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Systemic sclerosis: can we identify patients at risk?

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Chapter 4

Gastro-intestinal symptom severity and progression in systemic sclerosis

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Objectives: To evaluate the severity and evolution of patient-reported gastro-intestinal (GIT) symptoms in systemic sclerosis (SSc) patients, assess predictive factors for progression and determine the impact of standard of care treatment.

Methods: SSc patients from the Leiden and Oslo cohorts were included. We assessed clinical data and patient-reported GIT symptoms measured by the validated University of California, Los-Angeles Gastro-intestinal-tract (UCLA-GIT) score at baseline and annually. GIT severity and progression was determined for total GIT score and individual subdomains. Logistic regression was applied to identify risk factors associated with baseline GIT symptom severity. Linear mixed-effect models were applied to assess progression in GIT symptom burden and to identify predictive factors.

Results: We included 834 SSc patients with baseline UCLA GIT scores, 454 from Leiden and 380 from Oslo. Demographics and clinical characteristics at baseline were comparable in the cohorts. At baseline, 28% reported moderate-severe GIT symptoms, with increased risk for severity conferred by anti-centromere antibody (ACA), smoking and corticosteroid use, while use of calcium channel blockers appeared protective. After one and three years follow-up, 27% and 29% of patients reported increased GIT symptom severity, with reflux/bloating as the most prominently progressing symptoms. In the mixed-effect models, female sex and ACA predicted GIT symptom progression, while immunomodulatory therapies seemed to have no major impact.

Conclusion: In this large, multicenter SSc population high GIT symptom burden is present early in the disease course. Over one year, 27% of patients reported worsening of GIT symptoms, occurring independently of baseline GIT symptom severity and disease duration.

INTRODUCTION

Second to skin, the gastrointestinal tract (GIT) is the most commonly afflicted organ system in systemic sclerosis (SSc) (1). All segments of the gastrointestinal tract can be affected resulting in dysmotility and hypomotility of the oesophagus, the small intestine and the colon with possible life-threatening complications (2). GIT symptoms have negative impact on quality of life and severe GIT involvement associates with high mortality (3-8). Molecular mechanisms underlying GIT involvement in SSc are not clear, but the prevailing view is that immune-mediated inflammatory processes and progressive vascular abnormalities contribute to fibrotic changes of the bowel wall leading to disturbed intestinal blood flow, poor microcirculation, and altered contractility (9-12).

Currently, the approved treatment options for GIT involvement in SSc are limited, but this may, at least partially relate to the fact that very few intervention studies have addressed GIT-related outcome measures; and those that exist have focused on SSc patients with advanced GIT disease (2, 13-15). SSc patients are frequently treated with immune-modulating and/or vasodilating treatment regimens. GIT side effects have been reported to be frequent among these therapeutic agents, including corticosteroids, mycophenolate mofetil (MMF), methotrexate, hydroxychloroquine and azathioprine as well as nintedanib (16-22). Knowledge on how SSc-related GIT symptoms develop over time is in general limited, but from the European Scleroderma Observational Study (ESOS) we know that patients with recent-onset diffuse cutaneous SSc (dcSSc), the most severe form of SSc, have increasing cumulative incidence of GIT symptoms over 24 months. But this increase did not appear to be influenced by the immune-modulating therapies used by the patients (23).

From the above, it appears that more high quality evidence is needed to be able to address everyday clinical challenges including; how is the severity of GIT symptoms, how do GIT symptoms behave over time, and can we find predictors for GIT worsening in SSc patients? Lastly, does standard of care treatment in SSc has any influence on GIT symptoms?

To approach these important questions, we need to evaluate GIT symptoms presence and severity at time of diagnosis (before treatment) and over the disease course.

In the current study, we aim to evaluate patient-reported GIT symptoms at baseline and during follow-up, determine predictive factors for GIT symptom progression, and assess associations between standard of care treatment and GIT symptoms using two prospective SSc cohorts with annual standardized recording of GIT symptoms.

METHOD

SSc patient cohorts

All SSc patients from prospective, observational cohorts followed at the Leiden University Medical Center (LUMC) and Oslo University Hospital (OUH) were consecutively recruited and included in the total SSc cohort; if they (1) fulfilled the 2013 American College of Rheumatology classification criteria for SSc and (2) had at least one UCLA GIT score available which assessed the GIT symptoms (see below) (24). Clinical data were retrieved from the research databases "Combined Care in Systemic Sclerosis (CCISS) approved by the local Ethics Committee P09.003/SH/sh" in Leiden, and the "Norwegian systemic CTD and vasculitis registry (NOSVAR) approved by the Regional Committee for Medical&Health Research Ethics South East Norway;2016-119" in Oslo, and supplemented with data from electronic patient files (25, 26). All study patients with disease duration <24 months from disease onset, defined as first non-Raynaud symptom were included in the study inception cohort, allowing for separate analyses of GIT symptom severity at time of diagnosis, the natural evolution and the effect of standard of care treatment on GIT symptom severity and progression. The cohort study was designed in accordance with the ethical principles of the Declaration of Helsinki. All patients gave written informed consent.

Patient reported GIT symptoms, and assessment of GIT symptom severity and progression

In both SSc centers we started to collect the validated patient reported outcome UCLA GIT 2.0 in 2013 on an annual basis to assess GIT symptoms together with registration in the hospital databases (27). The UCLA GIT 2.0 questionnaire is a seven-item scale including reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being, and social functioning capturing SSc-related GIT symptoms and their severity. All scales are scored from 0 (better) to 3 (worse) except the diarrhea and constipation scales (ranges are 0–2 and 0– 2.5). The total UCLA GIT score is the sum of all scales (except constipation) and ranges from 0.00–2.83 providing an estimation of the severity of GIT involvement (27, 28) (supplementary file data S1). To evaluate progression of GIT involvement the reported and validated minimal clinical important differences (MCID) in the UCLA GIT score between 2 time points (yearly visits) were assessed (MCID values can be found in supplementary file data S1) (29).

Risk factors and treatment assessments for associations with severe GIT symptoms and for progressive GIT symptoms

Candidate baseline variables for associations with severe GIT symptoms and prediction of GIT symptom progression were selected based on reports from literature and expert opinion (supplementary data S2 for included variables). As SSc is a multiorgan disease,(8) general SSc disease severity at baseline was defined based on a composite score based on individual items which are all validated. Patients were classified as having severe SSc

disease in case of presence of one or more of the following: interstitial lung disease (ILD), defined by presence of lung fibrosis on high resolution computed tomography (HRCT) and a forced vital capacity (FVC) <70%; pulmonary arterial hypertension (PAH) with mean pulmonary arteria pressure ≥ 25 mmHg by right heart catheterization; scleroderma renal crisis; digital ulcers; and/or severe skin involvement defined as modified Rodnan Skin Score (mRSS) >15 (30). Information about standard of care treatment for SSc was collected and included immunomodulatory drugs for any indication (cyclophosphamide, methotrexate, MMF, azathioprine, corticosteroids, hydroxychloroquine), vasodilating drugs (calcium channel blocker [CCB], angiotensin-converting-enzyme inhibitors [ACE inhibitors], endothelin receptor antagonist [ET-1 inhibitors], phosphodiesterase 5 inhibitor [PDE-5 inhibitor], prostacyclin analogue), and specific GIT medications (proton pump inhibitor (PPI), H₂ antagonist). Use of immunomodulatory medication was collected at every visit, and at each time of completing the UCLA GIT questionnaire. Vasodilatory and GIT drugs were evaluated as ever used. Detailed explanation on organ involvement screening can be found in supplementary file data S3.

Statistical analysis

Statistical analyses were performed on SPSS version 25 and STATA version 15. Both the total cohort and the inception cohort were analyzed at baseline, the inception cohort (disease duration since first non-Raynaud symptom < 24 months) was analyzed to exclude the effect of longstanding disease, and the total cohort was included as this mirrors the daily clinical practice. For the longitudinal data we only used the inception cohort. Ordinal logistic regressions were used to identify baseline variables associated with baseline GIT disease and were expressed as odds ratios (OR) and the corresponding 95% confidence intervals (CI). Bonferroni-Holm correction was applied to adjust for multiple testing (indicated with * in tables). To adjust for SSc disease severity at baseline as a possible confounder on treatment effect on GIT symptoms, we included the above explained composite variable in the multivariable regression analyses (detailed explanation on generating models supplementary data S4). To assess whether other organ manifestations were associated with GIT symptom severity, we applied binary logistic regression analyses including the separate clinical characteristics that were assessed in the disease severity variable as predictors. To better understand the effect of immunosuppressive treatment on GIT symptoms we determined GIT symptom progression in patients naïve for immunosuppressive treatment and in treatment exposed patients. Linear mixed-effect models were used to assess changes in UCLA GIT score (all domains) over the observation time, to control for repeated measurements, and to identify risk factors predictive for any change in GIT symptoms during follow-up. Time and risk factors were fixed effects in the analysis. Interaction effects between time and fixed factors were checked. All models included random intercept and slope, and an unstructured correlation matrix was used.

