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Slow colonic transit in systemic sclerosis: an objective assessment of risk factors and clinical phenotype

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Abstract

Introduction: Up to 50% of patients with systemic sclerosis (SSc) experience slow colonic transit, which may be associated with severe outcomes. We therefore sought to identify specific clinical features associated with slow colonic transit in SSc.

Methods: SSc patients with gastrointestinal symptoms were prospectively enrolled and completed a scintigraphy-based whole gut transit study. Clinical features were compared between patients with and without slow colonic transit in univariate and multivariable logistic regression analyses.

Results: Forty-eight out of 100 (48%) patients in our cohort had slow colonic transit. In the univariate analyses, slow colonic transit was positively associated with female sex (OR 12.61, 95% CI 1.56–101.90), telangiectasia (OR 4.00, 95% CI 1.32–12.10), anti-centromere antibodies (OR 3.25, 95% CI 1.25–8.44), prior or current smoking (OR 2.56, 95% CI 1.06–6.21), and a Medsger GI severity score of ≥3 (OR 3.94, 95% CI 1.16–13.36). Patients were less likely to have significant restriction on pulmonary function tests (OR 0.23, 95% CI 0.09–0.63). In our multivariable model, the association between slow colonic transit and telangiectasia (OR=3.97, 95% CI 1.20–13.20) and less restrictive lung disease on PFTs (OR=0.28, 95% CI 0.09–0.86) remained statistically significant, though a trend with smoking remained (OR 2.16; 95% CI 0.82–5.75). Interestingly, there were no significant associations between slow colonic transit and delayed transit in other regions of the GI tract.

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Conclusions: Distinct clinical features are associated with slow colonic transit in SSc. Such features may provide insight in risk stratification and the study of disease mechanism in more homogenous subgroups.

Key indexing terms:

systemic sclerosis; scleroderma; motility; gastrointestinal; colon

Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy and fibrosis of the skin and internal organs.[1] The gastrointestinal (GI) tract is commonly implicated, with GI dysfunction affecting up to 90% of patients.[2] GI involvement is associated with profound morbidity, including depression, hospitalization, lower quality of life, and malnutrition.[3–5]

Slow colonic transit affects up to 50% of patients with SSc.[7] Manifestations are variable, ranging from mild disease to severe complications, such as recurrent pseudo-obstruction and the requirement of total parenteral nutrition.[8] The overall mortality of patients with SSc-related slow colonic transit is estimated to be as high as 27%.[8] Despite the significant consequences of SSc-related slow colonic transit, little is known about its associated clinical phenotype or disease mechanism. Interestingly, vasculopathy, autonomic dysfunction, and autoimmunity are all hypothesized to play a role in its pathogenesis.[3]

Recognizing patients at risk for severe GI outcomes is important for clinical practice and research. Prompt diagnosis of slow colonic transit allows for earlier intervention with promotility agents to control symptoms, possibly reducing the progression of smooth muscle atrophy.[7,9] In research, it allows for the study of homogenous subgroups, which is critical when examining disease mechanism and responses to targeted therapies. While previous studies identified male sex, myopathy, diffuse cutaneous disease, and myositis-related autoantibodies to be positively associated with severe GI dysfunction, none of these studies identified the specific region of the gut contributing to the GI severity.[10–12] Therefore, the clinical features associated with slow colonic transit specifically were not defined.

As distinct clinical phenotypes are a hallmark of SSc, and not all SSc patients have slow colonic transit, we hypothesized that specific clinical and serological features are associated with this complication of SSc and sought to define these features in the present study.

PATIENTS AND METHODS

Patients.

Patients seen at the Johns Hopkins Scleroderma Center (JHSC) who met the 2013 American College of Rheumatology(ACR)/European League Against Rheumatism criteria, ACR 1980, or CREST (Calcinosis, Raynaud's, Esophageal dysmotility, Sclerodactyly, Telangiectasia) criteria for SSc were evaluated with the GI Assessment Protocol at JHSC.[13–15] Participants who were willing and able to participate were prospectively enrolled. Patients with significant GI symptoms (early satiety, nausea, vomiting, unintentional weight loss, abdominal distension, bloating, diarrhea, and/or constipation) as determined by their treating physician underwent whole gut transit (WGT) studies as part of their routine clinical care.

Minimally symptomatic patients also underwent WGT study through our research protocol so that patients across the spectrum of GI disease would be captured. Written informed consent was obtained from participants. The present study was approved by the Johns Hopkins Institutional Review Board.

Clinical Phenotyping.

Demographic and clinical data were collected at patients' first encounters and every 6 months thereafter, including age, sex, race, disease duration, SSc subtype (diffuse cutaneous SSc or limited cutaneous SSc based on the extent of skin involvement), smoking status, cancer history, specific organ involvement and Mesdger severity scores.[1] In this study, the primary assessment of disease duration was defined as the interval between the first SSc-associated symptom (Raynaud's or non-Raynaud's) though we also examined the interval between the first non-RP symptom the date of WGT study. The extent of specific organ involvement was captured every 6 months on all actively followed patients. Maximum Medsger severity scores were used to characterize clinical phenotype.[16] Myopathy was present if patients had either an elevated creatinine phosphokinase with electromyography supporting myopathy, magnetic resonance imaging demonstrating muscle edema, or muscle biopsy suggesting myopathy.[16] Metrics of pulmonary involvement included minimum measurements of forced vital capacity (FVC) and single breath diffusing capacity of carbon monoxide (DLCO) using pulmonary function testing (PFT), and maximum measurements of estimated right ventricular systolic pressure (RVSP) using transthoracic echocardiogram.[17,18] Measurements of FVC <70% and DLCO <60% of predicted were considered significant restrictive lung disease and denoted as "significantly low FVC" or "significantly low DLCO". Presence of telangiectasia and calcinosis was determined by their JHSC rheumatologist.

