Running head: Systemic sclerosis GI disease

Title: Evaluation of patient and physician assessments of gastrointestinal disease activity in systemic sclerosis

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Funding:

The development of the Scleroderma Clinical Trials Consortium (SCTC) Activity Index has been supported by a Betty Z Benedict Award, SCTC Working Group Grants and private philanthropic donations.

LR is supported by a *Musculoskeletal Australia* PhD Scholarship and an Australian Government Research and Training Scholarship. MN is supported by a National Health and Medical Research Council of Australia Investigator Grant (GNT 1176538). KM holds a National Health and Medical Research Council of Australia Investigator Grant (APP 1197169).

The Australian Scleroderma Cohort Study is supported by Actelion Australia, Scleroderma Australia, Scleroderma Victoria, Arthritis Australia, Musculoskeletal Australia, The Scleroderma Clinical Trials Consortium (SCTC), St Vincent's Hospital Research Endowment Fund, The Australian Rheumatology Association, philanthropic donations, GlaxoSmithKline, Roche, Pfizer, Bayer, CSL Biotherapies and Bristol-Myers Squibb.

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Conflict of interest:

The authors have no conflicts of interest to declare.

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Key words: systemic sclerosis, gastrointestinal, disease activity, patient-reported outcomes

Abstract

Objective

To assess whether patient and physician global assessment of gastrointestinal disease in systemic sclerosis (SSc) are associated with a meaningful change in disease status.

Methods

One hundred and forty-three participants from the Australian Scleroderma Cohort Study were recruited to this study. Using logistic regression analysis, we evaluated the relationship between patient and physician assessed gastrointestinal disease status and symptoms, measures of health-related quality of life (Medical Short Form 36 (SF-36)) and gastrointestinal disease severity, measured by the Scleroderma Clinical Trials Consortium (SCTC) UCLA Gastrointestinal Tract 2.0 Score (GIT 2.0).

Results

Patient-reported worsening of gastrointestinal symptoms in the month preceding assessment was significantly associated with more severe gastrointestinal disease (OR 6.14, $p<0.01$) and progressive worsening gastrointestinal disease severity as measured by the GIT 2.0 score (OR 45.98, $p<0.01$). The new onset of reflux was the only specific symptom associated with patient reported gastrointestinal disease activity (OR 2.98, $p=0.04$). Physician assessed gastrointestinal disease activity was not significantly associated with higher GIT 2.0 scores or increasing severity of disease. Patient and physician assessed gastrointestinal activity was not associated with SF-36 scores.

Conclusion

In the absence of objective measures of gastrointestinal disease activity in SSc, patient-reported symptoms of gastrointestinal disease could be used to indicate disease activity and merit consideration for inclusion in a multi-system disease activity index.

Introduction

Systemic sclerosis (SSc) is a multi-system disease characterised by a triad of inflammation, vasculopathy and fibrosis.[1] Gastrointestinal tract (GIT) involvement is near-universal with involvement of all parts of the GIT from the mouth to anorectum.[2] GIT disease has commonly been assessed using the UCLA SCTC GIT 2.0 Score (GIT 2.0); a 34-item patient-reported scale that measures the severity of GIT involvement.[3] Gastrointestinal symptoms can also be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) GIT instrument.[4] The Medsger Severity Scale (MSS)[5] includes a gastrointestinal score and the SSc-specific Health Assessment Questionnaire includes a visual analogue scale assessing the impact of gastrointestinal disease on overall function.[6] These outcome measures evaluate GIT disease *severity*, meaning they capture both disease *activity*, aspects of disease which are considered reversible, and *damage* which is considered irreversible. There is currently no activity-specific instrument to evaluate only reversible aspects of GIT disease.

