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LETTER TO THE EDITOR

Reduced Health-Related Quality of Life in Patients With Systemic Sclerosis: A Cross-Sectional Analysis of PROMIS Global Health Data From the International COVAD-2 e-Survey

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Dear Editor,

Systemic sclerosis (SSc) is a multisystem disorder characterized by autoimmunity, fibrosis of the skin and internal organs, and vasculopathy [1–3]. SSc is associated with altered physical function, pain, and psychological consequences including depression and anxiety [4–7], leading to impaired health-related quality of life (HRQoL) [8]. However, there remains an unmet need for a thorough evaluation of the HRQoL status and its determinants in SSc patients.

Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of person-centered measures that evaluate and monitor physical, mental, and social health in individuals living with or without chronic conditions [9]. As for HRQoL, PROMIS global physical health (GPH) and global mental health (GMH) scores have demonstrated favorable reliability in evaluating physical and mental health [10]. In this study, we investigated PROMIS GMH and GPH scores in a global cohort of patients with SSc compared to those with non-SSc autoimmune inflammatory rheumatic diseases (AIRDs), non-rheumatic autoimmune diseases (nrAIDs), and individuals without autoimmune diseases using PROMIS global health data obtained through the second COVID-19 vaccination in autoimmune disease (COVAD-2) survey.

The complete list of authors part of the COVAD Study Group, as well as their affiliations, are provided in Supporting Information.

Vikas Agarwal and Masataka Kuwana are co-senior authors.

The COVAD-2 study is an international, multicenter, self-reported e-survey designed to evaluate several facets covering COVID-19 infection and vaccination as well as validated patient-reported outcome measures (PROMs) in a variety of autoimmune diseases including SSc, which was conducted between February and June 2022. The detailed study design was published elsewhere [11]. Data on demographics, diagnosis of autoimmune diseases including the subtypes of SSc [12], clinical characteristics, patient-reported disease activity assessed using a 4-point scale (inactive, active but stable, active and improving, active and worsening), and PROMs including PROMIS global health items were extracted from the COVAD-2 database. The COVAD-2 survey form questions relevant to the present study are presented in Table S1. Respondents were divided into four disease groups: SSc, non-SSc AIRDs, nrAIDs, and those without autoimmune diseases (controls). Comorbidities were grouped into several categories to avoid extreme sparsity in the design matrix (Figure S1).

The primary outcomes were PROMIS GPH and GMH scores calculated using PROMIS global health items as previously described [10], in which higher scores indicated better HRQoL. Secondary outcomes included PROMIS Short Form v2.0 Physical Function-10a (PROMIS PF-10a), pain visual analog scale (VAS), and PROMIS Short Form v1.0 Fatigue 4a (PROMIS Fatigue-4a) scores. Higher PROMIS PF-10a scores indicate better physical function, while higher PROMIS Fatigue-4a scores suggest increased fatigue. Continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (25%–75%) as appropriate, whereas categorical variables were reported as frequencies with proportions. We employed analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables, and the chi-square test or Fisher's exact tests for categorical variables, respectively. *p*-values were adjusted using Dunnett's test for continuous variables and the Bonferroni method for categorical variables where we performed multiple comparisons. Demographics, clinical characteristics, and PROMs were compared between SSc and the other three disease groups, followed by stratification according to SSc phenotype. Factors associated with lower PROMIS GPH or GMH scores in SSc patients were identified using multivariable regression analysis. Along with clinical context, we employed the least absolute shrinkage and selection operator (LASSO) regression to address multicollinearity and select the optimal set of variables incorporated into multivariable models. Variables with non-zero coefficients in the LASSO regression model were incorporated into multivariable models. A linear regression model was employed to perform multivariable analysis. As for variables with more than 10% of missing data, we performed a sensitivity analysis excluding the variables.