Autoantibody Profile.

Patients with available serum underwent an autoantibody screen with the Euroline immunoblot assay [Scleroderma Nucleoli Profile Euroline (IgG); Euroimmuno]. Autoantibodies with moderate to high titers according to the manufacturer's cutoff were considered positive.

Whole Gut Transit Study.

All patients in this study underwent whole gut scintigraphy. Patients were asked to avoid taking promotility agents, stool softeners, opiates, benzodiazepines, and antibiotics three days prior to the study, and to begin fasting at midnight prior to the study. For the esophageal and liquid gastric emptying assessment, patients consumed a standard amount of radiolabeled In-111 water. To assess solid gastric emptying, patients consumed a standard radiolabeled Tc-99m egg meal. A gamma camera was used to obtain anterior and posterior standing images of patients at 1 hour (hr), 2hr, 4hr, 6hr, 24hr, 48hr, and 72hr to evaluate meal transit. The same protocol was applied to all patients. Slow colonic transit was defined as <14% emptying at 24hr, <41% emptying at 48hr, and <67% emptying at 72hr.[19] In this study, "slow colonic transit" refers to delayed transit at the final time point of WGT study (72 hr) unless otherwise specified.

Statistical Analysis

Cross-sectional analysis.

We compared SSc patients with and without slow colonic transit in our cross-sectional analysis. Chi-square test and Fisher's exact tests were used to evaluate the association of dichotomous variables between two groups. For parametric continuous variables, we performed the Student's t-test to compare the means between the two groups. The Wilcoxon-Mann-Whitney test was utilized to non-parametrically examine the relationship between two continuous variables, and the Kruskal-Wallis test was used to nonparametrically evaluate the relationship between variables with >2 groups. To assess the linear association between two continuous variables, we utilized the Pearson correlation coefficient. We explored the associations between slow colonic transit (dependent variable) and independent variables (demographic variables, SSc characteristics, and autoantibody types) using univariate logistic regression. Associations were expressed as odds ratios (OR) with 95% confidence intervals (95% CI), and/or p-values (considered significant when ≤0.05). We constructed a multivariable logistic regression model including statistically significant covariates from the univariate analysis to determine whether associations remained after adjusting for these variables. We used multiple imputation for incomplete clinical measurements, so that all patients in our cohort contributed to estimates. We imputed all missing measurements in the multivariable model sequentially based on age and other patient measurements with five fully conditional random imputations according to standard practice.[20] All analyses were conducted in Stata version 16.[21]

RESULTS

Demographic characteristics of the SSc GI cohort.

One hundred patients with SSc were enrolled and completed WGT studies. Patients completed the study as part of routine clinical care (n=94) or as minimally symptomatic controls (n=6). The mean age of our patients at the time of the study was 57 ± 11 years. Mean disease duration, from the onset of first SSc-associated symptom, was 16 ± 12 years. Our cohort consisted of 88% (n=88) females and 12% (n=12) males. Seventy-seven percent (n=77) of patients were white and 21% (n=21) were non-white. Sixty-nine percent (n=69) of patients had limited cutaneous SSc (lcSSc) and 31% (n=31) had diffuse cutaneous SSc (dcSSc).

Of note, we previously published a manuscript focused on examining the correlation between GI symptoms and severity with findings on the WGT in patients with SSc. In that study we also compared patients with SSc who underwent WGT studies (n=71; all in this study) with patients with SSc who did not received WGT studies (n=1445) during the same time period at JHSC. At the time we found that the demographics (age, sex, BMI, and ethnicity) of the cohort were not significantly different. As expected, patients who completed the WGT study had slightly more severe GI disease, slightly less severe Raynaud's, and less severe restrictive lung disease on PFT. Otherwise, disease severity was comparable.[22]

Prevalence, distribution, and severity of slow colonic transit in the SSc GI cohort.

In our cohort of 100 patients, slow colonic transit was identified in 48–60%, depending on the time point measured (24, 48, 72 hours). In patients with normal colonic transit, the radiolabeled meal is generally present in the transverse colon in the first 24 hours, in the descending colon by 48 hours, and in the rectosigmoid colon or largely evacuated by 72 hours (Figure 1).[19] We found a strong positive correlation between slow colonic transit at 48 and 72 hours ($r=0.74$, $p<0.01$), and a moderate positive correlation at 24 and 48 hours ($r=0.69$, $p<0.01$) and at 24 and 72 hours ($r=0.47$, $p<0.01$).

Although we utilized delays at 72 hours as our standard for slow colonic transit, slow colonic transit was not homogenous throughout the colon. Colonic transit was most frequently delayed at 24 and 48 hours [60% (n=60) and 56% (n=56), respectively], though it was still delayed in almost half the cohort at 72 hours [48% (n=48)]. Eleven percent (n=11) of patients had delayed transit only at 24 hours, 11% (n=11) at both 24 and 48 hours, and 38% (n=38) at all 3 time points (24, 48, 72 hours). Nine percent (n=9) of patients had normal transit at 24 hours but delayed transit at 48 and/or 72 hours.