The Scleroderma Clinical Trials Consortium (SCTC) has convened a working group (WG) to develop an Activity Index (AI). Measurement of GIT disease activity has been a significant hurdle in the development of the AI as many common manifestations of GIT disease are irreversible, representing damage rather than activity. Also, there is the recognised discordance between certain patient-reported symptoms and objective measures of GIT involvement.[7] There are no validated clinical measures or biomarkers to differentiate gastrointestinal damage from activity.[8]

A potential solution to the absence of symptoms or biomarkers of disease activity is to use patient or physician-reported assessments. Global assessments are included in other multi-system outcome measures in an effort to capture involvement of organ systems that are otherwise challenging to measure.[9] We have previously demonstrated that patient-reported symptoms are significantly associated with meaningful progression of disease in specific organ systems.[10] The use of a GIT-specific assessment by either the physician or patient has not previously been investigated. Therefore, we sought to evaluate whether a patient and physician-reported GIT disease assessment could be used to assess clinically meaningful changes in disease status. We hypothesised that patient-reported worsening of GIT symptoms (PRW) and physician-reported GIT disease activity (PhGA) would be associated with a clinically meaningful progression of gastrointestinal disease. Secondly, we explored whether a PRW and PhGA were associated with the development of new symptoms of gastrointestinal involvement.

Methods

Participants

All patients were enrolled in the Australian Scleroderma Cohort Study (ASCS). ASCS data are prospectively collected at annual review. Consecutive patients, aged $\geq$ 18 years, who fulfilled the 2013 ACR/EULAR Classification Criteria for SSc[11], who had data available to define disease subtype and were reviewed by face-to-face consultation between January 2020 and November 2021 were included in this study. The ASCS is carried out in accordance with the *National Statement on Ethical Conduct in Research Involving Humans (May 2015).* The Human Research Ethics Committees at St Vincent's Hospital, Melbourne and Royal

Adelaide Hospital approved the study (HREC-A 020/07) and written informed consent was provided before any data were collected.

Clinical data

Demographic data collected included age, sex and duration of disease. Disease duration was recorded from onset of the first non-Raynaud's manifestation. Annual data collected from all participants included examination findings, presence of SSc disease manifestations (recorded yes/no), medications, and patient-reported outcomes including the GIT 2.0, the Medical Outcome Short Form 36 (SF-36) and PROMIS-29. All participants had baseline autoantibody testing. Any routinely collected data that were not collected were recorded as missing. GIT investigations were performed at the discretion of the treating clinician.

Outcomes measured

Physicians (n=6) were informed of the definition of disease activity, as defined through consensus by the SCTC AI Working Group: '*Disease activity in SSc refers to aspects of disease, attributable to systemic sclerosis, that are potentially reversible, or can be arrested, with time and/or effective therapy. Disease activity may be associated with morbidity and uncontrolled activity may lead to organ dysfunction and mortality'.* Physicians were asked: 'Do you think your patient currently has active, progressive GIT disease?'; (the PhGA). Potential responses were: (i) Cannot assess (ii) No (iii) Low activity (iv) Moderate activity (v) High activity. Patients were asked 'Do you think any of your gastrointestinal symptoms have worsened in the past month?'; (the PRW) with the possible responses of (i) No (ii) A little worse (iii) Mild worsening (iv) Severe worsening (v) Very severe worsening (need for hospitalisation). This ASCS review for the purposes of this study was termed the study entry

visit. Any PRW response of any of a little, mild, severe or very severe worsening was considered a positive response and in study analyses considered to indicate the presence of patient-reported worsening of GIT symptoms. Any physician rating of low, moderate or high disease activity was considered to indicate the present of GIT disease activity. We assessed the relationship between the PRW and PhGA and GIT 2.0 score measured at the study entry visit as well as the change in GIT 2.0 score from the preceding study visit. Progression of GIT disease severity was defined as increase in GIT 2.0 scores of >0.12, in accordance with the previously defined minimally important difference (MCID).[12] In the absence of an established standard for screening investigations for GIT involvement and the infrequent nature of invasive GIT investigations performed in this cohort, the PRW and PhGA were compared to the GIT organ score of the MSS[5] and the gastrointestinal component of the SCTC Damage Index (DI) score.[13] The MSS score rates GIT severity on a numeric scale from 0 – normal; 1 (mild) – distal oesophageal hypoperistalsis, abnormal small bowel series; 2 (moderate) – antibiotics required for small intestinal bacterial overgrowth (SIBO); 3 (severe) – malabsorption syndrome, episodes of pseudo-obstruction; 4 (endstage) – hyperalimentation.[5] In the absence of a defined MCID of the MSS, a MSS increase of ≥ 1 was considered significant. The DI is a weighted score of organ damage that includes oesophageal dysmotility (1 point), oesophageal stricture (1 point), refractory gastro-oesophageal reflux disease (1 point), gastric antral vascular ectasia (GAVE) (2 points), pseudo-obstruction (3 points) and low body mass index<18.5kg/m^2 or weight loss of >10% over 12-months (2 points).[13] A significant increase in DI score was considered present if an increase of GIT DI score ≥ 1 was recorded, consistent with the DI authors' definition of worsening damage.[13]