A total of 9277 responses from 261 SSc, 5441 non-SSc AIRD, 465 nrAID patients, and 3110 controls as of May 2022 were included in the analysis (Figure S2). Rheumatoid arthritis (32.4%) was the most common non-SSc AIRD, followed by systemic lupus erythematosus (22.6%) and idiopathic inflammatory myopathies (17.7%). In terms of nrAIDs, autoimmune thyroid disease (58.7%) was the most common, followed by inflammatory bowel disease (21.9%) and type 1 diabetes (10.1%). Table S2 summarizes the demographics and clinical characteristics of participants in each disease group. Patients with SSc reported a higher prevalence of interstitial lung disease (ILD) and treatment with mycophenolate mofetil (MMF) compared to those in other disease groups ($p < 0.001$). Among the SSc group, diffuse cutaneous SSc (dcSSc) patients accounted for 46% and received MMF more frequently than those with limited cutaneous SSc (lcSSc) ($p < 0.001$) (Table S3).

Patients with SSc had lower GPH median scores compared to those with nrAIDs or controls (SSc: 13 [IQR 11–15] vs. non-SSc AIRDs: 13 [11–15] vs. nrAIDs: 15 [13–17] vs. controls: 17 [15–18], $p < 0.001$) (Figure 1A). The GMH median scores were also lower in SSc compared to nrAIDs or controls (SSc: 13 [IQR 10–15] vs. non-SSc AIRDs: 13 [10–15] vs. nrAIDs: 13 [11–16] vs. controls: 15 [13–17], $p < 0.001$) (Figure 1B). SSc was independently associated with lower PROMIS GPH and GMH scores in the entire cohort when adjusted for demographics and comorbidities (Table S4). Consistent with these findings, patients with SSc reported lower PROMIS PF-10a median scores (Figure 1C) and higher median pain VAS (Figure 1D) and PROMIS Fatigue-4a scores (Figure 1E) compared to those with nrAIDs or controls.

When stratified by SSc subtypes, PROMIS GPH (dcSSc: 12 [IQR 10–14] vs. lcSSc: 14 [11–16], $p < 0.001$) (Figure 2A) and PROMIS GMH (dcSSc: 12 [IQR 10–14] vs. lcSSc: 13 [10–15], $p = 0.013$) (Figure 2B) median scores were lower in dcSSc than in lcSSc. PROMIS PF-10a median scores (Figure 2C) were lower, whereas pain VAS (Figure 2D) and PROMIS Fatigue-4a (Figure 2E) median scores were higher in dcSSc.

Multivariable regression analyses were performed to identify factors independently associated with PROMIS GPH or GMH scores in SSc patients. The independent factors for lower PROMIS GPH scores in SSc included dcSSc subtype ($p = 0.046$), mental disorder ($p < 0.001$), disease activity (active and getting worse) ($p = 0.003$), and low- or medium-dose glucocorticoid (GC) use (prednisolone/prednisone-equivalent dose of < 10 mg/day: $p < 0.001$; 10–20 mg/day: $p = 0.001$) (Table S5A). On the other hand, longer disease duration ($p = 0.044$) and higher PROMIS Fatigue-4a scores ($p < 0.001$) were identified as independent factors for lower PROMIS GMH scores in SSc (Table S5B). We also performed sensitivity analyses excluding disease activity from covariates, considering more than 10% of missing data in patient-reported disease activity. The independent factors associated with lower PROMIS GPH scores or GMH scores were largely consistent with the primary analysis (Table S6A,B).

Our large-scale, global e-survey demonstrated that both mental and physical health were significantly impaired in SSc patients compared to those with nrAIDs or those without autoimmune diseases, and the level of impairment was comparable to those with non-SSc AIRDs. Patients with dcSSc had significantly lower PROMIS GPH and GMH scores than those with lcSSc, indicating considerable impairment of HRQoL in dcSSc, which is consistent with a previous report [13]. Factors associated with lower PROMIS GPH scores in SSc patients included dcSSc subtype, mental disorders, and GC use. On the other hand, only higher PROMIS Fatigue-4a scores were associated with lower PROMIS