The median (IQR) percent emptying of the colon across the whole cohort was 4% (0%, 24%) at 24 hours, 25% (0%, 65%) at 48 hours, and 63% (3%, 86%) at 72 hours (abnormal when <14% at 24 hrs, <41% at 48 hrs, and <67% at 72 hrs). Representative images of colonic emptying at each time point in SSc patients with and without abnormal colonic transit are depicted in Figure 1. Among patients with slow colonic transit, the median percent emptying was significantly lower at the three measured time points with 0% emptying (0%, 3%) at 24 hours, 1% emptying (0%, 21.5%) at 48 hours, and only 5% emptying (0%, 35%) at 72 hours. It was striking that half of the SSc patients with any slow colonic transit (n=24/48) had less than 5% emptying of the colon at 72 hours.

Slow colonic transit is not associated with transit delays in other GI regions in SSc.

We then sought to determine whether slow colonic transit correlated with transit delays in other regions of the gut. Among the SSc patients with slow colonic transit, esophageal, gastric, and small bowel transit were delayed in 69% (n=33), 19% (n=9), and 19% (n=9), respectively. However, there were no significant associations between slow colonic transit and transit delays in other regions of the gut.

The presence, severity, and extent of slow colonic transit is not associated with disease duration.

SSc is a progressive disease, therefore, we sought to investigate the relationship between disease duration and the presence, severity (% emptying), and extent of slow colonic transit (number of time points affected by slow colonic transit). Among patients with and without slow colonic transit, there was no significant difference in disease duration as assessed from first Raynaud's or non-Raynaud's SSc symptom (median of 12.1 vs. 11.5 years respectively, $p=0.96$). When examining disease duration as measured from the first non-Raynaud's symptom, there was also no significant difference in disease duration between patients with and without slow colonic transit (median 10.7 vs. 6.7 years respectively, $p=0.40$). When examining the prevalence of slow colonic transit across patients with early, moderate and

late disease, we found that among patients with a disease duration of ≤5 years from first non-Raynaud's symptom, 44% (n=12/27) patients had slow colonic transit. Among patients with a disease duration of 6–15 years, 58% (n=18/31) had slow colonic transit. Finally, among those with a disease duration of >15 years, 53% (n=16/30) had slow colonic transit.

To determine whether the severity of slow colonic transit was associated with disease duration, we compared median percent emptying at 72 hrs across the early, moderate and late disease duration subgroups (≤5 years, 6–14 years, ≥15 years of disease), and found no significant differences in median (IQR) percent colonic emptying across groups [≤5 years=68% (13%, 85%), 6–14 years=53% (0%, 86%), ≥15 years=58% (0%, 86%), p=0.77]. We also did not find a significant association when examining the association between percent colonic emptying at 72 hrs and disease duration from first Raynaud's or non-Raynaud's symptom as a continuous variable with a Spearman correlation (p=0.60).

We then examined the association between the extent of colonic involvement (the number of abnormal colonic time points measured) and disease duration. The extent of slow colonic transit was defined by the number of time points (24 hr, 48hr, and/or 72 hr) that had evidence of slow colonic transit based on the WGT study. There were no significant differences in disease duration between patients with delayed transit at only one time point (24, 48, or 72 hrs) vs. patients affected at ≥2 time points.

Clinical and serologic features of patients with SSc associate with slow colonic transit.

The clinical and phenotypic features of SSc patients with and without slow colonic transit are shown in Table 1. Patients with SSc and slow colonic transit were more likely to have smoked [43% (n=20/48) vs. 22% (n=11/52), p=0.04], have telangiectasia [89% (n=40/48) vs. 67% (n=32/52), p=0.01], have a GI Medsger score ≥3 [27% (n=12/48) vs. 9% (n=4/52), p=0.03], and were more likely to be female [98% (n=47/48) vs. 79% (n=41/52), p<0.01]. It is noteworthy that of the 12 male patients in the cohort (n=100), only 1 male patient had slow colonic transit, while 11 male patients had normal transit. The presence of slow colonic transit according to sex is displayed in Figure 2, which illustrates that slow colonic transit at multiple time points is more frequent in women compared to men. Additionally, patients with slow colonic transit were less likely to have significant restrictive lung disease on PFTs (determined as FVC <70%) compared to those without slow colonic transit [23% (n=9/48) vs. 56% (n=20/52), p<0.01]. When examining the correlation between GI symptoms using the UCLA GIT 2.0 and slow colonic transit, we found lower (less severe) diarrhea scores in patients with slow colonic transit compared to patients with normal colonic transit [0.5 (0.0, 0.5) vs. 1.0 (0.0, 1.5), p=0.03]. No other significant associations were identified.

We then sought to determine whether patients with specific autoantibodies were more likely to have slow colonic transit. Of the 100 patients enrolled, we had available antibody data on 75 patients, of which, 52 patients were positive for at least one of the antibodies of interest. We found that slow colonic transit was associated with the presence of anti-CENP autoantibodies [58% (n=22/48) vs. 31% (n=11/52), p=0.01]. No other associations between slow colonic transit and autoantibodies were identified (Table 1). Figure 3 further shows the time point(s) in which colonic transit was delayed according to sex and autoantibody.

Univariate logistic regression.