Any associations between gastrointestinal disease assessment ratings and new-onset symptoms were evaluated. Gastrointestinal symptoms collected as part of the ASCS protocol were considered to be new-onset if they were recorded as present at the study entry visit and had been absent at the preceding review. Gastrointestinal symptoms of interest were those that had been nominated by the AI WG as potential AI items in a Delphi exercise. Potential gastrointestinal activity items collected by the ASCS were reflux, dysphagia, bloating, anaemia, diarrhoea, constipation, faecal incontinence, number of bowel actions per day, weight loss, oesophageal strictures, GAVE, SIBO (defined the concurrent presence of diarrhoea and prescription of antibiotics for bacterial overgrowth) and episodes of pseudo-obstruction.

Statistical analysis

Data are presented as number (percentage) for categorical variables and mean ($\pm$ standard deviation (SD)) for normally distributed or median (inter-quartile range (IQR)) for non-normally distributed continuous variables. Differences in frequency were tested using the chi-square test. The agreement between the PRW and PhGA was assessed by Cohen's kappa coefficient. Univariable logistic regression analysis was performed to determine the association between the PRW and PhGA and GIT 2.0, SF-36, MSS and DI scores (analysed as continuous variables) and gastrointestinal symptoms of interest (analysed as dichotomous variables). The potential effects of confounding factors such as age, weight, medications, smoking and alcohol use and depression and anxiety (rated on the PROMIS-29 depression and anxiety scales) on GIT symptoms were evaluated using multivariable logistic regression analysis. Study data were managed using REDCap electronic data capture tools hosted at

The University of Melbourne. All statistical analyses were performed using STATA 14.2 (StataCorp, USA).

Results

Participant characteristics

This study included 143 participants. Patients had a median disease duration of 13.67 years (6.77-20.12) and a median interval of 378 days (364-574) between study visits. All patients had gastrointestinal symptom data available for analysis and 118 (82.52%) patients completed the GIT 2.0 score at the study entry visit with a median total score of 0.32 (0.09-0.66). One hundred and ten patients (76.92%) had SF-36 scores at study entry available for analysis, with a median physical component score (PCS) of 39.20 (29.86-51.56) and median mental component score (MCS) 48.21 (38.67-56.14). Thirty-one patients (21.68%) were found to have a significant change in GIT 2.0 score at their study entry visit compared to the previous ASCS review (see supplementary index 1). The mean MSS gastrointestinal organ score was 0.42 ± 0.88 and mean SCTC DI GIT score was 1.24 ± 1.66 at the study entry visit. Seven patients (4.90%) had an ≥ 1 point increase of MSS compared to their previous review. Baseline characteristics of the study population are summarised in Table 1.

Assessment of gastrointestinal disease

Thirty-three patients (23.08%) had physician-rated GIT activity (PhGA) and 29 (20.28%) of patients reported worsening of GIT symptoms (PRW). There was moderate agreement between the PRW and PhGA (κ0.51, p<0.01). No patient had new onset oesophageal stricture, GAVE or pseudo-obstruction during the study. One patient had a new, initial diagnosis of oesophageal dysmotility by barium swallow study and a further three patients

had new reflux oesophagitis confirmed by endoscopy for the first time. Only the patient with new dysmotility recorded a positive PRW. No patient who had new-onset SIBO reported any recent change in GIT symptoms.