RESULTS

Patient populations

The total study cohort included 834 SSc patients, all with baseline UCLA GIT scores. Demographics and clinical characteristics at baseline were comparable in patients from the LUMC and OUH cohorts (supplementary table S1). From the total cohort, 236 patients had disease duration <24 months and were included in study inception cohort (table 1).

Prevalence of patient-reported gastro-intestinal symptoms and baseline characteristics associated with GIT symptom burden

We assessed all baseline values of all the sub-items of the UCLA GIT score separately in the total and inception cohorts and found that the prevalence and distribution of symptoms did not differ, except for significantly lower frequencies of moderate-severe reflux and distension/bloating in the inception cohort (figure 1). At baseline, the total UCLA GIT score was equivalent to none-mild GIT symptoms in most of the patients (72%, n= 601), with 11% of these patients reporting a score of zero. Moderate or severe GIT symptom burden were reported by 28% of patients, with 21% moderate (n= 175) and 7% severe (n= 58). As shown in Figure 1, the frequency of severe symptom burden varied considerably between the UCLA GIT subdomains.

By multivariable analysis on the inception cohort, to control for the influence of longstanding disease, we found that female sex (OR 8.5 (1.1-36.01)) and ever smoking (OR 2.9 (1.2-7.3)) was associated with GIT symptom severity, while none of the standard of care therapies did reach the significance level (table 2). In the total cohort, the association of female sex (OR 1.76 (1.04-2.98)) and ever smoking (OR 1.69 (1.19-2.41)) was confirmed, and presence of anti-centromere antibody [ACA] (OR 2.07 (1.34-3.19)), and corticosteroid use (OR 1.92 (1.18-3.12)) were significantly associated with moderate-severe total GIT symptom burden at baseline, while CCB use (OR 0.55 (0.39-0.83)) seemed to be protective (supplementary file table S2). Other standard of care therapies were not associated with GIT symptom severity at baseline.

Baseline demographic and clinical characteristics of the total systemic sclerosis cohort*, and for patients with disease duration < 2 years since first non-Raynaud (inception cohort)

	Total cohort	Inception cohort	P
Demographic	n=834	n=236	
Female, n (%)	687 (82)	180 (76)	0.57
Age, yrs mean (SD)	55 (14)	54 (13)	0.91
SSc disease duration at inclusion, median (IQR)	5.9 (1.7-11.9)	0.7 (0.3-1.2)	<0.001
Smoking, ever n (%)	420 (50)	122 (62)	0.32
Organ involvement			
Diffuse cutaneous SSc, n (%)	186 (22)	67 (28)	0.24
Severe skin involvement, n (%)	96 (12)	43 (19)	0.32
Myositis, n (%)	51 (6)	18 (8)	0.46
DLCO% < 60% of predicted, n (%)	267 (33)	71 (31)	0.75
FVC% < 70% of predicted, n (%)	65 (8)	15 (7)	0.78
ILD on HRCT, n (%)	305 (37)	71 (30)	0.33
PAH, n (%)	57 (7)	18 (8)	0.67
SSc specific autoantibodies			
Anti RNA polymerase III, n (%)	62 (7)	29 (12)	0.23
Anti-centromere, n (%)	392 (47)	96 (41)	0.34
Anti-topoisomerase, n (%)	165 (20)	56 (24)	0.57
Treatment at baseline			
Calcium Channel Blockers, n (%)	305 (37)	95 (40)	0.67
H2 receptor blocker, n (%)	256 (31)	72 (31)	0.78
ET-1 inhibitors&prostacyclin analogue, n (%)	97 (12)	19 (5)	0.23
Proton Pump Inhibitor, n (%)	298 (36)	83 (35)	0.66
Methotrexate, n (%)	78 (9)	24 (10)	0.71
Mycophenolate mofetil, n (%)	38 (5)	13 (6)	0.81
Azathioprine, n (%)	13 (2)	2 (1)	0.91
Corticosteroids, n (%)	85 (10)	27 (11)	0.81
Cyclophosphamide, n (%)	11 (1)	10 (4)	0.54
Hydroxychloroquine, n (%)	27 (3)	7 (3)	0.68

Table 1. N = 454 patients of the Leiden University Medical Center and N= 380 patients of the Oslo University Hospital; DLCO= single-breath diffusing lung capacity for carbon monoxide, ET-1= endothelin receptor, FVC= forced vital capacity, ILD= interstitial lung disease, HRCT= high resolution computed tomography, PAH= pulmonary arterial hypertension, n= number, SD= standard deviation; IQR= interquartile range. ‡ based on modified Rodnan Skin Score > 15 points.



Figure 1. Severity of gastro-intestinal involvement at baseline in the total cohort and the inception cohort. Disease severity at baseline according to the UCLA GIT 2.0 score on every subdomain in the total and the inception cohort. This figure shows the percentage of SSc patients with none-mild, moderate and severe gastro-intestinal involvement for each subdomain at baseline.

Table 2: Logistic regression analyses of baseline characteristics associated with moderate/severe total UCLA GIT symptom score in the 236 systemic sclerosis patients from the Leiden and Oslo inception cohort

	Univariable			Multivariable		
	OR	95% CI	Significance p-value	OR	95% CI	Significance p-value
	Moderate / severe total GIT symptom score					
Female	3.03	1.22-7.5	0.01*	8.5	1.1-36.01	< 0.001*
Age, Years	1.01	0.99-1.03	0.30	-	-	-
Disease duration, yrs	0.61	0.37-1.01	0.06	0.65	0.43-1.11	0.13
Raynaud duration, yrs	1.01	0.97-1.04	0.68	-	-	-
Smoking ever	1.73	1.13-3.68	0.03*	2.9	1.2-7.2	<0.001*
Diffuse subset*	0.89	0.56-1.40	0.89	-	-	-
Disease severity#	1.22	0.63-2.45	0.56	1.34	0.78-2.66	0.62
Weight loss (>10% in 1 year)	0.67	0.25-1.82	0.43	-	-	-
Hemoglobine level	0.70	0.41-1.20	0.20	-	-	-
Myositis	1.01	0.32-3.22	0.98	-	-	-
Anti-centromere antibody	1.86	0.98-3.4	0.07	2.01	0.93-5.32	0.11
Anti-topoisomerase antibody	1.52	0.71-3.25	0.28	-	-	-
Anti-RNAPIII antibody	0.54	0.24-1.23	0.14	-	-	-
Proton pump inhibitor	0.65	0.25-1.20	0.17	-	-	-
H2 receptor blocker	1.62	0.73-3.56	0.23	-	-	-
ACE-inhibitor	0.89	0.41-1.96	0.78	-	-	-
Calcium channel blocker	1.06	0.57-1.98	0.84	-	-	-
Mycophenolate mofetil	0.38	0.09-1.03	0.06	0.43	0.08-1.05	0.09
Methotrexate	0.70	0.28-1.78	0.45	-	-	-
Azathioprine	0.26	0.22-1.03	0.09	0.43	0.34-1.18	0.23
Corticosteroids	0.65	0.27-1.57	0.33	-	-	-
Cyclophosphamide	1.09	0.22-5.35	0.91	-	-	-
Hydroxychloroquine	0.79	0.15-4.07	0.77	-	-	-
Prostacyclin & ET-1 inhibitor	0.34	0.09-1.28	0.11	-	-	-

*Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse cutaneous subset. CI= confidence interval, OR= odds ratio. # disease severity is a compound variable which included: interstitial lung disease, pulmonary arterial hypertension, renal crisis, severe skin disease or presence of digital ulcers. Medication is entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. ACE= angiotensin-converting-enzyme, ET-1= endotheline receptor. IQR= interquartile range, SD= standard deviation. In bold are the significant associations. * remains significant after Holm-Bonferroni correction.

Next, we evaluated associations of baseline clinical characteristics and use of standard-of care therapies separately for each of the individual subdomains of the UCLA GIT questionnaire in the total cohort with correction for disease duration and disease severity (supplementary table S2-S9). We identified dcSSc as a risk factor for more severe distension/bloating, diarrhea and for severe affection of social functioning. Presence of ACA was a risk factor for severity in every subdomain except for constipation. Regarding standard of care treatments, we found that ever use of corticosteroids associated with more severe fecal soilage (OR 3.91 (1.27-12.08)). The use of CCB was protective against severe distention/bloating (OR 0.56 (0.37-0.83)) and diarrhea (OR 0.61 (0.44-0.85)).

Regarding, reflux medication we found that ever use of PPI associated with more severe reflux (OR 1.39 (1.07-1.80)) and with more severe fecal soilage symptoms (OR 3.07 (1.28-7.49)). Ever use of H₂ receptor blockers was also associated with more severe reflux (OR 1.71 (1.28-2.32)), but was protective for severe distension/bloating (OR 0.66 (0.47-0.93)). The other therapeutics assessed were not associated with severity in any of the seven sub-items.