Univariate logistic regression analyses were then performed to examine the strength of the association between SSc-specific clinical features and the presence of slow colonic transit (Table 2). We found that telangiectasia (OR=4.00, 95%CI 1.32–12.10; p=0.01), GI severity (Medsger score ≥3) (OR=3.94, 95% CI 1.16–13.36; p=0.03), anti-CENP autoantibodies (OR=3.25, 95% CI 1.25–8.44; p=0.02), and female sex (OR=12.61, 95% CI 1.56–101.90; p=0.02) were associated with slow colonic transit. Patients with slow colonic transit were less likely to have a significantly low FVC (<70%) on PFTs (OR=0.23, 95% CI 0.09–0.63; p<0.01). A history of smoking was also positively associated with slow colonic transit (OR=2.56, 95% CI 1.06–6.21; p=0.04). When detailing the smoking history into never, former, and current smokers, and examining the prevalence of slow colonic transit in each group, we learned that slow colonic transit was more prevalent among former smokers [71% (n=17/24) vs. 29% (n=7/24)], while normal colonic transit was more prevalent among never smokers [59% (n=38/65) vs. 42% (n=27/65)]. There were few current smokers in our study but normal transit was slightly more common in this group [57% (n=4/7) vs. 43% (n=3/7)].

Cross-sectional multivariable logistic regression.

We then sought to determine whether clinical, and serologic features remained associated with slow colonic transit after adjusting for significant covariates from the univariate analysis and potential confounders. Of the variables included in our multivariable model (smoking history, telangiectasia, significantly low FVC, and anti-CENP autoantibody status; Table 3), 4–25% of the variables had incomplete data. To ensure that all 100 patients contributed to our analyses, we performed multiple imputation on all incomplete clinical measurements. A statistically significant, positive association remained between the presence of slow colonic transit and telangiectasia (OR=3.97, 95% CI 1.20–13.20, p=0.02). There was also a significant inverse association between the presence of slow colonic transit and a significantly low FVC (OR=0.28, 95% CI 0.09–0.86, p=0.03).

Discussion

Our study is the first to examine the clinical features associated with objectively determined slow colonic transit in a large cohort of well-characterized patients with SSc. Prior scintigraphy studies have established that slow colonic transit is more common in patients with SSc than those without SSc.[23,24] However, these studies did not explore the clinical phenotype associated with slow colonic transit. Here, we report that female sex, smoking, anti-CENP autoantibodies, and telangiectasia are positively associated with slow colonic transit in SSc, and that significant restrictive lung disease (defined as FVC <70%) is inversely associated. Furthermore, telangiectasia remained significantly associated with slow colonic transit in SSc patients, while a significantly low FVC (<70%) was negatively associated with slow colonic transit even after adjusting for significant covariates from the univariate analysis. These results are important because they augment our ability to risk stratify patients with SSc, allowing for earlier evaluation in high-risk subgroups.

Interestingly, we did not find an association between the presence or severity of slow colonic transit and disease duration in our study, though our study did not consistently

capture patients early in their disease course, and was enriched for patients with more severe disease. Steen et al. demonstrated that among patients who develop severe GI involvement (characterized by malabsorption, recurrent pseudo-obstruction, and/or need for hyperalimentation), 45% developed severe GI disease within 3 years after the onset of the first symptom attributed to SSc. This suggests that an inverse association exists between the severity of GI disease and disease duration in a subset of patients.[6] Battle et al. investigated 10 patients with SSc and found that those with longer disease duration had decreased colonic spike and contractile activity after meals and metoclopramide/neostigmine stimulation.[9] Madsen and colleagues' utilized colonic scintigraphy and found no correlation between disease duration and mean colonic transit time.[24] Govoni et al. examined colonic abnormalities in 35 patients with SSc using barium enema and similarly did not identify an association between colonic disease and duration of SSc.[25]

Our results suggest that patients do not develop a higher burden of colonic disease over time. Whether this implies that patients may develop slow colonic transit at any point during their disease course, or that specific environmental exposures increase the susceptibility of patient subsets to slow colonic transit independent of disease duration remains to be explained.

Previous studies describing the clinical phenotype associated with objective evidence of slow colonic transit are limited. In Govani et al.'s study, correlation between radiographical colonic changes using barium enema in 35 patients with SSc demonstrated no association between radiographic changes, extra-intestinal organ involvement, or with anti-CENP and anti-Scl70 antibodies.[25] This discrepancy may be attributed to the fact that early functional changes may be too subtle to be captured by barium enema. Our study not only evaluated a larger cohort of SSc patients with WGT studies, but also compared clinical features between SSc patients with and without slow colonic transit using data from a cohort with detailed information about patients' clinical phenotype and autoantibodies.

We also identified an association between female sex and slow colonic transit among patients with SSc in our univariate analysis. This variable, which had 1 male patient out of 48 patients with slow colonic transit, introduced instability to our multivariable model and therefore this variable was excluded in the final model. However, it is striking that only 1 out of 12 male patients in the cohort had slow colonic transit. Previous studies exploring colonic motility in SSc did not specifically look at associations with sex.[23,26,27] However, a study of 361 constipated patients in the general population demonstrated that women were more likely than men to have slow transit constipation (42.3% vs. 26.5%, p=0.04).[28] It appears that female sex is associated with slow transit constipation in the general population and also with slow colonic transit in patients with SSc. Our findings suggest that male patients may be less likely to suffer from slow colonic transit, however, further studies are warranted to validate this finding.

