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Impact of gastrointestinal symptoms and psychological distress on quality of life in systemic sclerosis: a cross-sectional study

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ABSTRACT

Background Systemic sclerosis (SSc) is a chronic autoimmune disease characterised by microvascular damage and fibrosis. Mortality in patients with SSc has significantly decreased. Consequently, patients with SSc have longer life expectancy, and health-related quality of life (HrQoL) has become more relevant in the comprehensive management of the disease.

Objective To evaluate the impact between gastrointestinal (GI) symptom burden and psychological well-being on HrQoL in patients with SSc.

Design Nested cross-sectional study conducted between January and July 2022.

Participants A single-centre cohort of 166 patients with SSc, including 103 (55%) with limited cutaneous SSc, 43 (24%) with diffuse SSc and 37 (21%) with sine-sclerosis SSc.

Main measures GI symptom burden was assessed using the University of California Los Angeles Scleroderma Clinical Trial Consortium gastrointestinal tract 2.0 (UCLA SCTC GIT 2.0) questionnaire, psychological well-being was measured with the Hospital Anxiety and Depression Scale (HADS), and HrQoL was evaluated using the Short Form 36 (SF-36) questionnaire. Demographic, clinical and immunological data were collected from a prospectively maintained database.

Key results Patients with moderate to severe GI symptoms (UCLA SCTC GIT 2.0 score >0.5, n=95, 57%) reported decreased HrQoL in all subdomains except vitality by SF-36, and higher anxiety and depression scores by HADS (all $p<0.05$). The severity of GI symptom burden and depression were independently associated with a decline in the physical component of QoL ($\beta=-0.273$ and $\beta=-0.411$, respectively, $p<0.01$ for both). Only the severity of depression and anxiety ($\beta=-0.482$ and $\beta=-0.213$, respectively, $p<0.05$), but not GI symptom burden, were independently associated with a decline in the mental component of QoL.

Conclusions Our data suggest that in patients with SSc, GI and psychological burden negatively influence quality of life independently, highlighting the need for a holistic approach to patient's care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large number of patients with systemic sclerosis.
⇒ Gastrointestinal (GI) symptom burden, psychological well-being and health-related quality of life were systematically assessed in all patients.
⇒ The severity of self-reported GI symptoms was evaluated, but not the degree of objective GI impairment.
⇒ This study was conducted in a single, tertiary, high-volume referral centre.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease that results in microvascular damage and widespread fibrosis in the skin and visceral organs.[1] Skin involvement, with thickening, joint contractures, ulcer formation and disfiguration, is associated with significant morbidity. Furthermore, internal organ involvement, chiefly pulmonary, gastrointestinal (GI) and cardiac contribute with considerable functional disability, poor quality of life and reduced life expectancy.[1] GI involvement in SSc is highly prevalent and almost all patients have some degree of GI dysmotility.[2] From the mouth to the anus, all the segments of the GI tract (oesophagus, stomach, small bowel, colon and anorectum) can be affected, leading to a wide range of GI manifestations, including gastro-oesophageal reflux disease, dysphagia, gastroparesis, chronic nausea and vomiting, diarrhoea or constipation, and faecal incontinence.[3 4] GI involvement in patients with SSc is heterogeneous regarding the different organs affected and the severity of the wide array of symptoms in each particular patient, posing an important challenge both for clinical practice and research.[5]

Over the last two decades, as a result of advances in the treatment of scleroderma renal crisis and pulmonary involvement, mortality in patients with SSc has significantly decreased.[6] Consequently, patients with SSc have longer life expectancy, and

health-related quality of life (HrQoL) has become more relevant in the comprehensive management of the disease.[7 8]

In SSc, GI dysmotility plays a significant role in the reduction of HrQoL. Patients report that GI involvement contributes more to decreased HrQoL than heart or lung involvement.[9] On the other hand, psychological distress also contributes to decreased HrQoL. There is increasing evidence that depression and anxiety are frequent in the SSc population, with depression rates being particularly high compared with other systemic autoimmune diseases.[10] Both GI symptoms and psychological disorders negatively impact HrQoL in patients with SSc,[11] but the relationship and mediating effect between GI symptom burden and psychological well-being remain unknown.

