderate ESs). Presence of skin 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 ES). Involvement of the gastrointestinal tract was consistently associated with worse outcomes across all 8 PROMIS-29v2 domains, with moderate or moderate to large ES in 6 of 8 domains. Presence of digital ulcers (at any time, now or in the past) was significantly associated with more pain interference and intensity (small ES). Current tendon friction rubs were associated with worse physical function, greater pain interference and intensity, and less ability to perform roles (all small to moderate ES). Joint contractures (in small and/or large joints) were significantly associated with worse outcomes across 7 of 8 domains, with small to moderate ES for function, pain interference, pain intensity, depression, and social roles and small ES for fatigue, and anxiety. Presence of telangiectasias was significantly associated with less anxiety (small ES). Presence of at least one overlap syndrome was significantly associated with worse physical function, pain interference and severity (all small ES), as well as more fatigue and less ability to perform roles (small to moderate ES). Lung disease was associated with worse physical functioning (small to moderate ES), as well as more fatigue and less ability to perform roles (small ES). Pulmonary hypertension was associated with worse physical function (moderate to large ES) and less ability to perform roles (small to moderate ES).

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 ES in 6 of 8 domains. Patients with joint contractures had decrements with small to moderate ES for 7 domains. Other clinical variables with decrements in at least 5 domains included: skin thickening, diffuse disease, and presence of overlap syndromes (all small or small to moderate ES).

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 to the US general population, the mean PROMIS-29v2 domain scores reflected between 0.1 and 0.7 SD worse physical and mental HRQL in patients with SSc. Consistent with evidence from previous studies, there were substantial decrements in the physical functioning, fatigue, pain interference domains (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 (MDD) 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 SD 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 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 versus 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. examined only three PROMIS-29 domains 11). 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 does not experience anxiety or depression, has little or no interference from pain, or has good physical functioning and ability and meet their social roles (32). 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 in 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, and patients with severe disease may be unable or more likely to choose not to participate. 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.

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 to the US general population as well as other chronic diseases. Data also inform priorities for future patient-centered research, particularly underlining the importance of GI symptoms and joint contractures in reduced HRQL across physical and mental health domains.

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Table 1. Demographic characteristics (N=696)

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

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

[†]Higher scores reflect worse outcomes

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

PROMIS-29v2 domain	N	Legacy instrument(s)	Hypothesis for correlation[1]	Pearson correlation [95% CI]	Hypothesis confirmed
Function	690	Health Assessment Questionnaire-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	688	Brief Fear of Negative Evaluation	Moderate, positive	0.51 [0.45, 0.56]	No
Depression	687	Patient Health Questionnaire (PHQ)-8	Large, positive	0.72 [0.68, 0.75]	Yes
Fatigue	689	PHQ-8 item 4 (Feeling tired)	Large, positive	0.78 [0.75, 0.81]	Yes
Sleep disturbance	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	688	Pain interference numeric rating scale	Large, positive	0.78 [0.75, 0.81]	Yes
Pain intensity	688	Pain severity numeric rating scale	Large, positive	0.87 [0.87, 0.90]	Yes

[1]The magnitude of the correlations was interpreted as small ($|r| \leq 0.3$), moderate ($0.3 < |r| < 0.5$), or large ($|r| \geq 0.5$).