Associations between severe GI involvement in general and other clinical features of SSc [i.e. myositis, telangiectasia, cutaneous fibrosis, and myositis-related autoantibodies (anti-U3RNP, anti-Ku, anti-SRP)] are reported.[11,12] While we did identify an association with telangiectasia, we did not find associations with myositis or cutaneous fibrosis. Furthermore, Nishimagi et. al. determined that SSc patients with severe GI disease (characterized by

malabsorption, recurrent pseudo-obstruction, need for hyperalimentation, and/or ≥10% weight loss) had a lower frequency of anti-CENP antibodies compared to those without severe GI disease.[12] We suspect that these distinctions exist because prior studies were not specifically examining colonic transit, and classified GI disease based on patient symptoms instead of objective measurements of delayed transit. This implies that “severe GI disease” is comprised of heterogenous groups of patients with a variety of GI pathology, and there is a need for the characterization of specific patient subsets.

It is interesting that features observed in vascular disease, such as telangiectasia, anti-CENP autoantibodies, and smoking are associated with slow colonic transit in the univariate analysis. Although the relationship between anti-CENP antibodies and smoking with slow colonic transit lost significance in our multivariable model, other groups have demonstrated an association between smoking and GI symptom severity.[29,30] Hudson et. al. examined the effects of smoking on self-reported GI symptoms in patients with SSc using the Comprehensive Smoking Index, a tool that integrates smoking intensity, duration, and time since cessation into a covariate.[30] Smoking was significantly associated with a negative impact on a number of GI symptoms, including chronic constipation, early satiety, severity of GI symptoms, and number of GI symptoms. Interestingly, when female sex was included in the multivariable model (Supplemental Table 1), there was a significant association between slow colonic transit and smoking (p=0.01). Future longitudinal studies in patients with SSc may provide further insight into the effects of smoking on slow colonic transit and may provide a point of intervention when counseling patients with SSc at risk for slow colonic transit.

Notable strengths of our study include a large cohort of SSc patients who underwent WGT study, and the use of an extensive database with standardized data collection, longitudinal follow-up, and robust antibody data to classify our patients. Limitations include referral bias, as patients who are referred to JHSC often have more severe disease and present later in their disease course, and the time investment of the WGT study may have limited access for some patients. There is also a potential for selection bias because the majority of patients enrolled in our study were symptomatic, making it possible that they had a longer disease duration. However, prior studies suggest that a subset of SSc patients have rapidly progressive GI symptoms and disease, which may also contribute to the lack of correlation between GI disease and disease duration in our study.[6,31] There is also potential for misclassification, as we accounted for missing data with imputation in our multivariable logistical regression model, though we minimized this risk by utilizing a statistically rigorous approach.

In conclusion, our study demonstrates that slow colonic transit is common and often severe in patients with SSc. We established that disease duration does not appear to associate with the presence or severity of slow colonic transit in SSc. We also determined that specific clinical features (female sex, telangiectasia, anti-CENP autoantibodies, and smoking) are positively associated, and a significantly low FVC is negatively associated with slow colonic transit in SSc. Defining the clinical and serological characteristics of patients with slow colonic transit may help us identify high-risk patients, even when GI symptoms are not specific, expediting diagnosis and treatment of colonic dysfunction. Prospective longitudinal

studies are needed to determine whether the presence of these clinical features at baseline are useful in identifying patients at high risk of progressive slow colonic transit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATIONS

- The identification of clinical and serological features associated with colonic hypomotility is important in the diagnostic evaluation and risk stratification of SSc patients
- Slow colonic transit is not associated with transit delays in other GI regions in SSc
- The presence, severity, and extent of slow colonic transit is not associated with disease duration
- Slow colonic transit was positively associated with female sex, telangiectasia, anti-centromere antibodies, prior or current smoking, lower FVC and a Medsger GI severity score of ≥3 in the univariate analyses, and associated with telangiectasia and less restriction on PFTs in the multivariable model