We hypothesised that GI symptom burden would significantly correlate with lower HrQoL scores, independently of psychological distress. Therefore, the primary objective of the present study was to evaluate the correlation between GI symptom burden and psychological well-being with HrQoL in unselected patients with SSc.

METHODS

Participants

All patients with a diagnosis of SSc that met the ACR/EULAR 2013 criteria[12] and/or LeRoy classification criteria[13] and actively followed up at the Scleroderma Consult at Hospital Universitari Vall d'Hebron were assessed for inclusion in a cross-sectional study conducted from October 2021 to July 2022.

Study design

Patients were contacted telephonically and received a full explanation of the project. If willing to participate, a personal e-mail was sent with a unique identifier code and a link to access a REDCap survey to complete clinical questionnaires (see below). The REDCap database was regularly reviewed to check completeness to avoid missing data; in case of incomplete survey completion, patients were contacted again and asked to complete the missing parts if possible. Patients with incomplete survey questionnaires were excluded from the analysis.

Survey questionnaires

The survey was divided into three questionnaires.

1. University of California Los Angeles Scleroderma Clinical Trial Consortium gastrointestinal tract 2.0 (UCLA SCTC GIT 2.0) (Spanish version): a seven multi-item scale that evaluates reflux, distention/bloating, diarrhoea, faecal soiling, constipation, emotional well-being and social functioning, giving single scores and an overall score for GI burden. It has been validated to capture GI symptom burden over the preceding 2 weeks.
2. Hospital Anxiety and Depression Scale (HADS) questionnaire (Spanish version): a 14-item scale, divided into two subscales evaluating anxiety and depression, with 7 items each. The HADS questionnaire has been previously validated in patients with SSc.[14]
3. The Short Form 36 Health Survey Questionnaire (SF-36) (Spanish version): a 36-item instrument encompassing the following eight domains of health-related quality-of-life: physical functioning physical role, bodily pain, general health, vitality, social functioning, role emotional role and mental health. The results of the SF-36 can be grouped in two main component summaries derived from the eight domains as follows. For the physical component summary (PCS): physical functioning, role limitations due to physical health, bodily pain and general health. For the mental component summary (MCS): role limitations due to emotional problems, vitality, emotional well-being and social functioning. Each domain and both summaries' results were standardised to responses from the Spanish general population, with a mean score fixed at 50 and SD at 10.[15] The SF-36 has been previously validated in patients with SSc.[16]

Clinical and demographic features

Clinical and demographic characteristics were retrieved from a prospectively collected database maintained by the Scleroderma Unit at Hospital Universitari Vall d'Hebron, as defined in previous reports.[17 18] Briefly, all patients were classified as either limited cutaneous SSc (lcSSc) (when the skin sclerosis was confined distally to the elbows and knees and/or the face), diffuse cutaneous SSc (when the skin thickening extended proximally to the elbows and knees or included the trunk) or sine sclerosis SSc (defined by the occurrence of internal organ involvement and serologic abnormalities of SSc without skin changes of limited or diffuse SSc). The disease onset was described as the date of first symptom attributable to SSc including Raynaud's phenomenon (RP). Peripheral vascular manifestations were defined by the presence of RP, ischaemic digital ulcerations or telangiectasias. Interstitial lung disease was established if a pulmonary interstitial pattern was present in high-resolution CT scan. Pulmonary arterial hypertension was defined as mean pulmonary arterial pressure ≥20 mm Hg in right heart catheterisation with pulmonary artery wedge pressure ≤15 mm Hg and pulmonary vascular resistance >2 Wood units. GI involvement was defined as the presence of oesophageal hypomotility, gastroparesis, the presence of gastric antral vascular ectasia (watermelon stomach), radiological signs suggestive of intestinal-pseudo-obstruction or diagnosis of small intestinal bacterial overgrowth. Myopathy was defined as the presence of proximal muscle weakness or myalgia and at least one of the following abnormalities: a serum creatine kinase above normal value, a myopathic pattern in the electromyogram or findings of myositis in muscle biopsy. Calcinosis cutis was defined as widespread or localised soft-tissue calcification. Joint involvement was evaluated for the presence of arthritis or tendon friction rubs. Cardiac involvement was defined as following: pericarditis, pericardial effusion, ischaemic cardiopathy without