To assess whether any of the specific organ manifestations of SSc associate with GIT symptom severity we applied multivariable logistic regression with each of the single organ manifestations. Presence of digital ulcers showed significant associations with total GIT symptom score (OR 1.5 (1.1-2.2)) and with distension/bloating (OR 1.7 (1.2-2.4)).

Progression of GIT symptoms from baseline to follow-up

To account for effects of longstanding disease leading to more organ damage, we evaluated progression of GIT symptoms in the inception cohort. In the inception cohort, after one year of follow-up, 27% of patients had clinically important GIT symptom progression, defined by increase in total GIT score from baseline, with sub-item analysis showing progression of reflux symptoms in 26%, distension/bloating in 29% and constipation in 21%. By evaluating the mean scores in the inception cohort over time our understanding of GIT progression improved, as shown by figure 2 the mean scores vary greatly over time, in all subdomains the scores after 5 years are higher, indicating worse GIT symptoms, compared to the baseline scores. Especially for the subdomains diarrhea, social functioning, emotional wellbeing and distension/bloating the figures show slow progression during follow-up (figure 2).

GIT symptom progression was not associated with GIT symptoms severity at baseline, neither for the total GIT score (OR 0.8 (0.3-2.6)), nor for any of the subdomains.

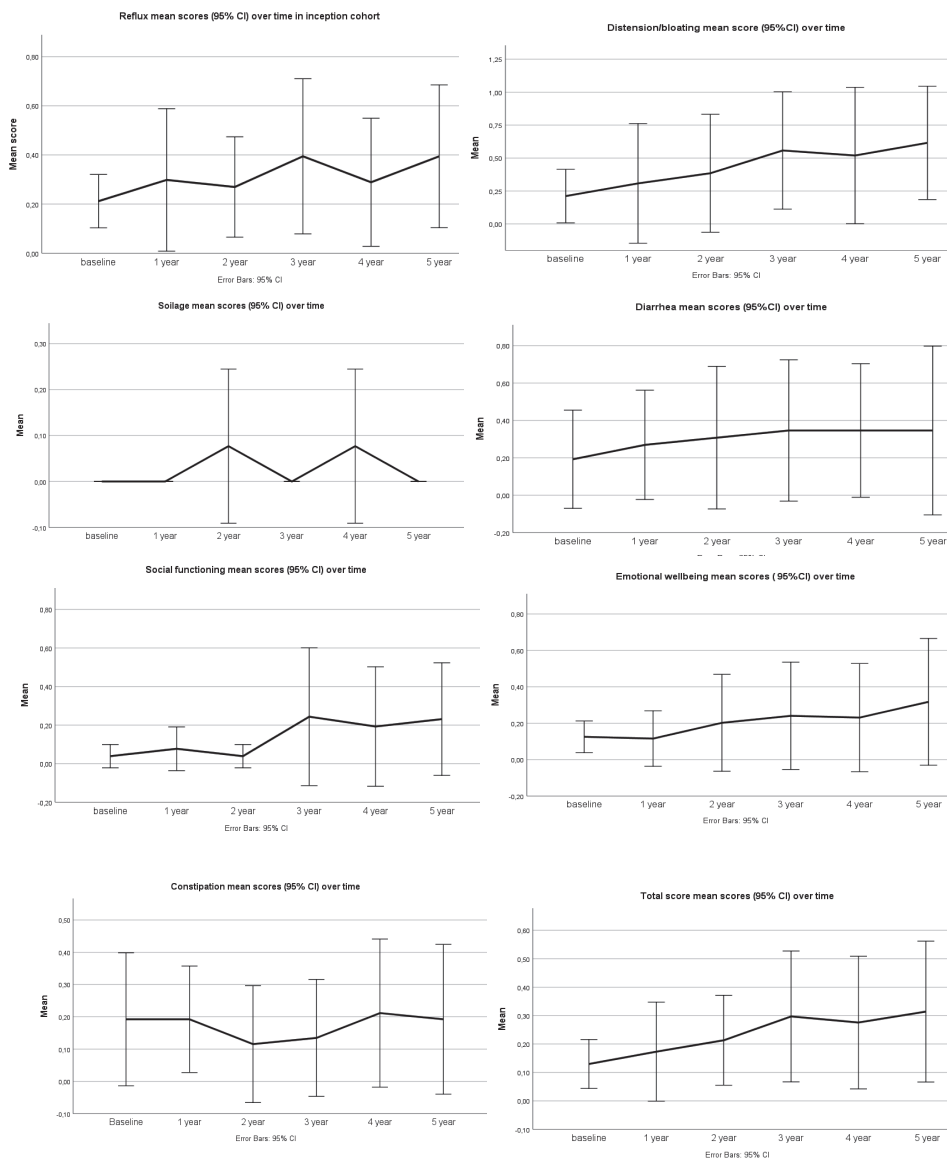


Figure 2. Mean scores per GIT subdomain over the follow-up period in the inception cohort. Higher scores indicates worse GIT symptoms, lower scores indicate less GIT symptoms.

GIT symptom progression in treatment naïve patients and in patients starting with immunosuppressive treatment

To assess natural evolution of GIT symptoms in SSc, we determined change in UCLA GIT scores from baseline to follow-up in patients who were naïve for immunosuppressive treatment across the observation period. In the inception cohort, 81% (n= 192) were treatment naïve at baseline and 48% (n= 72) remained so at follow-up.

We found that more patients at each subsequent visit had worsened since baseline over the first three years in inception patients naïve for immunosuppressive treatment, except for the diarrhea and emotional subdomain (supplementary figure S1).

To evaluate impact of start with immunomodulatory therapies, we determined GIT symptom progression in treatment exposed patients. Typical indications for immunomodulatory therapies in SSc are severe skin and lung disease. Hence, it was not unexpected to find that patients exposed to treatment had more frequently ILD, diffuse cutaneous SSc and positive ATA than the treatment naïve patients, while age and sex were comparable.

We found no significant difference in GIT symptom progression between immunosuppressive treatment naïve patients and patients exposed to methotrexate, MMF, azathioprine, hydroxychloroquine, corticosteroids or cyclophosphamide after one year or follow-up. Numerically, more patients that started with corticosteroids, or MMF had progressive GIT symptoms after one year in the inception cohort (figure 3).

Predictors of GIT symptom progression during the follow-up period

For these multivariable linear mixed-effect model analyses, we focused primarily on the inception cohort, arguing that patients with short disease duration would have more active disease and less structural damage, and therefore be more liable to react to standard-of-care therapies. Of the variables of interest only treatment with CCB was identified as a predictor of marginal worsening of total GIT symptoms, with significant interaction effects between time and CCB treatment. The estimated difference of 0.04 in total GIT symptom score between CCB treated and CCB untreated patients was below the MCID previously defined for UCLA GIT (29).

Supplementary analyses of the total cohort showed that female gender and smoking were predictive for progression of bloating and diarrhoea with significant interaction effects over time. None of the other variables were predictive for time-dependent progression in total GIT or subdomain scores.

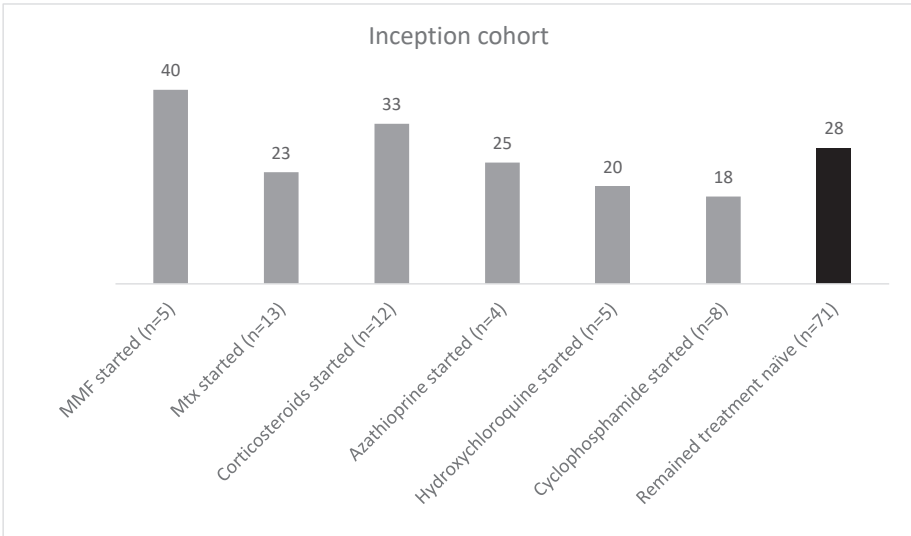


Figure 3. Percentage of progressors (inception cohort) for the total GIT score after 1 year of follow-up stratified for start of immunomodulatory treatment (no treatment are patients who remained treatment naïve). Description: Inception cohort: n= 118 inception patients with available UCLA GIT after one year, n= 71 remained treatment naïve, n= 47 started with immune-modulating therapy.