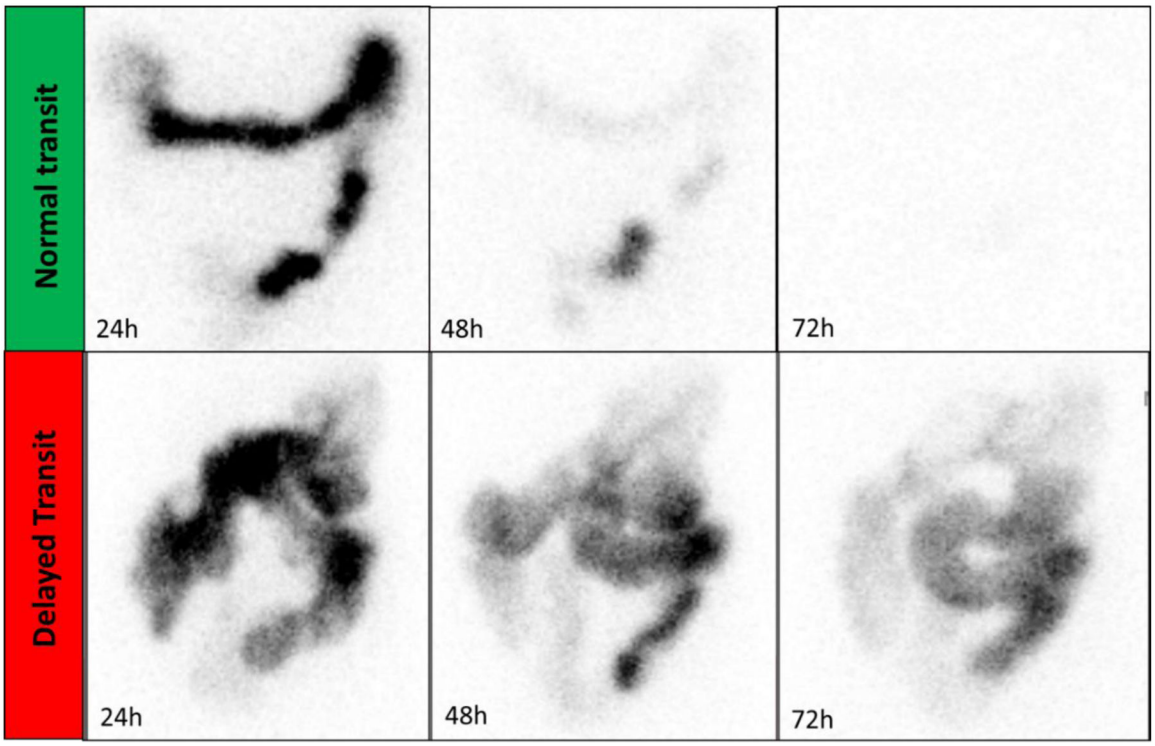

Figure 1.

Serial images of colonic transit by nuclear scintigraphy at 24, 48, and 72 hours are captured in the two panels. The top panel of images are from a patient with systemic sclerosis and normal colonic transit, where radionucleotide is largely evacuated at the 72 hour time point. In contrast, in the bottom panel, the images are from a patient with systemic sclerosis and slow colonic transit, with residual radionucleotide remaining at the 72 hour time point.

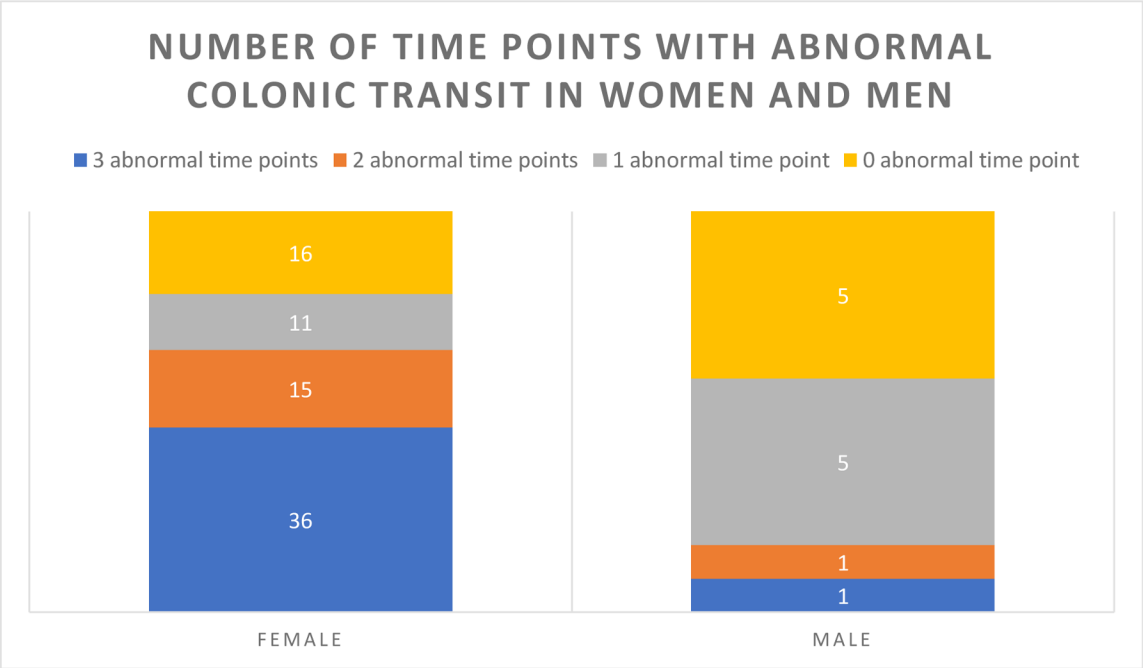

Figure 2.

Number of time points with abnormal colonic transit in females (n=78) and males (n=12). Only patients with complete WGT study data across all 3 time points were included. 10 females had incomplete WGT data and were excluded. Cutoffs for normal transit are <14% emptying at 24hr, <41% emptying at 48hr, and <67% emptying at 72hr.