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

	N	Function M (SD)	Effect size [95% CI]	Fatigue M (SD)	Effect size [95%CI]	Pain interference M (SD)	Effect size [95% CI]	Pain intensity M (SD)	Effect size [95% CI]
Sex:									
Female	608	42.7 (8.7)	0.12	56.3 (11.0)	0.11	56.1 (9.8)	-0.04	3.8 (2.7)	0.03
Male	88	41.7 (8.5)	[-0.11, 0.34]	55.0 (10.8)	[-0.11, 0.34]	56.5 (9.0)	[-0.26, 0.19]	3.7 (2.6)	[-0.19, 0.25]
Disease subtype:									
Limited/Sine	394	43.7 (8.8)	**0.31**	55.7 (11.2)	-0.08	55.4 (9.5)	**-0.17**	3.6 (2.6)	-0.15
Diffuse	295	41.1 (8.5)	**[0.16, 0.46]**	56.6 (10.6)	[-0.23, 0.07]	57.1 (9.8)	**[-0.32, -0.02]**	4.0 (2.7)	[-0.30, 0.00]
Disease duration									
Early (≤2 years)	52	41.2 (9.1)	-0.17	59.1 (10.3)	**0.30**	56.8 (9.9)	0.08	3.9 (2.7)	0.05
Late (>2 years)	644	42.7 (8.7)	[-0.45, 0.11]	55.9 (11.0)	**[0.01, 0.58]**	56.1 (9.7)	[-0.21, 0.36]	3.7 (2.7)	[-0.23, 0.33]
Puffy fingers:									
No	227	41.7 (8.5)	-0.12	57.0 (10.5)	0.08	56.5 (9.6)	0.02	3.7 (2.6)	-0.05
Yes	437	42.7 (8.8)	[-0.28, 0.04]	56.1 (11.0)	[-0.08, 0.24]	56.3 (9.7)	[-0.14, 0.18]	3.9 (2.7)	[-0.21, 0.11]
Sclerodactyly:									
No	118	43.2 (8.5)	0.08	56.2 (11.4)	0.01	55.6 (9.8)	-0.07	3.7 (2.7)	-0.02
Yes	574	42.5 (8.8)	[-0.12, 0.27]	56.1 (10.9)	[-0.19, 0.21]	56.3 (9.7)	[-0.27, 0.13]	3.8 (2.7)	[-0.22, 0.18]
Skin thickening:									
No	289	43.5 (8.5)	**0.18**	55.4 (11.6)	-0.12	54.5 (9.8)	**-0.30**	3.4 (2.7)	**-0.24**
Yes	399	41.9 (8.8)	**[0.03, 0.33]**	56.6 (10.4)	[-0.27, 0.04]	57.4 (9.5)	**[-0.45, -0.15]**	4.0 (2.7)	**[-0.39, -0.09]**
Digital ulcers[1]:									
No	422	43.0 (8.6)	0.11	55.9 (11.0)	-0.06	55.5 (9.7)	**-0.18**	3.5 (2.7)	**-0.22**
Yes	267	42.0 (9.0)	[-0.04, 0.27]	56.5 (10.9)	[-0.21, 0.09]	57.2 (9.6)	**[-0.33, -0.02]**	4.1 (2.7)	**[-0.38, -0.07]**
Current tendon friction rubs:									
No	559	43.1 (8.7)	**0.40**	55.7 (11.1)	**-0.25**	55.67 (9.66)	-0.24	3.55 (2.62)	**-0.41**
Yes	68	39. 7 (8.1)	**[0.14, 0.65]**	58.48 (9.5)	**[-0.51, 0.00]**	57.96 (9.68)	[-0.49, 0.01]	4.62 (2.73)	**[-0.66, -0.15]**

Joint contractures[2]:									
No	468	43.6 (8.7)	**0.42**	55.7 (10.9)	**-0.18**	55.1 (9.6)	**-0.39**	3.4 (2.6)	**-0.39**
Yes	194	40.0 (8.3)	**[0.25, 0.59]**	57.6 (10.6)	**[-0.35, -0.01]**	58.8 (9.5)	**[-0.56, -0.22]**	4.5 (2.7)	**[-0.56, -0.22]**
Telangiectasias:									
No	180	42.9 (8.1)	0.04	56.0 (10.6)	-0.01	55.4 (9.1)	-0.10	3.7 (2.6)	-0.01
Yes	509	42.5 (9.0)	[-0.13, 0.21]	56.1 (11.1)	[-0.18, 0.16]	56.4 (9.9)	[-0.27, 0.07]	3.8 (2.7)	[-0.18, 0.16]
Overlap syndrome:									
No	530	42.9 (8.6)	**0.23**	55.7 (10.7)	**-0.26**	55.9 (9.5)	**-0.20**	3.7 (2.6)	**-0.22**
Yes	155	40.9 (8.7)	**[0.05, 0.41]**	58.6 (10.8)	**[-0.44, -0.09**]	57.8 (9.9)	**[-0.38, -0.02]**	4.2 (2.8)	**[-0.40, -0.04]**
Any GI involvement[3]:									
No	79	47.4 (7.8)	**0.63**	49.8 (9.8)	**-0.67**	51.8 (9.4)	**-0.51**	2.7 (2.6)	**-0.47**
Yes	617	42.0 (8.6)	**[0.39, 0.87]**	56.9 (10.8)	**[-0.91, -0.43]**	56.7 (9.6)	**[-0.75, -0.27]**	3.9 (2.7)	**[-0.70, -0.23]**
Interstitial Lung disease:									
No	426	43.5 (9.0)	**0.28**	55.2 (11.0)	**-0.19**	55.7 (9.7)	-0.13	3.6 (2.7)	-0.09
Yes	250	41.0 (8.2)	**[0.12, 0.44]**	57.3 (10.9)	**[-0.34, -0.03]**	57.0 (9.6)	[-0.29, 0.02]	3.9 (2.6)	[-0.24, 0.07]
Pulmonary hypertension:									
No	554	42.9 (8.8)	**0.50**	56.1 (11.1)	-0.01	55.9 (9.7)	-0.26	3.7 (2.7)	-0.10
Yes	63	38.5 (8.8)	**[0.23, 0.76]**	56.1 (10.5)	[-0.27, 0.25]	58.4 (10.1)	[-0.52, 0.00]	4.0 (2.6)	[-0.36, 0.17]