Results of linear mixed model in the inception cohort of systemic sclerosis patients on total GIT symptom score over a 3 years' time period.

Predictor variable	Univariable			Multivariable		
	Coefficient	95% CI	p value	Coefficient	95% CI	p value
Sex	0.02	-0.03-0.06	0.52			
Age	0.0003	-0.001-0.002	0.71			
Disease duration	-0.011	-0.04-0.01	0.37			
Ever smoking	0.04	-0.003-0.08	0.07			
Anti-centromere antibody	-0.004	-0.04- 0.04	0.85			
Anti-topoisomerase antibody	0.006	-0.04-0.05	0.81			
Skin involvement*	0.001	-0.0004-0.003	0.13			
Diffuse disease subset	0.04	- 0.0008-0.09	0.05	0.03	-0.001-0.08	0.12
ESR	-0.0001	- 0.0005-0.0002	0.43			
Myositis	0.04	-0.05 - 0.12	0.41			
PAH	0.05	-0.02-0.13	0.18			
ILD	0.02	-0.02-0.06	0.41			
ACE	0.02	-0.02-0.06	0.33	0.02	-0.02-0.06	0.29
CCB	0.04	0.001-0.08	0.04	0.04	0.0006-0.08	0.04
PPI	0.02	-0.02-0.06	0.34	0.02	-0.02-0.06	0.22
ET-1	0.05	-0.02-0.13	0.22	0.05	-0.03-0.14	0.19
H2 blocker	0.0003	-0.04-0.04	0.99	0.002	-0.04-0.04	0.94
Corticosteroids	0.02	-0.03-0.06	0.48	0.02	-0.03-0.06	0.46
Methotrexate	-0.011	-0.06-0.04	0.68	0.006	-0.04-0.05	0.79
Azathioprine	-0.06	-0.14-0.05	0.18	-0.05	-0.13-0.03	0.22
Hydroxychloroquine	-0.03	-0.10-0.03	0.28	-0.04	-0.10-0.03	0.26
MMF	-0.01	-0.08-0.06	0.76	-0.006	-0.07-0.06	0.87
Cyclophosphamide	0.04	-0.006-0.09	0.090	0.04	-0.006-0.09	0.08

Table 3. Coefficients shown are the interactions terms (predictor * time). Mean between group change during three years of follow-up. Separate multivariable regression analyses with adjustment for time, age, sex and ACA. ILD= interstitial lung disease, PAH= pulmonary arterial hypertension, mRSS= modified Rodnan Skin Score, CCB= calcium channel blockers, PPI = proton pump inhibitors, ET-1= endotheline receptor antagonist, ACE= Angiotensin-converting-enzyme inhibitors, ESR= erythrocyte sedimentation rate, MMF= Mycophenolate mofetil. Time effects of the mixed model can be found in supplementary file *assessed by the modified Rodnan Skin score. Significant results are not significant after Bonferroni-Holm Correction.

DISCUSSION

GIT involvement is reported as highly frequent in SSc, with major impact on patient's quality of life and survival. Here, we show that about 1/3 of patients in a large, unselected SSc population reports high GIT symptom burden early in the disease course, with reflux and distention/bloating as the most troublesome early symptoms. Over one year observation, 27% of patients reported worsening of GIT symptoms. Interestingly, this worsening occurred independent of baseline GIT symptom severity and disease duration.

To our knowledge, this is the first large, multicenter study prospectively mapping GIT symptom burden in a well characterized SSc cohort. The identification of high symptomatic burden from early in the disease course and the progressive behaviour of the GIT symptoms have impact at several levels. Firstly, knowledge about severity and the natural behaviour of GIT symptoms is a prerequisite to identify patients for inclusion in clinical trials and to assess treatment effects. This is particularly important in times of evolving new therapeutic options, like fecal microbiota transplantation (FMT) (31, 32). Secondly, it is of major clinical relevance for physicians following these patients and argues for the necessity of multidisciplinary team (MDT) assessment including rheumatologists and gastroenterologists in SSc. MDT assessments are important and well-functioning for other diseases, like Crohn's disease and in ILD (33, 34). We strongly advocate to build up MDT for GIT in all SSc expert centers, and initiate work on recommendations for the management of this devastating organ affliction in SSc. The specific need for further development of GIT care was also highlighted in the recently published international standard for longitudinal follow-up of SSc patients, where only reflux symptom assessment and dysphagia, diarrhoea, and weight loss were included (35).

For this study, we performed the first ever systematic assessment of associations between SSc characteristics including standard-of-care therapies and GIT symptoms in two large SSc cohorts mapping the whole SSc population. Interestingly, we found that corticosteroid use might associate with high GIT symptom burden. The associations to corticosteroids was not identified in the inception cohort subset. The smaller sample size could be one explanation for this, another could be that GIT side effects of corticosteroids accumulate over time. ACA was associated with more severe GIT symptoms. We can only speculate about the background of this association; 1) ACA positive SSc patients might have a longer 'prodrome' as a consequence of a more indolent disease course. Indeed, disease duration since RP was significantly longer in ACA positive patients compared to ATA positive patients. On the other hand, the association between ACA and GIT symptoms remained significant after correcting for disease duration 2) ACA are directly implicated in SSc-related vasculopathy and consequently GIT symptom severity (still unknown) (36-39).

In apparent contrast to the association findings, there were no differences in GIT symptom progression between patients who were treatment naïve at all time-points and patients that started standard of care immune-modulating drug treatment during follow-up. These results argue that immunomodulatory treatment for SSc do not seem to have major impact on GIT disease evolution in SSc. Although, the exact etiology of GIT symptoms in SSc is and remains largely unknown and therefore can be influenced by multiple (unknown) factors. Previous data on this subject are highly limited, but it appears that our results are in line with McMahan et al. who showed no effect of immunomodulatory treatment on severe dysmotility assessed by the Medsger activity score (40). Notably, that study did not use a patient reported GIT outcome measure, it did not include treatment naïve patients, and it did not assess effects of vasodilatory treatments.

The mechanisms behind the GIT involvement in SSc are not well understood, but appear multifactorial. Vasculopathy is an important factor in SSc pathogenesis, and some reports indicate associations between GIT symptoms and progressive vasculopathy (41, 42). Interestingly in our study, patients showing progression of GIT symptoms had also more often digital ulcers, while no association was found with other organ manifestations as ILD or skin involvement. Although this is not a mechanistic study, we speculate that the digital ulcer association, and possibly also the effects of CCB in the cross-sectional data set, implicates vasculopathy in the pathophysiology of SSc GIT disease.

Our study is not without limitations. The UCLA GIT is a validated questionnaire, however it remains a self-reported questionnaire and this can always introduce bias. The UCLA GIT captures symptoms in the past seven days, we included annual follow-up which might not capture all short-term changes. Many assessments were performed in this study, by using Bonferroni correction we have reduced the risk of type I errors. A relatively low percentage of patients experienced fecal soilage, which might be underestimation due to recruitment bias and patients' reluctance to talk about this symptom. It should also be mentioned, that using the MCID could still miss patients with clinical relevant GIT development, as there is an inherent uncertainty around MCID estimates (29). Unfortunately, objective measurements are not performed as standard assessment in SSc patients and therefore we were not able to include this in our manuscript. Other than gastroduodenoscopy few assessments are performed at all and for dysmotility evaluation none are even routinely available to date. We suggest that for a better understanding of the etiology this would be a next step to evaluate and this highlights a clear clinical unmet need. We should also be aware of the possibility of confounding by indication in the analyses evaluating GIT treatment and GIT symptom progression as patients with more severe reflux symptoms are also more likely to receive GIT treatment. By collecting patient reported outcome measures not more than once a year, we are not positioned to fully capture medication

driven side effects. In addition, we did not adjust for treatment indication; but we believe this is of minor interest as medication despite indication may have an influence on all organ manifestations. The medication included in this study was based on standard of care therapy in SSc and availability in the database. Unfortunately, GIT medication outside of gastroesophageal reflux disease (GERD) medication has not been collected to incorporate this in the analysis. In addition, only a minority of SSc patients uses other GIT treatments and then often only occasionally or for short-term treatment. In the Leiden cohort ever use of metoclopramide, domperidone and antibiotics is collected since 2018. In 483 SSc patients, 4% used domperidone (n= 20), 4% used metoclopramide (n= 16), 8% laxatives (n= 42), loperamide 1% (n= 4), and 1% used antibiotics for bacterial overgrowth (n= 4). The power to evaluate progression of GIT symptoms in the inception cohort is not sufficient enough to draw firm conclusions, more follow-up data and more patients are needed to validate these data.