Associations of patient and physician reported gastrointestinal disease assessments

There was a significant association between the PRW and higher GIT 2.0 scores as well as a strong association with increased GIT 2.0 scores between study visits (Table 2). There was a non-significant trend towards an association between the PhGA and higher GIT 2.0 scores (Table 3). The PRW was most closely associated with the onset of symptoms of the upper GIT (reflux, p=0.04; dysphagia, p=0.08; bloating, p=0.08) as well as constipation (p=0.06). However, only new onset reflux reached statistical significance. Controlling for potential confounders strengthened the association between new onset GIT symptoms and the PRW, except for upper GI symptoms and co-morbid depression and anxiety (Table 2). There was no significant association between the PhGA and symptoms (Table 3). Neither patient nor physician GIT assessment was associated with change in SF-36 scores. The PRW was associated with higher MSS GIT scores (p=0.01). There was a trend towards a positive PRW and higher burden of gastrointestinal disease damage measured by the DI (p=0.07).

Discussion

This study has shown that a PRW is associated with more severe GIT disease as measured by the GIT 2.0 and MSS. The PRW was most likely to be associated with the new-onset of upper gastrointestinal system symptoms and development of new constipation. A PhGA was not associated with any other measure of GIT disease status or the onset of new GIT symptoms.

Gastrointestinal disease is highly burdensome to patients[2] and the measurement of gastrointestinal disease continues to prove challenging. There are no recommendations for the regular investigation of the GIT and there is ongoing reliance on clinical symptoms for the longitudinal assessment of the GIT.[14] Existing measures such as the GIT 2.0 score can be used to measure overall GIT disease severity.[3] However, the inclusion of aspects of both activity and damage mean that longitudinal assessment of progressive GIT disease is limited when using these instruments and has compelled the AI working group to consider a novel method of capturing gastrointestinal disease activity. We have shown that PRW is significantly associated with more severe gastrointestinal involvement, as measured by the GIT 2.0 score and MSS. These results suggest that a recall of change in symptoms over the preceding month is associated with the onset of new, clinical important symptoms of GIT involvement, supporting the inclusion of patient-reported gastrointestinal symptoms as a measure of disease in the AI.

Whether GIT symptoms reflect an active, potentially reversible disease process or are evidence of irreversible damage remains controversial. Our results indicate that the new-onset of individual symptoms correlate poorly with both the patient and physician-assessment of gastrointestinal disease. The exception to this may be symptoms of the upper GIT as we did observe trends towards an association between PRW and symptoms of reflux, dysphagia and bloating. Conceivably each of these symptoms may reflect a component of activity; reflux oesophagitis can be reversible with aggressive gastric acid suppression and SIBO may be improved with antibiotics.[2] The potential reversibility of these symptoms with treatment is consistent with the construct of disease activity defined

by the AI working group. However, the validity of individual symptoms to measure disease activity requires careful evaluation in future studies given the often-non-specific nature of symptoms and recognised discordance between symptoms and invasive measures of SSc gastrointestinal manifestations.[7]

These results need to be considered within the limits of our study design. The sample size was small, from a single cohort with long-standing SSc and results may not be applicable to SSc populations with differing demographics. Each patient was assessed at one individual time point by a single assessor. It was not possible to assess the inter or intra-rater reliability of these measures. There were six independent physicians who contributed data to this study. Whilst all physicians were informed of the definition of disease activity at the time of assessment, it is possible that variability of physician interpretation of this definition influenced the PhGA. The ASCS collects data on an annual basis. Therefore, a comparison between patient-recalled changes in symptoms over of one month could only be compared to the onset of new symptoms and change in other measures of disease over a 12-month period. It may be the case that a comparison between the PRW, recalled over one month, and individual symptom changes over the same period of time may yield different results.

Furthermore, the ASCS does not include protocolised routine GIT investigation, thus it is not possible to correlate the PRW with investigation abnormalities. Consequently, the frequency of accrual of new GIT manifestations may be under-reported in this study. The ASCS does not record GIT investigations that have been performed with no abnormality detected, further limiting the accuracy of the estimates of accrual of new GIT disease manifestations. The relatively short duration of follow up means that rarer events such as

new oesophageal strictures, GAVE and pseudo-obstruction were not recorded in this study. The ASCS does not collect data on the dosage of medications, so it was not possible to account for change in medication dose as a contributing factor to PRW.