[1]At any time, now or in the past; [2]small and/or large joints; [3]Esophageal, stomach and/or intestinal involvement

492 **Table 3b.** Mean differences of PROMIS-29v2 anxiety, depression, sleep, and role domains between subjects with different disease

493 characteristics

	N	Anxiety M (SD)	Effect size [95% CI]	Depression M (SD)	Effect size [95% CI]	Sleep M (SD)	Effect size [95% CI]	Roles M (SD)	Effect size [95% CI]
Sex:									
Female	608	51.6 (9.9)	0.08	50.6 (9.3)	-0.08	52.8 (8.9)	-0.03	47.6 (9.5)	0.06
Male	88	50.8 (9.6)	[-0.14, 0.30]	51.4 (9.3)	[-0.31, 0.14]	53.1 (7.5)	[-0.26, 0.19]	47.1 (10.1)	[-0.17, 0.28]
Disease subtype:									
Limited/Sine	394	50.7 (9.8)	**-0.19**	49.9 (9.1)	**-0.19**	52.8 (8.9)	0.01	48.6 (9.7)	**0.26**
Diffuse	295	52.5 (9.8)	**[-0.34, -0.04]**	51.7 (9.5)	**[-0.34, -0.04]**	52.8 (8.4)	[-0.14, 0.16]	46.1 (9.2)	**[0.11, 0.41]**
Disease duration									
Early (≤2 years)	52	53.2 (9.8)	0.18	47.0 (7.6)	**-0.46**	56.1 (9.1)	**0.40**	51.6 (9.1)	**0.48**
Late (>2 years)	644	51.4 (9.8)	[-0.10, 0.46]	51.2 (9.4)	**[-0.68, -0.23]**	52.6 (8.7)	**[0.12, 0.68]**	47.0 (9.5)	**[0.26, 0.71]**
Puffy fingers:									
No	227	51.9 (9.2)	0.02	51.1 (9.2)	0.02	52.3 (8.9)	-0.12	47.3 (9.4)	0.01
Yes	437	51.7 (10.2)	[-0.14, 0.18]	50.8 (9.5)	[-0.14, 0.18]	53.3 (8.8)	[-0.28, 0.05]	47.3 (9.6)	[-0.16, 0.16]
Sclerodactyly:									
No	118	51.8 (10.8)	0.05	51.4 (9.7)	0.09	52.7 (8.8)	-0.02	48.1 (9.4)	0.07
Yes	574	51.4 (9.7)	[-0.15, 0.24]	50.6 (9.3)	[-0.11, 0.28]	52.9 (8.7)	[-0.22, 0.18]	47.4 (9.7)	[-0.13, 0.26]
Skin thickening:									
No	289	50.2 (10.0)	**-0.23**	49.6 (9.2)	**-0.21**	52.5 (8.8)	-0.07	48.9 (9.8)	**0.24**
Yes	399	52.5 (9.7)	**[-0.38, -0.08]**	51.6 (9.4)	**[-0.37, -0.06]**	53.1 (8.7)	[-0.22, 0.08]	46.6 (9.4)	**[0.09, 0.40]**
Digital ulcers[1]:									
No	422	51.4 (9.8)	-0.03	50.5 (9.1)	-0.07	52.9 (8.5)	0.02	47.7 (9.6)	0.03
Yes	267	51.7 (10.0)	[-0.19, 0.12]	51.1 (9.7)	[-0.22, 0.09]	52.7 (9.2)	[-0.13, 0.18]	47.4 (9.8)	[-0.12, 0.18]
Current tendon friction rubs:									
No	559	51.3 (9.9)	-0.05	50.6 (9.4)	-0.10	52.4 (8.6)	-0.16	48.1 (9.6)	**0.31**
Yes	68	51.8 (9.6)	[-0.3, 0.21]	51.5 (8.7)	[-0.35, 0.15]	53.8 (9.5)	[-0.41, 0.09]	45.1 (9.8)	**[0.06, 0.56]**