Strengths of this study were the large and prospective cohort, and the amount of questionnaires at baseline and over the observation period with a very small amount of missing data (<5%) and a high compliance rate (>90%). Biomarkers for GIT disease activity are still not defined, making it challenging to assess the effects of existing therapies. The UCLA GIT questionnaire allows for a standardized assessment of important clinical response measures in SSc and may play a role for informing both clinical practice and trial design. Based on the results of our analyses we can identify several important points to consider for future SSc trials focusing on GIT involvement : 1) the total UCLA GIT score does not capture all important GIT symptoms, 2) between 10-25% (depending on the domain) of the patients show improvement of GIT symptoms based on the UCLA GIT 2.0; in trial design one should take into account the natural course of GIT symptoms, and 3) validated outcome measures on GIT disease are still lacking; ideally, for clinical trials focusing on treatment of GIT involvement objective measurements should be taken into account. These novel data provide important insights regarding the high frequency of severe GIT symptoms early in the disease course, and the progressive nature of GIT symptoms in patients with SSc. We confirm ACA positive and female patients are specifically at risk for GIT symptoms, but very few other variables can help identify patients at risk of disease progression.

REFERENCES

1. Butt S, Emmanuel A. Systemic sclerosis and the gut. *Expert Rev Gastroenterol Hepatol.* 2013;7:331-9.
2. Nagaraja V, McMahan ZH, Getzug T, Khanna D. Management of Gastrointestinal Involvement in Scleroderma. *Curr. Treat. Options Rheumatol.* 2015;1:82-105.
3. Khanna D, Hays RD, Park GS, Braun-Moscovici Y, Mayes MD, McNearney TA, et al. Development of a preliminary scleroderma gastrointestinal tract 1.0 quality of life instrument. *Arthritis Rheum.* 2007;57:1280-6.
4. Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum.* 2000;43:2437-44.
5. Richard N, Hudson M, Wang M, Gyger G, Proudman S, Stevens W, et al. Severe gastrointestinal disease in very early systemic sclerosis is associated with early mortality. *Rheumatology (Oxford).* 2019;58:636-44.
6. Frantz C, Avouac J, Distler O, Amrouche F, Godard D, Kennedy AT, et al. Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. *Semin. Arthritis Rheum.* 2016;46:115-23.
7. Hoffmann-Vold A-M, Volkman ER. Gastrointestinal involvement in systemic sclerosis: Effects on morbidity and mortality and new therapeutic approaches. *J Scleroderma Relat Disord.* 2019;2397198319891282.
8. Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, Garen T, et al. Multidimensional tracking of phenotypes and organ involvement in a complete nationwide systemic sclerosis cohort. *Rheumatology (Oxford).* 2020. Oct 1;59:2920-2929.doi: 10.1093/rheumatology/keaa026.g.
9. D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med.* 1969;46:428-40.
10. Hendel L, Kobayasi T, Petri M. Ultrastructure of the small intestinal mucosa in progressive systemic sclerosis (PSS). *Acta Pathol Microbiol Scand A.* 1987;95:41-6.
11. Sjogren RW. Gastrointestinal features of scleroderma. *Curr Opin Rheumatol.* 1996;8:569-75.
12. Gyger G, Baron M. Gastrointestinal manifestations of scleroderma: recent progress in evaluation, pathogenesis, and management. *Curr Rheumatol Rep.* 2012;14:22-9.
13. Schulz SW, O'Brien M, Maqsood M, Sandorfi N, Del Galdo F, Jimenez SA. Improvement of severe systemic sclerosis-associated gastric antral vascular ectasia following immunosuppressive treatment with intravenous cyclophosphamide. *J Rheumatol.* 2009;36:1653-6.
14. Raja J, Nihtyanova SI, Murray CD, Denton CP, Ong VH. Sustained benefit from intravenous immunoglobulin therapy for gastrointestinal involvement in systemic sclerosis. *Rheumatology.* 2015;55:115-9.
15. Stern EK, Carlson DA, Falmagne S, Hoffmann AD, Carns M, Pandolfino JE, et al. Abnormal esophageal acid exposure on high-dose proton pump inhibitor therapy is common in systemic sclerosis patients. *Neurogastroenterol Motil.* 2018;30.
16. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *NEJM.* 2019;380:2518-28.
17. Adler S, Huscher D, Siegert E, Allanore Y, Czirjak L, DelGaldo F, et al. Systemic sclerosis associated interstitial lung disease - individualized immunosuppressive therapy and course of lung function: results of the EUSTAR group. *Arthritis Res Ther.* 2018;20:17.

18. Meyer KC, Decker C, Baughman R. Toxicity and monitoring of immunosuppressive therapy used in systemic autoimmune diseases. *Clin. Chest Med.* 2010;31:565-88.
19. McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. *Curr Opin Rheumatol.* 2008;20:131-7.
20. Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. *Chest.* 2006;130:30-6.
21. Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. *NEJM.* 1985;312:818-22.
22. Srinivasa A, Tosounidou S, Gordon C. Increased Incidence of Gastrointestinal Side Effects in Patients Taking Hydroxychloroquine: A Brand-related Issue? *J Rheumatol.* 2017;44:398.
23. Herrick AL, Pan X, Peytrignet S, Lunt M, Hesselstrand R, Mouthon L, et al. Treatment outcome in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study (ESOS). *Ann Rheum Dis.* 2017;76:1207-18.
24. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum.* 2013;65:2737-47.
25. Meijs J, Schouffoer AA, Ajmone Marsan N, Kroft LJ, Stijnen T, Ninaber MK, et al. Therapeutic and diagnostic outcomes of a standardised, comprehensive care pathway for patients with systemic sclerosis. *RMD open.* 2016;2:e000159.
26. Hoffmann-Vold AM, Midtvedt O, Molberg O, Garen T, Gran JT. Prevalence of systemic sclerosis in south-east Norway. *Rheumatology (Oxford).* 2012;51:1600-5.
27. Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *Arthritis Rheum.* 2009;61:1257-63.
28. Khanna D, Nagaraja V, Gladue H, Chey W, Pimentel M, Frech T. Measuring response in the gastrointestinal tract in systemic sclerosis. *Curr Opin Rheumatol.* 2013;25:700-6.
29. Khanna D, Furst DE, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *J Rheumatol.* 2011;38:1920-4.
30. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord.* 2017;2:11-8.
31. Fretheim H, Chung BK, Didriksen H, Bækkevold ES, Midtvedt Ø, Brunborg C, et al. Fecal microbiota transplantation in systemic sclerosis: A double-blind, placebo-controlled randomized pilot trial. *PLoS one.* 2020;15:e0232739.
32. Hoffmann-Vold AM, Fretheim H, Didriksen H, Molberg Ø. The potential of fecal microbiota transplantation in systemic sclerosis. *Expert Rev. Clin. Immunol.* 2020;16:117-8.
33. Gasparetto M, Angriman I, Guariso G. The multidisciplinary health care team in the management of stenosis in Crohn's disease. *J. Multidiscip. Healthc.* 2015;8:167-79.
34. Furini F, Carnevale A, Casoni GL, Guerrini G, Cavagna L, Govoni M, et al. The Role of the Multidisciplinary Evaluation of Interstitial Lung Diseases: Systematic Literature Review of the Current Evidence and Future Perspectives. *Front Med (Lausanne).* 2019;6(246).
35. Hoffmann-Vold AM, Distler O, Murray B, Kowal-Bielecka O, Khanna D, Allanore Y. Setting the international standard for longitudinal follow-up of patients with systemic sclerosis: a Delphi-based expert consensus on core clinical features. *RMD open.* 2019;5(1):e000826.

36. Herrick AL, Moore TL, Murray AK, Whidby N, Manning JB, Bhushan M, et al. Nail-fold capillary abnormalities are associated with anti-centromere antibody and severity of digital ischaemia. *Rheumatology (Oxford)*. 2010;49:1776-82.
37. Nunes JPL, Cunha AC, Meirinhos T, Nunes A, Araújo PM, Godinho AR, et al. Prevalence of auto-antibodies associated to pulmonary arterial hypertension in scleroderma - A review. *Autoimmun Rev*. 2018;17:1186-201.
38. Kampolis C, Plastiras S, Vlachoyiannopoulos P, Moysakakis I, Tzelepis G. The presence of anti-centromere antibodies may predict progression of estimated pulmonary arterial systolic pressure in systemic sclerosis. *Scand j rheumatol*. 2008;37:278-83.
39. N.M van Leeuwen JB, A. Grummels, C Wortel, S Jordan, O Distler, H fretheim, A Hoffman-Vold, H Scherer, R Toes, T Huizinga, J.K de Vries-bouwstra. Anticentromere Antibody Levels and Isotypes Associate with Disease Severity in Systemic Sclerosis. *Arthritis Rheumatol*. 2019;71(acraabstracts).
40. McMahan ZH, Paik JJ, Wigley FM, Hummers LK. Determining the Risk Factors and Clinical Features Associated With Severe Gastrointestinal Dysmotility in Systemic Sclerosis. *Arthritis Care Res (Hoboken)*. 2018;70:1385-92.
41. Mostmans Y, Cutolo M, Giddelo C, Decuman S, Melsens K, Declercq H, et al. The role of endothelial cells in the vasculopathy of systemic sclerosis: A systematic review. *Autoimmun Rev*. 2017;16:774-86.
42. Frech T WG, Murtaugh M. . Serial Sublingual Videomicroscopy in Systemic Sclerosis Clinic: Are the Microcirculation Measurements Correlated with Gastrointestinal Symptoms? [abstract]. *Arthritis Rheumatol*. 2019;71.