In conclusion, gastrointestinal disease is highly prevalent in SSc and of great clinical importance to patients. For these reasons, the SCTC AI WG has nominated to include measures of gastrointestinal disease in the AI. In the absence of consensus as to which individual symptoms or investigation findings could be used to measure activity, we have shown that measurement of PRW has partial face, construct and criterion validity and is a feasible method of assessing change in disease status. Therefore, it may be an appropriate item to measure gastrointestinal disease activity pending the development of more robust outcome measures.

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Table 1: Baseline population characteristics (n=143)

Demographics	
Age (years, median, IQR)	62.56 (53.86-71.94)
Female (n, %)	118 (83.10%)
Disease duration (years, median, IQR)	13.67 (6.68-20.13)
Diffuse disease (n, %)	41 (28.67%)
Body mass index (median, IQR)	25.10 (22.97-29.73)
Ever smoked cigarettes (n, %)	66 (46.15%)
Autoantibodies	
Centromere (n, %)	60 (41.96%)
Scl 70 (n, %)	26 (18.18%)
RNA polymerase III* (n, %)	22 (16.42%)
Disease manifestations	
Modified Rodnan Skin Score (median, IQR)	4 (2-9)
Reflux oesphagitis (n, %)	46 (32.17%)
Oesophageal dysmotility (n, %)	24 (16.78%)
GAVE (n, %)	12 (8.39%)
SIBO (n, %)	8 (5.59%)
Pseudo-obstruction (n, %)	6 (4.20%)
Digital ulcers (n, %)	75 (52.45%)
Interstitial lung disease** (n, %)	42 (29.37%)
Pulmonary arterial hypertension*** (n, %)	10 (6.99%)
Myositis**** (n, %)	19 (13.29%)

Cardiac involvement***** (n, %)	11 (7.69%)
Scleroderma renal crisis****** (n, %)	4 (2.80%)
Treatment at baseline study visit	
Proton pump inhibitor (n, %)	101 (70.63%)
H2 receptor antagonist (n, %)	7 (4.90%)
Calcium channel antagonist (n, %)	58 (40.56%)
Mycophenolate (n, %)	31 (21.68%)
Methotrexate (n, %)	22 (15.38%)
Prednisolone (n, %)	27 (18.88%)

*134 patients have RNA polymerase III antibody testing

** Interstitial lung disease was defined by the presence of pulmonary fibrosis on HRCT. Patients were referred for HRCT if ILD was suspected due to abnormal RFTs or abnormal clinical examination.

*** Pulmonary arterial hypertension was defined as a mean pulmonary arterial pressure of $\geq$ 20mmHg, pulmonary arterial wedge pressure of $\leq$ 15mmHg and pulmonary vascular resistance of $\geq$ 3 Woods units on right heart catheterisation.

**** Myositis considered present with clinical weakness and elevated creatine kinase, typical magnetic resonance imaging or electromyography findings, or positive muscle biopsy.

***** Cardiac involvement was determined by physician assessment based on the presence of systolic or diastolic dysfunction or rhythm disturbance attributed to SSc.

****** Scleroderma renal crisis defined by the presence of new onset hypertension, acute renal impairment with or without microangiopathic haemolytic anaemia.

Abbreviations: GAVE: gastric antral vascular ectasia; IQR: interquartile range; Scl70: anti-topoisomerase I antibody; SIBO: small intestinal bacterial overgrowth

Note: Reflux oesophagitis confirmed by endoscopy; Oesophageal dysmotility confirmed by barium swallow or manometry; GAVE confirmed by endoscopy; SIBO considered present if patient required use of cyclical antibiotics for management of diarrhoea; Pseudo-obstruction confirmed by patient report of requirement of management of episode(s) of large bowel pseudo-obstruction

Table 2: Logistic regression analysis of patient-reported gastrointestinal disease status and clinical variables