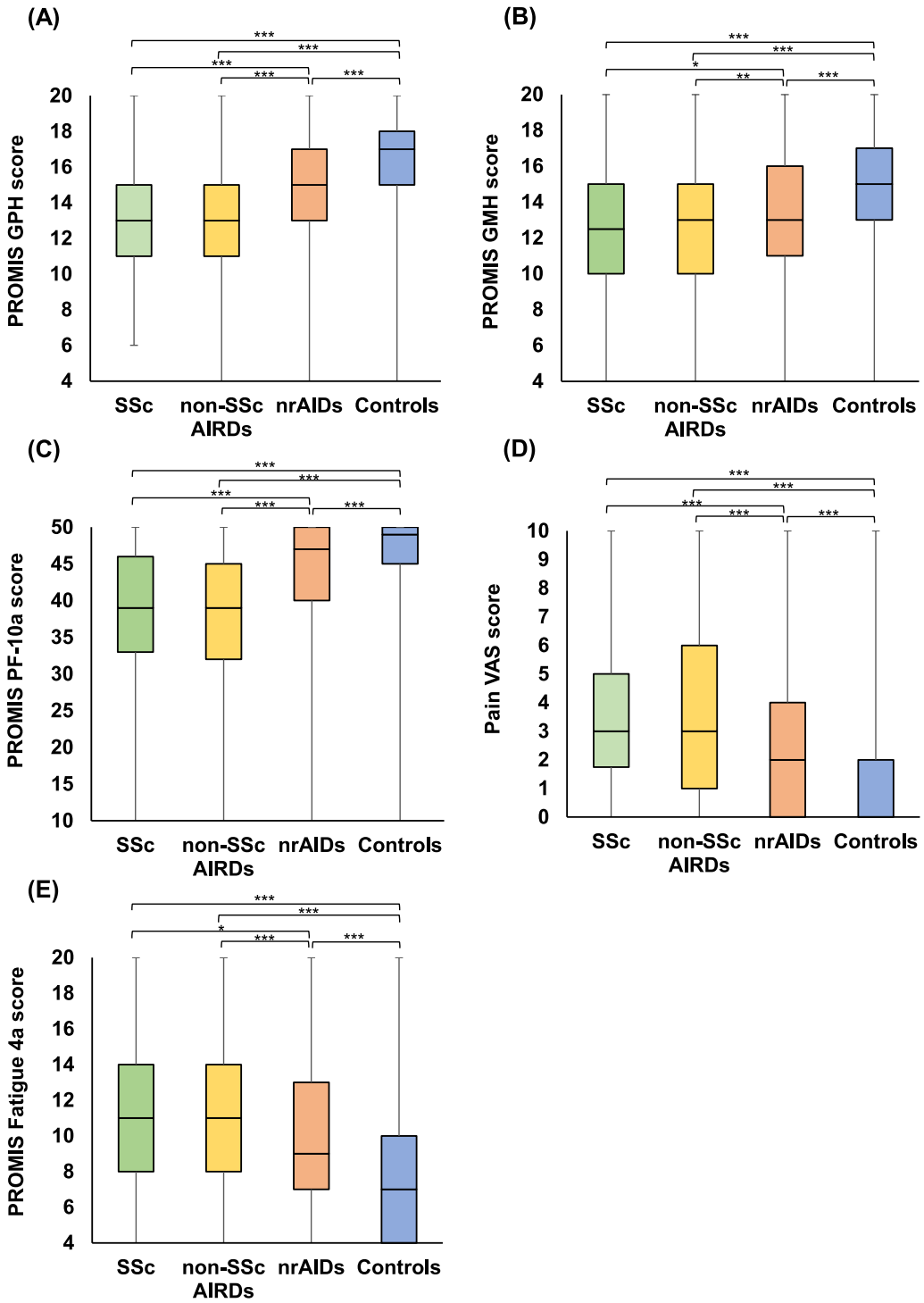

FIGURE 1 | Patient-reported outcomes in each disease group. (A) PROMIS GPH score†, (B) PROMIS GMH score††, (C) Pain VAS, (D) PROMIS PF-10a score, (E) PROMIS Fatigue-4a score, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; AIRDs, autoimmune inflammatory rheumatic diseases; GMH, global mental health; GPH, global physical health; nrAIDs, non-rheumatic autoimmune inflammatory diseases; PF, physical function; PROMIS, Patient-Reported Outcome Measurement Information System; SSc, systemic sclerosis; VAS, visual analog scale.