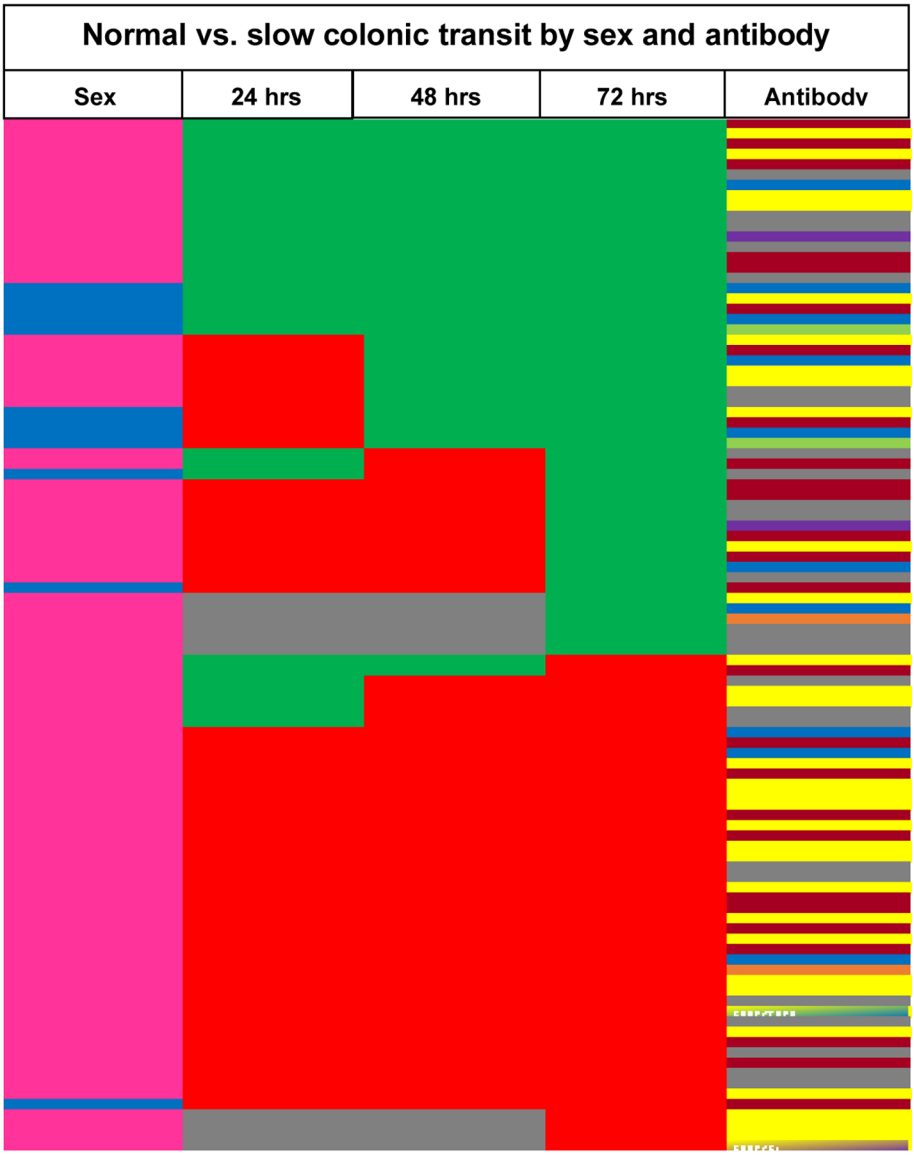

Figure 3.

Results of colonic WGT study based on sex and antibody. In the “sex” column, females are depicted in pink and males are depicted in blue. Normal colonic transit at its respective time point (24h, 48h, or 72h) is depicted in green, delayed transit is depicted in red and incomplete values are depicted in grey. Cutoffs for normal transit are <14% emptying at 24hr, <41% emptying at 48hr, and <67% emptying at 72hr.

In the “antibody” column, anti-CENP is depicted in yellow, anti-topoisomerase I is depicted in blue, anti-RNA polymerase III in light green, anti-U3RNP in orange, and anti-Ku in purple. Patients without any of the aforementioned antibodies are depicted in dark red, and patients with unknown antibody status are depicted in grey. Notably, 2 patients had 2 autoantibodies, one patient had for anti-CENP and anti-topoisomerase I and another patient had anti-CENP and anti-Ku.

Table 1.

Characteristics of the SSc patients with and without colonic hypomotility by WGT study in the Johns Hopkins Scleroderma Center cohort

Clinical and demographic features	n (%) of patients out of 100 with data	Colonic Hypomotility (n=48)	No colonic hypomotility (n=52)	p-value
Age at first symptoms, mean (SD)	100 (100)	58.8 (10.8)	56.4 (11.9)	0.29
Disease duration from first SSc-associated symptom (Raynaud's or non-Raynaud's) to date of WGT study, median (IQR)	96 (96)	12.1 (8.0, 18.3)	11.5 (5.6, 23.7)	0.96
Disease duration from first non-Raynaud's symptom to date of WGT study, median (IQR)	88 (88)	10.7 (5.0, 17.2)	6.7 (4.0, 17.3)	0.40
Female sex, % (n)	100 (100)	98 (47)	79 (41)	**<0.01**†
UCLA GIT 2.0				
Reflux, median (IQR)	55 (55)	1.1 (0.4, 1.4)	0.9 (0.5, 1.3)	0.49
Distension/bloating, median (IQR)	56 (56)	1.5 (0.8, 2.5)	1.5 (1.0, 2.0)	0.86
Soilage, median (IQR)	56 (56)	0.5 (0.0, 1.0)	0.0 (0.0, 1.0)	0.34
Diarrhea, median (IQR)	56 (56)	0.5 (0.0, 0.5)	1.0 (0.0, 1.5)	**0.03**†
Constipation, median (IQR)	55 (55)	0.5 (0.3, 1.0)	0.8 (0.5, 1.3)	0.31
Social functioning, median (IQR)	57 (57)	0.4 (0.2, 1.2)	0.5 (0.2, 1.3)	0.46
Emotional well-being, median (IQR)	56 (56)	0.6 (0.3, 1.1)	0.7 (0.2, 1.2)	0.90
GIT total, median (IQR)	54 (54)	0.8 (0.6, 1.3)	0.8 (0.5, 1.2)	0.84
Race/Ethnicity				
White, % (n)	98 (98)	83 (39)	75 (38)	0.31
Ever smoker, % (n)	96 (96)	43 (20)	22 (11)	**0.04**†
SSc Type				
Limited cutaneous disease, % (n)	100 (100)	67 (32)	71 (37)	0.63
Maximum MRSS, median (IQR)	88 (88)	4 (2, 10.5)	4 (2, 6)	0.14
Severe GI involvement, (≥3), %(n)	90 (90)	27 (12)	9 (4)	**0.03**†
Cardiac involvement (≥1), % (n)	72 (72)	6 (2)	11 (4)	0.67
Myopathy, % (n)	87 (87)	14 (6)	13 (6)	0.90
Raynaud's severity (≥3), % (n)	90 (90)	45 (20)	33 (15)	0.21
Lung involvement (≥1), % (n)	71 (71)	22 (8)	37 (13)	0.17
Cancer, % (n)	88 (88)	27 (12)	20 (9)	0.45
Telangiectasia, % (n)	93 (93)	89 (40)	67 (32)	**0.01**†
Calcinosis, % (n)	93 (93)	24 (11)	27 (13)	0.77
Pulmonary function parameters				
Low FVC, % (n)	76 (76)	23 (9)	56 (20)	**<0.01**†
Low DLCO, % (n)	74 (74)	36 (14)	57 (20)	0.067
RVSP by echo (mmHg), median (IQR)	37 (37)	30 (25, 35)	34.5 (28, 36)	0.53
Antibodies, % (n)				
Scl-70 (i.e. Topoisomerase-1)	75 (75)	11 (4)	19 (7)	0.35
Centromere (CENP)	75 (75)	58 (22)	31 (11)	**0.01**†