Joint contractures[2]:									
No	468	50.9 (9.8)	**-0.21**	50.1 (9.0)	**-0.26**	52.6 (8.4)	-0.09	48.3 (9.5)	**0.30**
Yes	194	53.0 (9.8)	**[-0.38, -0.04]**	52.5 (9.9)	**[-0.43, -0.1]**	53.3 (9.4)	[-0.25, 0.08]	45.5 (9.5)	**[0.13, 0.47]**
Telangiectasias:									
No	180	52.9 (10.1)	**0.19**	51.7 (9.5)	0.14	53.1 (8.4)	0.04	47.7 (8.6)	0.02
Yes	509	51.0 (9.7)	**[0.02, 0.36**]	50.4 (9.2)	[-0.03, 0.31]	52.7 (8.9)	[-0.13, 0.21]	47.5 (9.9)	[-0.15, 0.19]
Overlap syndrome:									
No	530	51.5 (9.5)	-0.08	50.53 (9.1)	-0.14	52.8 (8.5)	-0.09	47.9 (9.4)	**0.25**
Yes	155	52.3 (11.0)	[-0.26, 0.10]	51.88 (9.9)	[-0.32, 0.03]	53.6 (9.3)	[-0.27, 0.09]	45.5 (9.6)	**[0.07, 0.43]**
Any GI involvement[3]:									
No	79	47.6 (8.6)	**-0.45**	46.2 (6.9)	**-0.55**	50.9 (8.8)	**-0.26**	52.3 (9.0)	**0.57**
Yes	617	52.0 (9.9)	**[-0.69, -0.22]**	51.3 (9.4)	**[-0.79, -0.32]**	53.1 (8.7)	**[-0.49, -0.02]**	46.9 (9.5)	**[0.33, 0.80]**
Esophageal involvement:									
No	88	48.4 (9.0)	**-0.36**	47.0 (7.6)	**-0.46**	50.8 (8.8)	**-0.27**	51.6 (9.1)	**0.48**
Yes	607	51.9 (9.9)	**[-0.59, -0.14]**	51.2 (9.4)	**[-0.68, -0.23]**	53.2 (8.7)	**[-0.50, -0.05]**	47.0 (9.5)	**[0.26, 0.71]**
Interstitial Lung disease:									
No	426	51.2 (9.7)	-0.07	50.1 (9.1)	-0.15	52.7 (8.8)	-0.02	48.2 (9.8)	**0.19**
Yes	250	51.9 (10.1)	[-0.22, 0.09]	51.5 (9.7)	[-0.30, 0.01]	52.9 (8.5)	[-0.18, 0.13]	46.4 (9.2)	**[0.04, 0.35]**
Pulmonary hypertension:									
No	554	51.6 (10.0)	0.01	50.7 (9.4)	-0.01	52.9 (8.9)	0.04	47.7 (9.6)	**0.33**
Yes	63	51.5 (9.2)	[-0.25, 0.27]	50.8 (8.3)	[-0.27, 0.25]	52.5 (8.8)	[-0.22, 0.30]	44.6 (10.0)	**[0.06, 0.59]**

[1]At any time, now or in the past; [2]small and/or large joints; [3]Esophageal, stomach and/or intestinal involvement