GMH scores in SSc, suggesting that fatigue is the major determinant of impaired mental health and needs greater attention to optimize mental health in SSc.

Our study has the advantage of being the first, global evaluation of PROMIS global health items in SSc patients using the large-scale international COVAD-2 database. Our study has several limitations. First, we acknowledge selection bias owing to convenience sampling, as well as information bias inherent to self-reported e-surveys. Given the fluctuating disease course and inter-individual variability in disease perception, subjective bias could have affected the patient-reported disease activity. Moreover, although PROMIS-29 demonstrated reliability and construct validity in a cohort of SSc-ILD patients [14], PROMIS GPH, GMH, PF-10a, and Fatigue-4a short forms have not been validated in an academic cohort of SSc. Second, organ involvement in SSc

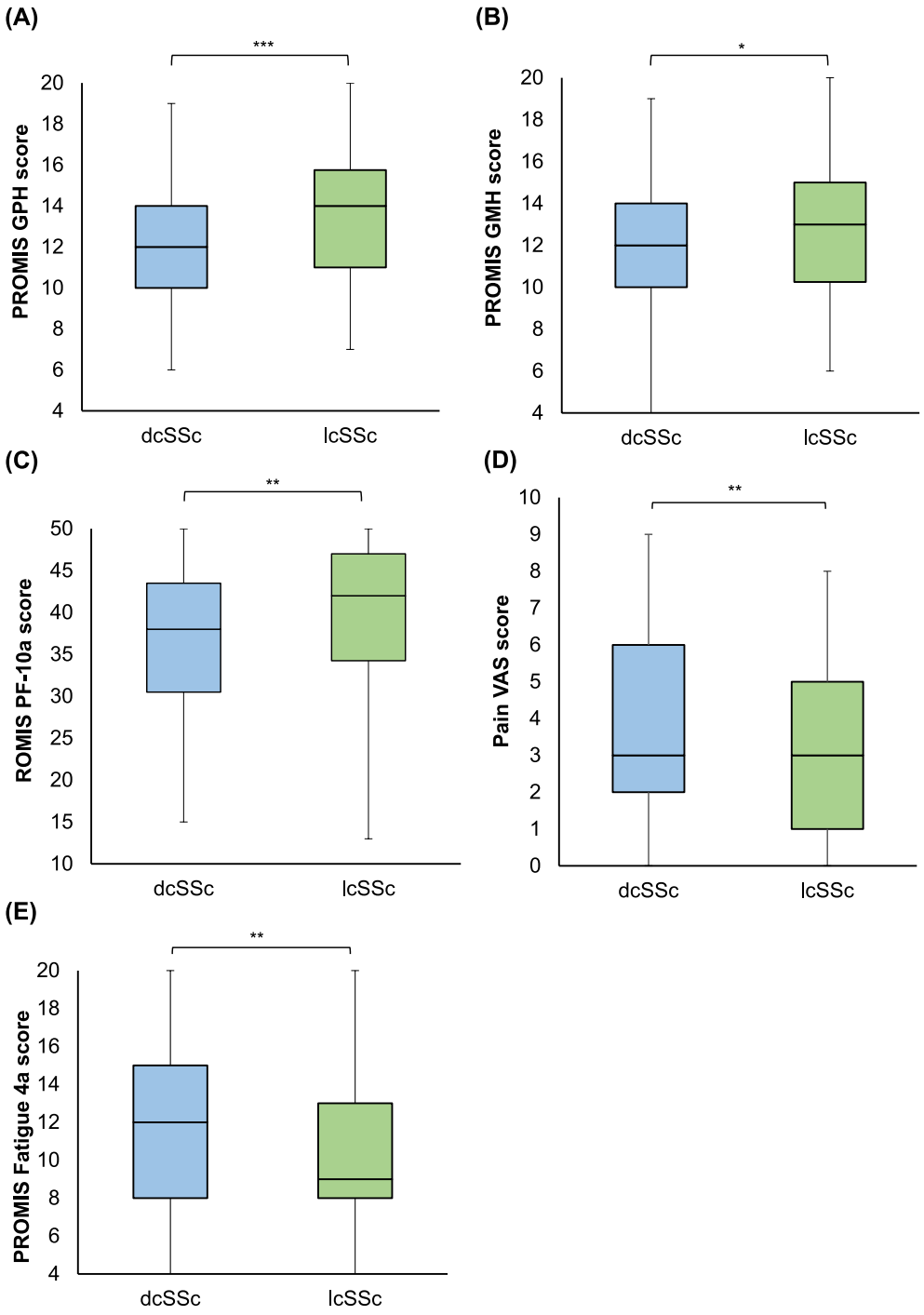

FIGURE 2 | Patient-reported outcomes stratified by SSc subtypes. (A) PROMIS GPH score†, (B) PROMIS GMH score††, (C) Pain VAS, (D) PROMIS PF-10a score, (E) PROMIS Fatigue-4a score, $*p<0.05$, $**p<0.01$, $***p<0.001$; AIRDs, autoimmune inflammatory rheumatic diseases; GMH, global mental health; GPH, global physical health; nrAIDs, non-rheumatic autoimmune inflammatory diseases; PF, physical function; PROMIS, Patient-Reported Outcome Measurement Information System; SSc, systemic sclerosis; VAS, visual analog scale. †PROMIS GPH score is the sum of Global03 (physical health), Global06 (physical function), Global07 (pain), and Global08 (fatigue). ††PROMIS GMH score is the sum of Global02 (quality of life), Global04 (mental health), Global05 (satisfaction with social activities), and Global10 (emotional problems).

was not evaluated except for ILD. Furthermore, SSc respondents were at relatively late disease stages with a median disease duration of 9 years, and our results might not be generalizable to those with early SSc. Our findings need to be verified in a large, international, multicenter cohort comprising SSc patients with various disease duration and organ involvement.