Clinical and demographic features	n (%) of patients out of 100 with data	Colonic Hypomotility (n=48)	No colonic hypomotility (n=52)	p-value
RNA polymerase-3	75 (75)	0 (0)	5 (2)	0.24
U3RNP	75 (75)	3 (1)	3 (1)	1.00
PMScl	75 (75)	3 (1)	8 (3)	0.36

† statistically significant

MRSS = modified Rodnan skin score; GI = gastrointestinal; severe GI involvement = maximum Medsger GI severity score ≥3; Cardiac involvement = maximum Medsger cardiac severity score ≥ 1; Lung involvement = maximum Medsger cardiac severity score ≥ 1; Low FVC = forced vital capacity <70%; Low DLCO = diffusing capacity of carbon monoxide <60%; RSVP = estimated right ventricular systolic pressure by echocardiogram.

Table 2.

Cross-sectional univariate model evaluating the association between clinical, demographic, serologic features and colonic hypomotility in patients with SSc

Clinical and demographic features	n (%) of patients out of 100 with data	Odds Ratio	95% Confidence Interval	p-value
Age at first symptom	100 (100)	1.02	0.98–1.06	0.29
Disease duration from first SSc-associated symptom (Raynaud's or non-Raynaud's) to date of WGT study	96 (96)	1.00	0.97–1.03	0.99
Disease duration from first non-Raynaud's symptom to date of WGT study, median (IQR)	88 (88)	1.02	0.98–1.08	0.31
Female sex	100 (100)	12.61	1.56–101.90	**0.02**†
Race/Ethnicity				
White	98 (98)	1.67	0.62–4.48	0.31
Ever smoker	96 (96)	2.56	1.06–6.21	**0.04**†
SSc Type				
Limited cutaneous disease	100 (100)	0.81	0.35–1.89	0.63
Maximum MRSS	88 (88)	1.04	0.97–1.11	0.31
Severe GI involvement (≥3)	90 (90)	3.94	1.16–13.36	**0.03**†
Cardiac involvement (≥1)	72 (72)	0.47	0.08–2.75	0.40
Myopathy	87 (87)	1.08	0.32–3.67	0.90
Raynaud's severity (≥2)	90 (90)	1.72	0.73–4.05	0.21
Lung involvement (≥1)	71 (71)	0.48	0.17–1.37	0.17
Telangiectasia	93 (93)	4.00	1.32–12.10	**0.01**†
Calcinosis	93 (93)	0.87	0.34–2.21	0.77
Cancer	88 (88)	1.46	0.54–3.92	0.45
Pulmonary function parameters				
Low FVC‡	76 (76)	0.23	0.09–0.63	**<0.01**†
Low DLCO‡	74 (74)	0.42	0.16–1.07	0.07
RVSP by echo (mmHg)	37 (37)	0.97	0.88–1.07	0.55
Antibodies				
Scl70 (i.e. Topoisomerase-1)	75 (75)	0.50	0.13–1.89	0.31
Centromere (CENP)	75 (75)	3.25	1.25–8.44	**0.02**†
RNA polymerase-3	75 (75)	1	Omitted	
U3RNP	75 (75)	0.97	0.06–16.15	0.99
PmScl	75 (75)	0.31	0.03–3.09	0.32

† statistically significant

‡ Based on minimum value across all visits

MRSS = modified Rodnan skin score; GI = gastrointestinal; Severe GI involvement = maximum Medsger GI severity score ≥3; Cardiac involvement = maximum Medsger cardiac severity score ≥ 1; Lung involvement = maximum Medsger cardiac severity score ≥ 1; Low FVC = forced vital capacity <70%; Low DLCO = diffusing capacity of carbon monoxide <60%; RSVP = estimated right ventricular systolic pressure by echocardiogram.

Table 3.

Multivariable model evaluating the association between clinical, demographic, and serological features and colonic hypomotility after adjusting for significant covariates from the univariate analysis among entire cohort of 100 patients.

Covariate	Odds Ratio	95% Confidence Interval	p-value
Ever smoker	2.16	0.82–5.75	0.12
Telangiectasia	3.97	1.20–13.20	**0.02**†
Low FVC‡	0.28	0.09–0.86	**0.03**†
Anti-centromere (CENP) autoantibody	1.14	0.36–3.60	0.82

† statistically significant

‡ Based on minimum value across all visits

Low FVC = forced vital capacity <70%.