common risk factors or disturbance secondary to SSc on color-Doppler echocardiography, cardiac magnetic resonance and/or gated myocardial perfusion Single Photon Emission Computed Tomography (SPECT). Nailfold capillaroscopy was described following patterns defined by Cutolo *et al*.[19]

Immunological features

Antinuclear antibodies were identified by indirect immunofluorescence assay using Hep-2 cell line (INOVA, San Diego). SSc-specific autoantibodies were determined by commercial line blot assay (Systemic Sclerosis Profile Euroline Blot test kit, Euroimmun, Lübeck, Germany). Anti-U1-RNP and anti-Ro52 autoantibodies were tested by chemiluminescence immunoassay (INOVA, San Diego) according to the manufacturer's instructions.

Ethical issues

All methods were performed in accordance with relevant guidelines and regulations, and the study was approved by the Hospital Vall d'Hebron Institutional Review Board (PR(AG)312/2021). Patients gave written informed consent for the management of clinical data. Verbal consent to participate in the survey was obtained and participation was voluntary. All personal data were managed in a secure REDCap database.

Patient and public involvement

There was no patient or public involvement in the design of this study.

Statistical analysis

All statistical analyses were performed using JASP V.0.18.3 (JASP TEAM, Amsterdam, The Netherlands). Normality of data distribution was evaluated by the Shapiro–Wilk test. Data were presented as median (and IQR) for non-normal continuous variables, mean and SD for normal continuous variables, and number and percentage for discrete variables. Comparisons of parametric, normally distributed data were made by Student's t-test and the Mann-Whitney U-test for non-parametric data. Correlations between the UCLA SCTC GIT 2.0 subscales and total score, HADS depression and anxiety scores and both the physical and MCS of QoL were performed using Pearson's R.

Our primary outcome measure was the PCS and MCS of HrQoL standardised to the Spanish population. To evaluate whether GI symptom burden (by the UCLA SCTC GIT 2.0 total score) and psychological burden (by HADS depression and anxiety scores) were independently associated with the decline in HrQoL, multiple linear regression models, adjusted for known factors associated with decreased HrQoL in patients with SSc, such as diffuse cutaneous subset, age and duration of disease,[20] were performed. Tolerance and variance factor analysis were performed to evaluate for collinearity. Differences were considered statistically significant at a p value<0.05.

Table 1 Demographic, clinical characteristics and serologic profiles of all patients included

Characteristics	Overall (n=166)
Age, years (median IQR)	58.5 (50–67)
Gender, female (n, %)	137 (83%)
Age at diagnosis, (median IQR)	45 (37–53)
Duration of disease, (median IQR)	12 (7–18)
Body mass index (median IQR)	25.0 (21.6–27.7)
Smoking status	
Current smoker (n, %)	25 (15%)
Former smoker (n, %)	42 (25%)
SSc subtype	
DcSSc (n, %)	39 (24%)
LcSSc (n, %)	96 (58%)
Sine-sclerosis SSc (n, %)	31 (19%)
Raynaud phenomenon (n, %)	161 (97%)
Digital ulcers (n, %)	59 (36%)
Telangiectasias (n, %)	130 (78%)
Calcinosis (n, %)	27 (16%)
Arthritis (n, %)	31 (19%)
Tendon friction rubs (n, %)	8 (5%)
Myositis (n, %)	13 (8%)
ILD (n, %)	66 (41%)
PAH (n, %)	15 (9%)
Lung transplant (n, %)	13 (8%)
Cardiac involvement (n, %)	93 (57%)
Gastrointestinal involvement (n, %)	9 0 (54%)
Scleroderma renal crisis (n, %)	2 (1%)
Capillaroscopy late pattern (n, %)	32 (21%)
Antinuclear antibodies (n, %)	160 (96%)
ACA antibodies (n, %)	55 (33%)
SCL 70 antibodies (n, %)	38 (23%)
RNA polymerase III antibodies (n, %)	14 (8%)
PM/SCL antibodies (n, %)	9 (5%)
RNPC-3 antibodies* (n, %)	5/124 (4%)
Ro52 antibodies (n, %)	31 19%)
Ku antibodies (n, %)	3 (2%)
RNP antibodies (n, %)	5 (3%)