SUPPLEMENTARY FILE

Gastro-intestinal symptom severity and progression in systemic sclerosis

Data S1. UCLA GIT 2.0

Clinical GIT involvement by the UCLA GIT score was defined as apparent if the patients reported symptoms resulting in a total score or at least one of the seven GIT items ≥ 0.01 and was segregated into none-mild (including patients with a score of 0, or < 0.5 or for fecal incontinence and distention/bloating < 1.01), moderate (≥ 0.5 or for fecal incontinence and distention/bloating ≥ 1.01) or severe GIT symptoms (> 1.01 or for distension/bloating > 1.61 or for fecal soiling > 2.01) (1).

The minimal clinical important difference (MCID) somewhat worse threshold was used to assess disease progression and cut-offs were defined as: Reflux: 0.19, Distension/bloating: 0.12, Diarrhoea: 0.07, Constipation: 0.13, Fecal Soilage 0.06, Emotional well-being: 0.16, Social functioning: 0.21, Total GIT score 0.12 (2).

Data S2. Candidate variables

The following variables were included as candidate baseline variables for associations with GIT symptoms and prediction of GIT symptom progression: sex, age at registration, disease duration since disease onset, smoking, SSc specific antibodies (anti-centromere antibody [ACA], anti-topoisomerase antibody [ATA], anti-RNA polymerase III antibody [ARA]), SSc subset (diffuse cutaneous and limited cutaneous SSc), myositis (defined as increased creatine kinase AND proximal muscle weakness and/or confirmed with muscle biopsy), weight loss ($> 10\%$ of body weight in 1 year), and hemoglobin level (3-10).

Data S3. Organ involvement screening

Skin involvement was assessed using the modified Rodnan skin score (mRSS), a validated measure of skin thickening in SSc.(11) Skeletal myopathy was considered present when patients had an abnormal creatinine phosphokinase (CPK) and muscle weakness and/or abnormal electromyography or muscle biopsy. The presence of interstitial lung disease (ILD) was considered present if a high resolution CT scan of the thorax showed ground glass opacifications, honey combing and/or reticular infiltrations interpreted by an experienced radiologist. Pulmonary function tests were performed by every patient, and the percent predicted FVC and DLCO were determined. Pulmonary arterial hypertension was defined as an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest as assessed by RHC; including presence of pre-capillary PH, defined by a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and a PVR > 3 Wood units (WU) on RHC.

Data S4. Generating univariable and multivariable model

At the first stage, we used subject-specific knowledge to derive a list of independent variables which in principle are relevant as predictors or adjustment variables for the study in question. This list was also based on the availability of variables. With three researchers (NvL, JVB, AMH) we went through the list and critically questioned the role and further properties of each of the variables, such as chronology of measurement collection, quality of measurement, or availability also to the "user" of the model. Not for all independent variables pre-clinical knowledge was available, therefore we carried out an univariable analysis and selected those that reached a certain level of significance ($p < 0.10$). We selected the priori covariates based on biological mechanism, clinical expertise, evidence from published articles, and the univariable model. We checked the assumptions of linearity in logit for each continuous covariate and we checked for interactions. The proportional odds assumption was met. The following covariates were fixed in the model based on their clinical relevance and expert opinion: age, sex, disease duration NR, cutaneous subtype, smoking, autoantibodies and disease severity. The medication covariates were included based on hypothesis testing, frequency of use in clinical practice and availability.

Table S1: Baseline demographic and clinical characteristics of the total systemic sclerosis cohort, stratified by origin (Leiden University Medical Center, LUMC, or Oslo University Hospital, OUH)

	LUMC	OUH	P
Demographic	n=454	n=380	
Female, n (%)	336 (81)	307 (81)	0.9
Age, yrs mean (SD)	55 (14)	56 (13)	0.8
SSc disease duration at inclusion, median (IQR)	3.8 (1.1-10.2)	4.3 (1.8-8.8)	0.6
Smoking, ever n (%)	245 (55)	122 (45)	0.4
Organ involvement			
Diffuse cutaneous SSc, n (%)	88 (21)	84 (22)	0.5
Severe skin involvement, n (%)±	37 (8)	59 (16)	0.2
Myositis, n (%)	13 (3)	48 (13)	0.2
DLCO% < 60% of predicted, n (%)	134 (32)	100 (29)	0.6
FVC% < 70% of predicted, n (%)	36 (9)	26 (8)	0.8
ILD on HRCT, n (%)	180 (39)	120 (32)	0.5
PAH, n (%)	20 (4)	34 (9)	0.6
SSc specific autoantibodies			
Anti RNA polymerase III, n (%)	25 (6)	37 (10)	0.7
Anti-centromere, n (%)	184 (40)	208 (55)	0.3
Anti-topoisomerase, n (%)	117 (26)	48 (13)	0.3
Treatment at baseline			
Calcium Channel Blockers, n (%)	190 (42)	114 (30)	0.4
H2 receptor blocker, n (%)	150 (33)	106 (28)	0.5
ET-1 inhibitors&prostacyclin analogue, n (%)	62 (14)	56 (15)	0.7
Proton Pump Inhibitor, n (%)	179 (39)	121 (32)	0.6
Methotrexate, n (%)	79 (17)	20 (5)	0.2
Mycophenolate mofetil, n (%)	28 (6)	19 (5)	0.5
Azathioprine, n (%)	14 (3)	5 (1)	0.7
Corticosteroids, n (%)	71 (16)	37 (10)	0.6
Cyclophosphamide, n (%)	20 (4)	6 (2)	0.8
Hydroxychloroquine, n (%)	32 (7)	3 (1)	0.7

DLCO= single-breath diffusing lung capacity for carbon monoxide, ET-1= endothelin receptor, FVC= forced vital capacity, ILD= interstitial lung disease, HRCT= high resolution computed tomography, PAH= pulmonary arterial hypertension, n= number, SD= standard deviation; IQR= interquartile range. ± based on modified Rodnan Skin Score > 15 points.

Table S2: Logistic regression analyses of baseline characteristics associated with moderate/severe total UCLA GIT symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	OR	95% CI	Significance p-value	OR	95% CI	Significance p-value
	Moderate / severe total GIT symptom score					
Female	1.97	1.25-3.10	<0.001*	1.76	1.04-2.98	0.03
Age, Years	0.99	0.99-1.004	0.28	0.99	0.98-1.01	0.07
Disease duration, yrs	1.04	1.02-1.06	<0.001*	1.05	1.03-1.07	<0.001*
Raynaud duration, yrs	1.01	1.00-1.02	0.04	-	-	-
Smoking ever	1.50	1.07-2.08	0.02	1.69	1.19-2.41	<0.001*
Diffuse subset*	1.11	0.66-1.87	0.69	1.88	0.94-3.76	0.08
Disease severity#	1.13	0.82-1.54	0.46	1.02	0.70-1.48	0.91
Weight loss (>10% in 1 year)	1.20	0.74-1.97	0.46	-	-	-
Hemoglobine level	1.10	0.88-1.39	0.40	-	-	-
Myositis	1.12	0.64-1.96	0.69	-	-	-
Anti-centromere antibody	1.77	1.30-2.39	<0.001*	2.07	1.34-3.19	<0.001*
Anti-topoisomerase antibody	0.57	0.37-0.86	0.01	0.78	0.46-1.33	0.36
Anti-RNApIII antibody	0.90	0.41-1.99	0.79	-	-	-
Proton pump inhibitor	1.26	0.95-1.67	0.11	-	-	-
H2 receptor blocker	0.92	0.68-1.24	0.58	-	-	-
ACE-inhibitor	0.75	0.53-1.06	0.10	-	-	-
Calcium channel blocker	0.77	0.56-1.07	0.10	0.56	0.39-0.83	<0.001*
Mycophenolate mofetil	1.23	0.64-2.33	0.54	-	-	-
Methotrexate	0.88	0.55-1.42	0.60	-	-	-
Azathioprine	0.53	0.15-1.86	0.32	-	-	-
Corticosteroids	1.25	0.83-1.88	0.10	1.92	1.18-3.12	<0.001*
Cyclophosphamide	0.77	0.31-1.93	0.58	-	-	-
Hydroxychloroquine	0.99	0.48-2.09	0.99	-	-	-
Prostacyclin & ET-1 inhibitor	1.57	0.92-2.67	0.09	1.49	0.96-2.33	0.13

*Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse cutaneous subset. CI=confidence interval, OR= odds ratio. # disease severity is a compound variable which included: interstitial lung disease, pulmonary arterial hypertension, renal crisis, severe skin disease or presence of digital ulcers. Medication is entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. ACE= angiotensin-converting-enzyme, ET-1= endotheline receptor. IQR= interquartile range, SD= standard deviation. In bold are the significant associations. * remains significant after Holm-Bonferroni correction.