Clinical symptoms of GIT disease	**Univariable analysis* Odds Ratio (95% CI)**	**Multivariable analysis of patient assessed GIT disease activity and clinical symptoms of GIT disease, controlled for covariates of interest** Odds Ratio (95% CI)**								
		Age	*BMI*	*Current immunosuppressive*** treatment*	*Current Immunosuppressive*** & CCB treatment*	*PPI treatment*	*Current smoking*	*Alcohol use*	*PROMIS depression scale*	*PROMIS anxiety scale*
New reflux	2.98 (1.04-8.54) p=0.04	2.98 (1.04-8.56) p=0.04	3.63 (1.17-11.24) p=0.03	3.81 (1.25-11.60) p=0.02	3.53 (1.18-10.60) p=0.03	3.69 (1.21-11.30) p=0.02	3.11 (1.07-9.07) p=0.04	3.42 (1.15-10.17) p=0.03	2.72 (0.81-9.13) p=0.11	3.13 (0.92-10.61) p=0.07
New dysphagia	4.27 (0.81-22.37) p=0.08	4.54 (0.85-24.31) p=0.08	4.18 (0.54-32.07) p=0.17	4.19 (0.78-22.41) p=0.09	4.72 (0.88-25.40) p=0.07	4.21 (0.78-22.61) p=0.09	4.23 (0.80-22.25) p=0.09	4.30 (0.81-22.84) p=0.09	1.05 (0.09-11.92) p=0.97	1.20 (0.10-13.97) p=0.88
New bloating	2.47 (0.88-6.91)	2.65	4.52	2.31 (0.81-6.52)	2.48 (0.88-6.98)	3.10	2.59	3.07	3.47	3.77

	p=0.08	(0.93-7.58) p=0.07	(1.40-14.60) p=0.01	p=0.12	p=0.09	(1.04-9.20) p=0.04	(0.87-7.66) p=0.09	(1.05-9.01) p=0.04	(1.04-11.51) p=0.04	(1.16-12.30) p=0.03
Increased number of daily bowel actions****	1.95 (0.62-6.14) p=0.25	1.95 (0.62-6.15) p=0.25	1.80 (0.49-6.63) p=0.38	1.96 (0.62-6.25) p=0.26	1.98 (0.63-6.28) p=0.25	2.15 (0.66-7.02) p=0.20	1.97 (0.62-6.20) p=0.25	2.19 (0.67-7.17) p=0.19	1.49 (0.37-6.07) p=0.58	1.45 (0.36-5.81) p=0.60
New diarrhoea	2.03 (0.70-5.90) p=0.20	2.08 (0.71-6.11) p=0.18	2.56 (0.80-8.13) p=0.11	1.98 (0.67-5.83) p=0.21	1.99 (0.68-5.84) p=0.21	2.23 (0.74-6.71) p=0.16	2.02 (0.69-5.89) p=0.20	2.27 (0.75-6.93) p=0.15	2.27 (0.68-7.53) p=0.18	2.37 (0.72-7.81) p=0.15
New constipation	2.70 (0.96-7.65) p=0.06	2.69 (0.95-7.62) p=0.06	4.26 (1.25-14.59) p=0.02	2.66 (0.93-7.61) p=0.07	2.61 (0.92-7.42) p=0.07	2.71 (0.93-7.84) p=0.07	2.69 (0.95-7.66) p=0.06	3.10 (1.05-9.09) p=0.04	2.24 (0.67-7.45) p=0.19	2.43 (0.74-7.98) p=0.14
New onset SIBO	Perfect prediction	-	-	-	-	-	-	-	-	-