*124 patients had RNPC-3 antibodies tested.
DcSSc, diffuse cutaneous SSc; ILD, interstitial lung disease; LcSSc, limited cutaneous SSc; PAH, pulmonary artery hypertension; SSc, systemic sclerosis.

RESULTS

Study population

All 234 patients on active follow-up at our centre were invited to participate, 207 (88%) accepted and started the questionnaires. Of these, 166 (78%) patients completed all the survey questionnaires and were included in the final

Table 2 Demographic characteristics, clinical manifestations and serologic profiles of all participants and according to the presence of at least one moderate GI symptom

	No or only mild GI symptoms	Moderate GI symptoms	P value
	n=47	n=119	
Age, years (median IQR)	62 (54–70)	58 (50–66)	0.111
Gender, female (n, %)	35 (74%)	102 (86%)	0.136
Age at diagnosis, (median IQR)	48 (40–55)	44 (37–52)	0.136
Duration of disease, (median IQR)	12 (5–17)	12 (8–18)	0.636
Body mass index (median IQR)	25.0 (22.9–28.7)	24.0 (21.0–27.5)	0.088
Smoking status			
Current smoker (n, %)	5 (11%)	20 (17%)	0.447
Former smoker (n, %)	11 (23%)	31 (26%)	0.877
SSc Subtype			
DcSSc (n, %)	9 (19%)	30 (25%)	0.062
LcSSc (n, %)	30 (64%)	66 (55%)	0.654
Sine-sclerosis SSc (n, %)	11 (23%)	20 (17%)	0.325
Clinical characteristics			
Raynaud phenomenon (n, %)	45 (96%)	116 (98%)	0.932
Digital ulcers (n, %)	16 (34%)	43 (36%)	0.941
Telangiectasies (n, %)	34 (72%)	96 (81%)	0.335
Calcinosis (n, %)	8 (17%)	19 (16%)	1.000
Arthritis (n, %)	6 (13%)	25 (21%)	0.293
Tendon friction rubs (n, %)	1 (2%)	7 (6%)	0.525
Myositis (n, %)	3 (6%)	10 (8%)	0.885
ILD (n, %)	25 (54%)	41 (35%)	0.037
PAH (n, %)	9 (8%)	6 (12%)	0.280
Lung transplant (n, %)	7 (15%)	6 (5%)	0.073
Cardiac involvement (n, %)	27 (57%)	66 (56%)	1.000
Scleroderma renal crisis (n, %)	2 (2%)	0	1.00
Immunologic characteristics			
Antinuclear antibodies (n, %)	45 (95%)	115 (97%)	1.000
ACA antibodies (n, %)	11 (24%)	44 (37%)	0.148
SCL 70 antibodies (n, %)	12 (25%)	26 (22%)	0.782
RNA polymerase III antibodies (n, %)	5 (11%)	9 (8%)	0.703
PM/SCL antibodies (n, %)	3 (7%)	6 (5%)	1.000
RNPC-3 antibodies* (n, %)	3/34 (9%)	2/90 (2%)	0.248
Ro52 antibodies (n, %)	6 (13%)	25 (21%)	0.303
Ku antibodies (n, %)	1 (2%)	2 (2%)	1.000
RNP antibodies (n, %)	1 (2%)	4 (3%)	1.000

*124 patients had RNPC-3 antibodies tested.
DcSSc, diffuse subtype ILD interstitial lung disease; LcSSc, limited subtype; PAH, pulmonary artery hypertension; SSc, systemic sclerosis.