In conclusion, both physical and mental health are significantly impaired in SSc patients, especially in those with dcSSc and increased fatigue. Our study is pioneering in assessing the HRQoL and its determinants in SSc patients globally using PROMIS global health items, which underscores the importance of patient-reported experiences including fatigue and warrants

future studies to investigate targeted interventions in high-risk populations to improve overall well-being in SSc patients.

Author Contributions

K.Y., A.Y., Y.L., V.M., N.R., and L.G. conceptualized the study. All authors contributed to the data curation. K.Y., A.Y., Y.L., V.M., N.R., Vik.A., and L.G. conducted the formal data analysis. P.S. and L.G. were responsible for the project administration. A.M., M.K., Vik.A. and L.G. supervised the study. K.Y., Y.L., V.M., and L.G. drafted the original letter. All authors reviewed and approved the final version of the letter for publication.

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Ethics Statement

Informed consent was obtained from all respondents electronically at the beginning of the survey form before proceeding with the questions. The COVAD study was approved by the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences (IEC code: 2021-143-IP-EXP-39) and performed in accordance with the Declaration of Helsinki.

Conflicts of Interest

The authors have relevant financial activities as follows: M.K., speaker honoraria/participated in advisory boards for Abbvie, Asahi-Kasei, Astellas, AstraZeneca, Boehringer-Ingelheim, Chugai, Corbus, Eisai, GSK, Horizon, Kissei, BML, Mochida, Nippon Shinyaku, Ono Pharmaceuticals, Tanabe-Mitsubishi; T.V., speaker honoraria from Pfizer and AstraZeneca. The other authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article is available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.