New faecal incontinence	1.35 (0.34-5.33) p=0.67	1.32 (0.33-5.25) p=0.79	1.39 (0.33-5.91) p=0.66	1.21 (0.30-4.89) p=0.78	1.24 (0.31-4.95) p=0.77	1.08 (0.27-4.33) p=0.91	1.35 (0.34-5.34) p=0.67	1.38 (0.34-5.63) p=0.65	1.67 (0.40-7.03) p=0.48	1.53 (0.37-6.31) p=0.56
Anaemia (Hb <120 g/L)	1.17 (0.47-2.93) p=0.74	1.14 (0.45-2.90) p=0.78	1.34 (0.49-3.70) p=0.57	1.18 (0.47-2.99) p=0.72	1.19 (0.47-3.01) p=0.71	1.09 (0.43-2.76) p=0.86	1.18 (0.47-2.97) p=0.72	1.37 (0.53-3.56) p=0.52	1.84 (0.67-5.04) p=0.24	1.89 (0.69-5.21) p=0.22
New anaemia	0.82 (0.22-3.08) p=0.77	0.81 (0.22-3.04) p=0.76	0.92 (0.22-3.78) p=0.91	0.87 (0.23-3.28) p=0.84	0.87 (0.23-3.29) p=0.84	0.73 (0.19-2.77) p=0.64	0.84 (0.22-3.17) p=0.80	0.96 (0.25-3.75) p=0.95	1.29 (0.32-5.13) p=0.72	1.22 (0.30-4.89) p=0.78
Weight loss	1.50 (0.66-3.43) p=0.33	1.50 (0.65-3.42) p=0.34	1.67 (0.63-4.41) p=0.30	1.47 (0.64-3.39) p=0.36	1.61 (0.69-3.72) p=0.27	1.47 (0.64-3.41) p=0.37	1.51 (0.66-3.46) p=0.33	1.64 (0.67-4.01) p=0.28	3.19 (1.19-8.55) p=0.02	3.09 (1.16-8.24) p=0.02
SF-36 PCS	0.97 (0.93-1.01)	0.98	0.98	0.97 (0.93-1.02)	0.97 (0.93-1.02)	0.98	0.97	0.98	0.97 (0.93-1.02)	0.97

	p=0.14	(0.93-1.02) p=0.28	(0.93-1.03) p=0.41	p=0.22	p=0.22	(0.94-1.03) p=0.45	(0.93-1.01) p=0.15	(0.94-1.03) p=0.44	p=0.26	(0.93-1.01) p=0.19
SF-36 MCS	0.98 (0.93-1.02) p=0.27	0.98 (0.93-1.02) p=0.25	0.97 (0.92-1.02) p=0.25	0.98 (0.94-1.02) p=0.33	0.98 (0.93-1.02) p=0.30	0.97 (0.93-1.02) p=0.21	0.98 (0.93-1.02) p=0.35	0.98 (0.93-1.02) p=0.31	0.99 (0.93-1.07) p=0.96	0.97 (0.91-1.04) p=0.37
Total UCLA GIT 2.0 Score	6.14 (2.60-14.50) p<0.01	6.10 (2.58-14.45) p<0.01	9.60 (2.96-31.21) p<0.01	5.83 (2.45-13.85) p<0.01	5.90 (2.49-13.99) p<0.01	5.36 (2.23-12.87) p<0.01	6.11 (2.58-14.47) p<001	9.11 (3.19-25.97) p<0.01	6.62 (2.44-17.97) p<0.01	7.63 (2.78-20.96) p<0.01
Change in UCLA GIT 2.0 Score*****	45.98 (4.04-523.61) p<0.01	53.71 (4.38-658.36) p<0.01	59.05 (2.36-1477.40) p=0.01	47.14 (4.01-553.66) p<0.01	45.85 (4.00-525.18) p<0.01	35.83 (3.29-390.81) p<0.01	40.44 (3.35-488.43) p<0.01	99.47 (4.02-2459.32) p<0.01	33.65 (2.95-383.81) p<0.01	36.79 (3.21-421.51) p<0.01
MSS Gastrointestinal Score	1.71 (1.15-2.56) p=0.01	1.76 (1.17-2.64)	1.61 (1.04-2.49)	1.66 (1.11-2.49) p=0.01	1.68 (1.12-2.52) p=0.01	1.62 (1.08-2.43)	1.71 (1.15-2.56)	1.77 (1.17-2.68)	1.52 (0.92-2.49) p=0.10	1.60 (0.95-2.67)