analysis. The baseline characteristics of patients included are summarised in table 1. Most patients were women (83%), with a median (IQR) age at the time of inclusion of 58.5 (50–67) years and a median (IQR) disease duration of 12 (7–18) years at the time of evaluation. LcSSc was the most common subtype in 96 (58%) patients. Overall, patients with SSc reported a lower physical and mental HrQoL by SF-36 than that of the Spanish general population (PCS score 37.3±8.5 and MCS score 42.3±11.6 vs 50±10 general population, both p<0.001) and only 12 (7%) and 57 (34%) patients reported scores of 50 or more for the PCS and MCS, respectively. Regarding GI symptom burden, 119 (72%) participants reported having moderate or severe GI symptoms (defined as a UCLA GIT

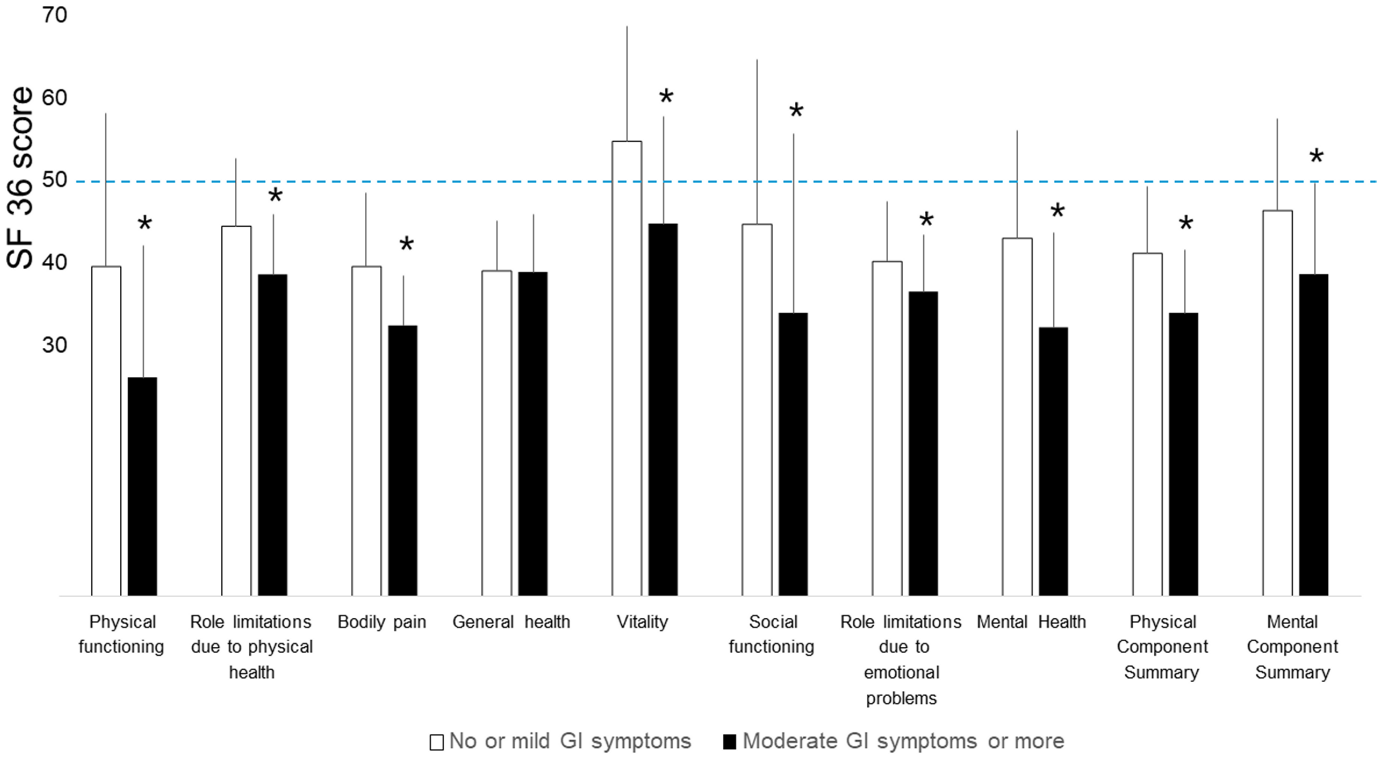

Figure 1 Comparison of QoL by SF-36 between patients without significant gastrointestinal (GI) symptom burden (UCLA GIT 2.0<0.5, n=71) and patients with moderate GI symptoms or more (UCLA GIT>0.5, n=95). Mean+SD SF-36 Scores for the eight domains and for the physical and mental component summaries are standardised. A score below 50 reflects worse HrQoL compared with the average of the general Spanish population *p<0.05: Significant differences by Mann Whitney U test. HrQoL, health-related quality of life; SF-36, Short Form 36; UCLA SCTC GIT 2.0, University of California Los Angeles Scleroderma Clinical Trial Consortium gastrointestinal tract 2.0.

2.0 score >0.5), 35 (21%) participants reported having mild GI symptoms (UCLA GIT 2.0 score between 0.02 and 0.49) and 12 (7%) participants reported not having any GI symptoms (UCLA SCTC GIT 2.0 score of 0). Regarding psychological well-being, HADS depression score summary was normal (0–7 points) in 118 (71%) patients, borderline (8–11 points) in 16 (10%) patients and abnormal (12 points or more) in 32 (19%) patients. HADS anxiety score summary was normal (0–7 points) in 94 (57%) patients, borderline (8–11 points) in 34 (20%) patients and abnormal (12 points or more) in 38 (23%) patients.