Table S3. Logistic regression analyses of baseline characteristics associated with moderate or severe reflux symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	Moderate or severe reflux symptom score					
	OR	95% CI for OR	Significance	OR	95% CI for OR	Significance
Female	1.75	1.16-2.64	0.01	1.60	1.00-2.55	0.05
Age, Years	0.99	0.99-1.003	0.72	0.99	0.98-1.01	0.46
Disease duration, years	1.02	1.007-1.040	0.01	1.02	1.004-1.04	0.02
Raynaud duration, years	1.01	1.005-1.034	0.03			
Smoking ever	1.17	0.87-1.58	0.31	1.19	0.86-1.63	0.30
Disease subset*	1.04	0.64-1.68	0.89	1.43	0.78-2.62	0.25
Disease severity#	1.15	0.86-1.55	0.35	1.09	0.78-1.54	0.62
Weight loss (>10% in 1 year)	1.74	1.09-2.77	0.02	2.20	1.33-3.63	<0.001*
Hemoglobin levels	0.89	0.72-1.12	0.32	-	-	-
Myositis yes/no	0.63	0.13-3.07	0.60	-	-	-
Anti-centromere antibody	1.71	1.22-2.27	<0.001*	1.76	1.10-2.27	0.01
Anti-topoisomerase antibody	0.51	0.34-0.76	<0.001*	0.57	0.34-0.90	0.02
Anti-RNAPIII	0.72	0.41-1.29	0.28	-	-	-
Proton pump inhibitor	1.39	1.07-1.80	0.01	1.16	0.82-1.66	0.40
H2 receptor blocker	1.71	1.28-2.32	<0.001*	1.71	1.23-2.59	0.003*
ACE inhibitor	1.17	0.82-1.63	0.38	-	-	-
Calcium channel blocker	1.09	0.84-1.41	0.54	-	-	-
Immunosuppressiva combined	1.34	0.93-1.93	0.12	-	-	-
Prostacyclin & ET-1 inhibitor	1.47	0.89-2.42	0.22	-	-	-

Univariable and multivariable logistic regression. *Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse subset. # disease severity is a compound variable which included: ILD with FVC<70%, PAH, renal crisis, mRSS>20 or presence of digital ulcers. Medication are entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. * significant after Holm-Bonferroni correction.

Table S4. Logistic regression analyses of baseline characteristics associated with moderate or severe distension/bloating symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	OR	95% CI for OR	Significance	OR	95% CI for OR	Significance
	Moderate or severe distention/bloating symptom score					
Female	2.34	1.48-3.67	<0.001*	2.38	1.40-4.03	<0.001*
Age, Years	0.99	0.99-1.003	0.14	0.99	0.98-1.00	0.06
Disease duration, years	1.02	1.002-1.04	0.03	1.03	1.01-1.05	<0.001*
Raynaud duration, years	1.00	1.00-1.02	0.04			
Smoking ever	1.46	1.05-2.01	0.02	1.86	1.32-2.64	<0.001*
Disease subset*	1.25	0.75-2.08	0.38	2.29	1.16-4.53	0.02
Disease severity	1.31	0.97-1.78	0.08	1.26	0.88-1.82	0.21
Weight loss (>10% in 1 year)	0.93	0.54-1.61	0.80	-	-	-
Hemoglobin	0.86	0.70-1.06	0.17	-	-	-
Myositis yes/no	1.21	0.73-2.02	0.47	-	-	-
ACA	1.54	1.20-1.97	<0.001*	1.65	1.08-2.52	0.02
ATA	0.64	0.47-0.88	0.06	0.84	0.50-1.40	0.50
Anti-RNAPIII	1.48	0.88-2.47	0.14	-	-	-
Proton pump inhibitor	1.10	0.85-1.43	0.45	-	-	-
H2 receptor blocker	0.66	0.47-0.93	0.02	0.85	0.56-1.27	0.42
ACE inhibitor	0.58	0.38-0.88	0.01	0.80	0.50-1.28	0.35
Calcium channel blocker	0.66	0.48-0.91	0.01	0.56	0.37-0.83	<0.001*
Immunosuppressiva combined	0.96	0.64-1.41	0.82	-	-	-
Prostacyclin & ET-1 inhibitor	1.30	0.83-2.09	0.29	-	-	-

*Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse subset. # disease severity is a compound variable which included: ILD with FVC<70%, PAH, renal crisis, mRSS>20 or presence of digital ulcers. Medication are entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. * Significant after Holm-Bonferroni correction.

Table S5. Logistic regression analyses of baseline characteristics associated with moderate or severe constipation symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	OR	95% CI for OR	Significance P	OR	95% CI for OR	Significance P
Moderate or severe constipation symptom score						
Female	1.76	1.16-2.67	0.008	1.51	0.94-2.42	0.08
Age, Years	1.001	0.99-1.01	0.48	1.00	0.99-1.01	0.97
Disease duration, years	1.01	0.99-1.03	0.29	1.02	0.99-1.03	0.13
Raynaud duration, years	0.99	0.98-1.02	0.61			
Smoking ever	0.76	0.56-1.04	0.09	0.96	0.67-1.30	0.68
Disease subset [#]	1.26	0.78-2.02	0.34	1.29	0.65-2.56	0.47
Disease severity	1.30	0.96-1.76	0.09	1.21	0.85-1.73	0.29
Weight loss (>10% in 1 year)	1.26	0.76-2.10	0.37	-	-	-
Hemoglobin	0.86	0.68-1.09	0.21	-	-	-
Myositis yes/no	1.11	0.62-1.99	0.73	-	-	-
ACA	1.18	0.88-1.57	0.28	1.26	0.84-1.89	0.27
ATA	0.67	0.45-0.99	0.05	1.04	0.64-1.67	0.89
Anti-RNAPIII	2.49	1.52-4.06	<0.001*	2.43	1.31-4.50	0.01
Proton pump inhibitor	0.98	0.75-1.29	0.91	-	-	-
H2 receptor blocker	0.76	0.48-1.08	0.11	-	-	-
ACE inhibitor	0.72	0.51-1.02	0.25	-	-	-
Calcium channel blocker	0.75	0.55-1.03	0.07	0.74	0.52-1.06	0.09
Immunosuppressiva combined	0.60	0.40-0.92	0.02	0.76	0.45-1.09	0.09
Prostacyclin & ET-1 inhibitor	1.34	0.73-2.23	0.58	-	-	-

[#]Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse subset. [#] disease severity is a compound variable which included: ILD with FVC<70%, PAH, renal crisis, mRSS>20 or presence of digital ulcers. Medication are entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. * Significant after Holm-Bonferroni correction.

Table S6. Logistic regression analyses of baseline characteristics associated with moderate or severe diarrhea symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	OR	95% CI for OR	Significance P	OR	95% CI for OR	Significance P
	Moderate or severe diarrhea symptom score					
Female	1.06	0.74-1.53	0.74	1.05	0.70-1.60	0.80
Age, Years	0.99	0.98-1.004	0.21	0.99	0.98-1.01	0.13
Disease duration, years	1.01	1.01-1.04	0.01	1.02	1.01-1.04	0.05
Raynaud duration, years	1.02	1.01-1.06	0.02			
Smoking ever	1.35	1.01-1.81	0.05	1.43	1.05-1.94	0.02
Disease subset*	2.27	1.37-3.76	<0.001*	2.59	1.40-4.79	<0.001*
Disease severity	1.39	1.05-1.85	0.02	1.33	0.96-1.85	0.08
Weight loss (>10% in 1 year)	1.40	0.87-2.26	0.16	-	-	-
Hemoglobin	1.21	0.95-1.53	0.12	-	-	-
Myositis yes/no	1.72	1.01-2.95	0.05	1.52	0.82-2.84	0.18
ACA	1.27	0.96-1.67	0.09	1.63	1.12-2.36	0.01
ATA	0.76	0.53-1.08	0.12	0.79	0.52-1.22	0.29
Anti-RNAPIII	0.92	0.54-1.56	0.76	-	-	-
Proton pump inhibitor	0.97	0.73-1.30	0.84	-	-	-
H2 receptor blocker	0.80	0.59-1.10	0.17	-	-	-
ACE inhibitor	0.82	0.57-1.17	0.26	-	-	-
Calcium channel blocker	0.69	0.52-0.93	0.01	0.61	0.44-0.85	<0.001*
Immunosuppressiva combined	0.71	0.49-1.03	0.07	0.73	0.52-1.13	0.11
Prostacyclin & ET-1 inhibitor	1.03	0.61-1.70	0.87	-	-	-

*Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse subset. # disease severity is a compound variable which included: ILD with FVC<70%, PAH, renal crisis, mRSS>20 or presence of digital ulcers. Medication are entered as yes or no, with a yes if the medication was used in the same year as the GiT questionnaire was completed. * Significant after Holm-Bonferroni correction.