		p<0.01	p=0.03			p=0.02	p<0.01	p<0.01		p=0.08
Change (≥ 1 point) in MSS Gastrointestinal Score	1.54 (0.91-2.59) p=0.11	1.61 (0.94-2.77) p=0.08	1.42 (0.84-2.42) p=0.19	1.44 (0.86-2.44) p=0.16	1.50 (0.89-2.52) p=0.13	1.49 (0.89-2.50) p=0.13	1.56 (0.92-2.63) p=0.10	1.55 90.91-2.62) p=0.11	1.67 (0.92-3.05) p=0.09	1.75 (0.95-3.24) p=0.07
SCTC Damage Index GIT Score	1.23 (0.10-1.53) p=0.07	1.23 (0.99-1.54) p=0.07	1.23 (0.96-1.58) p=0.10	1.21 (0.97-1.52) p=0.10	1.21 (0.97-1.52) p=0.10	1.16 (0.92-1.46) p=0.21	1.23 (0.99-1.54) p=0.07	1.28 (1.01-1.62) p=0.04	1.28 (0.95-1.74) p=0.10	1.29 (0.95-1.74) p=0.10

*Univariable analyses presented show results of logistic regression analysis with patient-reported worsening as dependent variable

**Multivariable analyses presented show results of logistic regression analysis evaluating association between patient-reported worsening (dependent variable) and each of the clinical symptoms of gastrointestinal disease listed in column 1, controlled for the covariates of interest that may also affect symptoms of gastrointestinal involvement. Each multivariable model is presented in columns 3-11.

***Immunosuppressive treatment refers to current use of either prednisolone, mycophenolate or methotrexate

****Increased number of bowel actions considered present if number of daily bowel actions greater than number recorded at preceding study visit.

*****Any increase in UCLA GIT 2.0 score between visits

Abbreviations: BMI: body mass index; CCB: calcium channel antagonist; CI: confidence interval; GIT: gastrointestinal; Hb: haemoglobin; MCS: mental component score; MSS: Medsger Severity Scale; PCS: physical component score; PPI: proton pump inhibitor; PROMIS: Patient-Reported Outcomes Measurement Information System Instrument SCTC: Scleroderma Clinical Trials Consortium; SF-36: Short Form 36; SIBO: small intestinal bacterial overgrowth; UCLA: University of California, Los Angeles

Table 3: Logistic regression analysis of physician-reported gastrointestinal disease activity and clinical symptoms

Clinical symptom of GIT disease	**Physician global assessment**	
	Odds Ratio (95% CI)	p value
New reflux	1.33 (0.44-4.05)	0.61
New dysphagia	3.57 (0.68-18.59)	0.13
New bloating	0.55 (0.15-2.00)	0.36
Increased number of daily bowel actions*	1.13 (0.34-3.76)	0.85
New diarrhoea	1.22 (0.41-3.70)	0.72
New constipation	2.20 (0.79-6.14)	0.13
New-onset SIBO	3.41 (0.21-56.00)	0.39
New faecal incontinence	1.12 (0.29-4.41)	0.87

Anaemia	1.15 (0.48-2.78)	0.75
New anaemia	0.69 (0.18-2.55)	0.57
Weight loss	1.86 (0.84-4.09)	0.12
SF-36 PCS	1.01 (0.97-1.05)	0.72
SF-36 MCS	0.97 (0.93-1.01)	0.20
Total UCLA GIT 2.0 Score	1.99 (0.94-4.18)	0.07
Change in UCLA GIT 2.0 Score**	1.35 (0.21-8.62)	0.75
MSS Gastrointestinal Score	1.38 (0.93-2.05)	0.11
Change ($\geq$ 1 point) in MSS Gastrointestinal Score	1.58 (0.94-2.65)	0.08
SCTC Damage Index GIT Score	1.11 (0.89-1.39)	0.35

Note: New onset of clinical symptoms denotes the newly recorded presence of specific GIT symptom that was recorded as absent at the immediately preceding study visit.
*Increased number of bowel actions considered present if number of daily bowel actions greater than number recorded at preceding study visit.
**Any increase in UCLA GIT 2.0 score between visits
Abbreviations: GIT: gastrointestinal; MCS: mental component score; MSS: Medsger Severity Scale; PCS: physical component score; SCTC: Scleroderma Clinical Trials Consortium; SF-36: Short Form 36; SIBO: small intestinal bacterial overgrowth; UCLA: University of California, Los Angeles