Clinical and serological profiles between patients with and without moderate GI symptoms

We first evaluated the demographic, clinical or immunological variables between patients with and without moderate GI symptoms, and we found no significant differences between groups (table 2).

Comparison of HrQoL and psychological burden between patients with and without moderate GI symptoms

We then performed a comparative analysis of HrQoL and psychological burden between patients experiencing moderate GI symptoms (UCLA SCTC GIT 2.0 score ≥0.5), and those who had mild or no GI symptoms (UCLA SCTC GIT 2.0 score <0.5). Patients with moderate GI symptoms reported worse scores in all SF-36 Health-related QoL domains, except for general health, which was equally affected in both groups (figure 1). Additionally, patients with GI symptoms reported worse psychological well-being, as indicated by higher scores for anxiety (8.9±4.4 vs 4.6±3.5, p<0.001) and depression (7.1±4.6 vs 3.4±3.4, p<0.001) measured by HADS.

Impact of GI symptom burden and psychological well-being on HrQoL

We evaluated the individual impact between UCLA SCTC GIT 2.0 subscales and total scores, HADS depression and anxiety scores and the SF-36 PCS and MCS scores in all patients are shown in figure 2. All UCLA SCTC GIT 2.0 subscales showed a moderate negative correlation with both the PCS and MCS of HrQoL and positive moderate correlations with HADS anxiety and HADS depression scores. The UCLA SCTC GIT 2.0 distension/bloating subscale showed the highest impact on the PCS and the UCLA SCTC GIT 2.0 emotional well-being the highest impact on the MCS. The HADS anxiety and HADS depression scores showed a negative correlation with both the PCS and MCS, which was stronger for the HADS depression score. To evaluate for independent associations, we performed a multiple linear regression analysis between GI symptom burden (by UCLA SCTC GIT 2.0 total score) and psychological well-being (HADS anxiety and depression scores), adjusted for known factors that