Table S7. Logistic regression analyses of baseline characteristics associated with moderate or severe fecal soilage symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	Moderate or severe fecal soilage symptom score					
	OR	95% CI for OR	Significance P	OR	95% CI for OR	Significance P
Female	2.08	0.48-9.01	0.33	1.39	0.28-6.89	0.69
Age, Years	1.04	1.001-1.08	0.02	1.04	0.99-1.08	0.13
Disease duration, years	1.06	1.02-1.10	<0.001*	1.08	1.04-1.13	<0.001*
Raynaud duration, years	1.04	1.03-1.06	0.02			
Smoking ever	1.69	0.66-4.33	0.28	1.44	0.52-3.99	0.48
Disease subset [#]	2.55	0.28-23.08	0.41	13.36	0.89-201.61	0.06
Disease severity	0.92	0.37-2.32	0.89	0.93	0.31-2.80	0.90
Hemoglobin	1.40	0.65-2.99	0.39	-	-	-
Myositis yes/no	0.80	0.11-6.12	0.83	-	-	-
ACA	3.76	1.36-10.35	0.01	4.28	1.08-16.95	0.04
ATA	0.20	0.03-1.46	0.11	0.26	0.02-2.62	0.23
Proton pump inhibitor	3.07	1.28-7.49	0.01	2.90	0.96-8.75	0.06
H2 receptor blocker	2.39	1.01-5.72	0.05	1.60	0.55-4.69	0.39
ACE inhibitor	1.77	0.68-4.64	0.25	-	-	-
Calcium channel blocker	0.89	0.35-2.17	0.76	-	-	-
Immunosuppressiva combined	1.11	0.37-3.33	0.86	-	-	-
Prostacyclin & ET-1 inhibitor	2.23	1.11-8.7	0.04	1.59	0.48-6.01	0.48

[#]Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse subset. [#] disease severity is a compound variable which included: ILD with FVC<70%, PAH, renal crisis, mRSS>20 or presence of digital ulcers. Medication are entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. * Significant after Holm-Bonferroni correction.

Table S8. Logistic regression analyses of baseline characteristics associated with moderate or severe emotional wellbeing symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	OR	95% for CI OR	Signifi- cance P	OR	95% for CI OR	Signifi- cance P
	Moderate or severe emotional wellbeing symptom score					
Female	1.94	1.15-3.27	0.01	1.98	1.08-3.64	0.03
Age, Years	1.04	0.99-1.02	0.43	0.99	0.98-1.01	0.66
Disease duration, years	1.03	1.01-1.05	0.02	1.04	1.02-1.06	<0.001*
Raynaud duration, years	1.01	1.00-1.04	0.03			
Smoking ever	1.68	1.15-2.46	0.007*	1.87	1.25-2.79	<0.001*
Disease subset*	1.04	0.58-1.86	0.90	1.71	0.80-3.67	0.17
Disease severity	1.28	0.91-1.82	0.16	1.12	0.74-1.70	0.59
Weight loss (>10% in 1 year)	1.13	0.63-2.06	0.68	-	-	-
Hemoglobin	1.09	0.81-1.47	0.55	-	-	-
Myositis yes/no	1.03	0.51-2.10	0.93	-	-	-
ACA	1.57	1.11-2.21	0.010	1.60	0.99-2.56	0.05
ATA	0.55	0.34-0.90	0.02	0.72	0.40-1.32	0.29
Anti-RNAPIII	1.01	0.53-1.94	0.97	-	-	-
Proton pump inhibitor	1.17	0.83-1.67	0.37	-	-	-
H2 receptor blocker	0.83	0.56-1.22	0.33	-	-	-
ACE inhibitor	0.60	0.37-0.99	0.05	0.63	0.40-1.05	0.11
Calcium channel blocker	0.91	0.64-1.30	0.60	-	-	-
Immunosuppressiva combined	0.80	0.49-1.27	0.33	-	-	-
Prostacyclin & ET-1 inhibitor	1.35	0.66-2.33	0.63	-	-	-

*Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse subset. # disease severity is a compound variable which included: ILD with FVC<70%, PAH, renal crisis, mRSS>20 or presence of digital ulcers. Medication are entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. * Significant after Holm-Bonferroni correction.

Table S9. Logistic regression analyses of baseline characteristics associated with moderate or severe social functioning symptom score in the 834 systemic sclerosis patients from the Leiden and Oslo cohort

	Univariable			Multivariable		
	Moderate or severe social functioning symptom score					
	OR	95% for CI	Signifi- cance P	OR	95% for CI	Signifi- cance P
		OR		OR	OR	
Female	1.57	0.95-2.58	0.08	1.45	0.83-2.54	0.19
Age, Years	1.00	0.99-1.01	0.95	0.99	0.98-1.01	0.35
Disease duration, years	1.03	1.01-1.05	<0.001*	1.04	1.01-1.06	<0.001*
Raynaud duration, years	1.01	1.01-1.07	0.01			
Smoking ever	1.48	1.02-2.15	0.04	1.65	1.12-2.45	0.01
Disease subset [#]	1.50	0.80-2.79	0.21	2.27	1.03-5.02	0.04
Disease severity	1.10	0.78-1.58	0.56	1.02	0.67-1.55	0.92
Weight loss (>10% in 1 year)	1.12	0.70-1.81	0.63	-	-	-
Hemoglobin	1.01	0.76-1.35	0.94	-	-	-
Myositis yes/no	1.04	0.51-2.11	0.92	-	-	-
ACA	1.83	1.25-2.14	<0.001*	1.91	1.18-3.09	0.01
ATA	0.62	0.38-0.99	0.05	0.87	0.49-1.56	0.64
Anti-RNApIII	0.59	0.27-1.28	0.17	-	-	-
Proton pump inhibitor	1.36	0.96-1.93	0.08	1.33	0.89-1.87	0.12
H2 receptor blocker	0.88	0.60-1.30	0.53	-	-	-
ACE inhibitor	0.94	0.60-1.46	0.77	-	-	-
Calcium channel blocker	1.12	0.85-1.48	0.41	-	-	-
MMF	1.43	0.71-2.90	0.31	-	-	-
Immunosuppressiva combined	1.29	0.84-1.99	0.25			
Prostacyclin & ET-1 inhibitor	1.88	0.88-2.67	0.33	-	-	-

[#]Disease subset: entered as ordinal variable with order: non-cutaneous, limited and diffuse subset. [#] disease severity is a compound variable which included: ILD with FVC<70%, PAH, renal crisis, mRSS>20 or presence of digital ulcers. Medication are entered as yes or no, with a yes if the medication was used in the same year as the GIT questionnaire was completed. * Significant after Holm-Bonferroni correction.

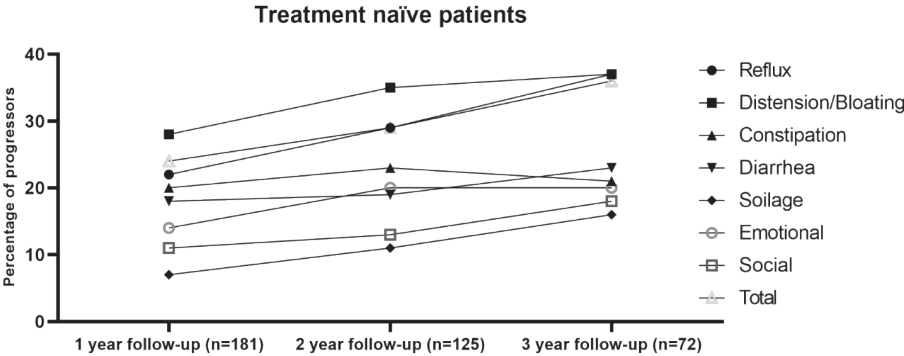


Figure S4. Percentage of progressors per GIT subdomain over the follow-up period in treatment naïve patients in the inception cohort (for immunosuppressive treatment). The line indicate years of follow-up and the numbers (n) the amount of treatment naïve patients at that time point. We calculated the percentage of progressors based on the MCID of the UCLA GIT 2.0 per subdomain after 1,2 and 3 years of follow-up.