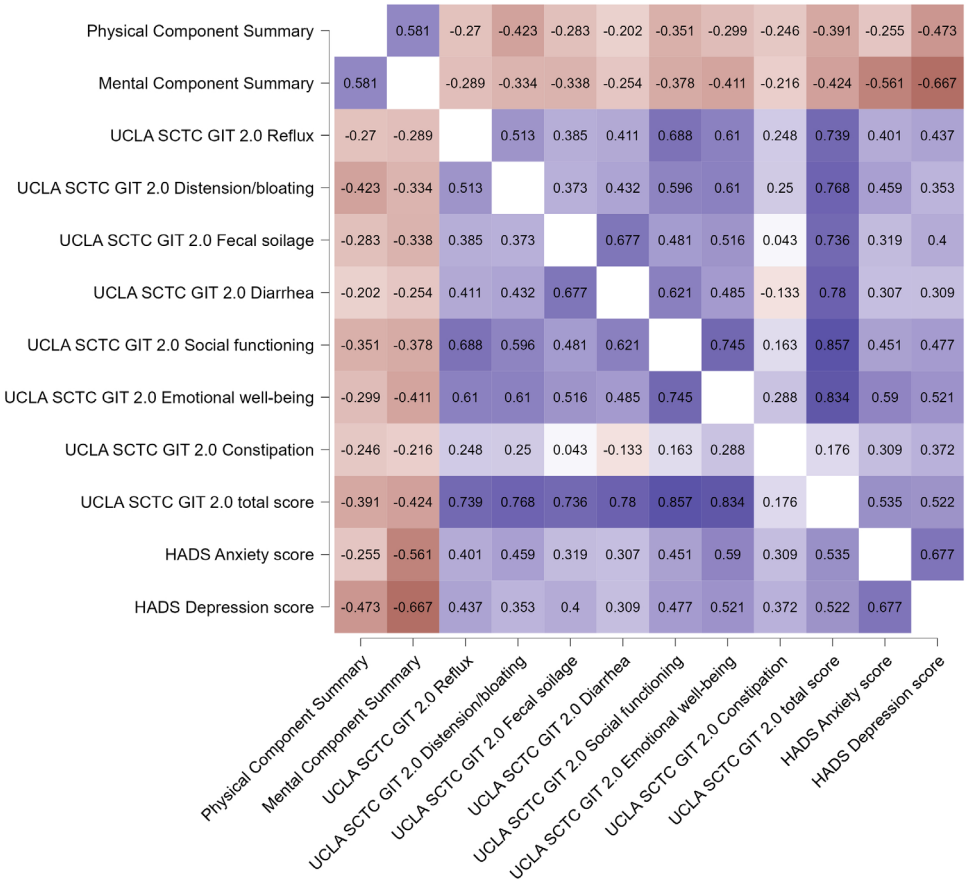

Figure 2 Correlation matrix between the results of the SF-36 physical and mental component summaries scores, the UCLA SCTC GIT 2.0 subscales and total scores, and HADS depression and anxiety scores. Correlation was evaluated using Pearson's R. HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form 36; UCLA SCTC GIT 2.0, University of California Los Angeles Scleroderma Clinical Trial Consortium gastrointestinal tract 2.0.

affect HrQoL in patients with SSc. The results are shown in online supplemental tables 1 and 2. Both the severity of GI symptom burden (UCLA SCTC GIT 2.0 total score, (β=−0.273, p<0.001) and depression (HADS depression score, β=−0.411, p<0.001) remained significantly associated with the decline in the PCS of HrQoL. On the other hand, only the severity of depression (β=−0.482, p<0.001) and anxiety (β=−0.213, p=0.017), but not GI symptom burden, remained significantly associated with the decline in the MCS of HrQoL.

DISCUSSION

This study further demonstrates that GI symptom burden is common and highly prevalent in unselected patients with SSc, regardless of subtype or duration of disease. Both GI symptom burden and psychological disorders, particularly depression, are independently associated with decreased HrQoL in patients with SSc.

GI involvement in SSc is almost universal, and the prevalence of self-reported GI symptoms reached 90% in a previous study.[21] In our study, we found similar results, only 7% of patients reported not having GI symptoms. From the remaining 93%, more than half of the patients reported moderate or severe GI symptoms at the time of evaluation. This prevalence of significant GI symptom burden is similar to a recent study in Spanish patients with SSc.[22] Although GI involvement is not a frequent cause of mortality in patients with SSc,[6 23 24] GI symptom burden has an important influence on HrQoL.[25] We found that patients presenting moderate or severe GI symptoms (UCLA GIT 2.0 >0.5) had worse results in almost all aspects of HrQoL evaluated by SF-36 except for vitality, and also higher scores of psychological burden (both anxiety and depression) by HADS. In one study evaluating HrQoL in patients with SSc from 60 countries,[9] self-reported GI involvement ranked as one of the top two organ involvements with most negative impact on HrQoL perceived by patients, ranking even higher than pulmonary or cardiac involvement. These observations suggest the importance of recognising and treating GI manifestations in patients with SSc in order to improve general well-being. Unfortunately, the management of GI involvement in patients with SSc has not significantly changed in recent decades. Current strategies for GI involvement management are focused on symptom control and include; for gastro-oesophageal reflux, using proton pump inhibitors or histamine H2 receptor antagonists, for acid suppression, optimising lifestyle measures

such as avoiding late meals and prokinetic agents, which may prove helpful in refractory cases to previous therapies.[26 27] For severe malnutrition or weight loss, diet modifications in the number of meals and quality are advised, and in severe cases, parenteral nutrition may be needed. Small intestinal bacterial overgrowth can be treated with antibiotics such as rifaximin, and anti-diarrheal agents or laxatives can manage alternating diarrhoea and constipation. For faecal incontinence, pelvic floor physiotherapy may be beneficial.[27 28]

We observed an independent negative association between GI symptom burden and psychological burden with decreased HrQoL. In patients with SSc, previous studies have shown an association between GI symptoms and psychological comorbidity like depression.[11] Also, in patients with SSc, emotional distress is related to GI symptoms of dysautonomia regardless of the severity of objective GI involvement.[29] In our study, we found that GI symptom burden and depression were independently associated with the decline in the PCS of HrQoL, while depression and anxiety, but not GI symptom burden, were associated with the decrease in the MCS of HrQoL. Therefore, even though GI symptom burden and psychological well-being are correlated, their association with decreased HrQoL is independent, indicating that both conditions should be specifically sought and treated accordingly. While there are no specific recommendations for managing depression in SSc, clinical trials have shown that combining psychotherapy with pharmacotherapy provides additional benefits when used as an initial treatment for depression.[30]

Our study has noteworthy strengths. It included a large number of patients with SSc. Furthermore, GI symptom burden, psychological well-being and HrQoL were systematically assessed in all patients at the time of inclusion. Still, our study has some limitations; first, it is a cross-sectional study, so we cannot ascertain the causality between GI symptoms, psychological well-being and disease-specific factors. Second, we only evaluated the severity of self-reported GI symptoms and did not evaluate objective test results, such as motility or imaging studies, which could provide a more accurate assessment of GI involvement. Additionally, some patients were undergoing pharmacological treatment for their GI complaints, which may have influenced the results. Furthermore, our study primarily focused on the relationship between HrQoL, GI symptoms and psychological distress, and while we adjusted our model for known factors that alter HrQoL, such as duration of disease or subcutaneous subset, other factors that may affect HrQoL, such as lung transplantation or other specific organ involvement, were not systematically assessed. Finally, this study was conducted in a single, tertiary, high-volume referral centre and as such, the results might not be generalisable.

In conclusion, two main findings of our study have clinical relevance. First, our study shows that GI symptoms and psychological distress are highly prevalent in unselected patients with SSc, Therefore, evaluating specific GI symptoms and addressing psychological well-being during diagnosis and follow-up are crucial. Second, higher GI symptom burden and worse psychological well-being are independently associated with decreased HrQoL, highlighting the need for a comprehensive approach to patient's care.

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Contributors LA: study management, study design, data analysis and manuscript preparation. AAC, CB, AMG, CC: collecting and interpreting data. CM, AG-D-C and CPS-A: study design, data analysis and manuscript preparation. LA is the guarantor of this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patients.

Ethics approval The study was approved by the Clinical Research Ethics Committee at Vall d'Hebron University Hospital [PR(AG)312/2021]. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request.

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