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Esophageal dilatation and interstitial lung disease in systemic sclerosis: A cross-sectional study[☆]

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Abstract

Objective—A patulous esophagus on high-resolution computed tomography (HRCT) of the thorax is frequently observed in patients with systemic sclerosis (SSc). Microaspiration has been purported to play a role in the development and progression of SSc interstitial lung disease (ILD), but studies examining the role of microaspiration in SSc ILD have yielded conflicting results. This study was conducted to determine the association between esophageal diameter and SSc ILD.

Methods—A cross-sectional study of Northwestern Scleroderma Registry patients with available HRCT exams was conducted. The predictor variable was the widest esophageal diameter (WED) on HRCT, and the primary and secondary outcome variables were radiographic ILD and pulmonary function tests respectively. The degree of radiographic ILD was assessed using a semi-quantitative score adapted from published methods. Estimated regression coefficients adjusted for age, sex, race, body mass index, smoking; SSc disease subtype, serum autoantibodies, and disease duration; modified Rodnan skin score, proton pump inhibitor, and immune suppressant medication use and erythrocyte sedimentation rate were calculated.

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Results—A total of 270 subjects were studied. In the adjusted analyses, there were positive associations between WED and total ILD score ($\beta = 0.27$; 95% CI: 0.09–0.41), fibrosis ($\beta = 0.15$; 95% CI: 0.07–0.23), and ground glass opacities ($\beta = 0.12$; 95% CI: 0.04–0.20); there were negative associations between WED and FVC % predicted ($\beta = -0.42$; 95% CI: -0.69 to -0.13), and adjusted DLCO % predicted ($\beta = -0.45$; 95% CI: -0.80 to -0.09) after adjusting for potential confounders.

Conclusions—Increasing esophageal diameter on HRCT in patients with SSc is associated with more severe radiographic ILD, lower lung volumes, and lower DLCO % predicted. Longitudinal studies are needed to determine if esophageal dilatation is associated with the incidence and/or progression of ILD in patients with SSc.

Keywords

Systemic sclerosis; Esophagus; Interstitial lung disease; Dilation; Pulmonary fibrosis

Introduction

A patulous esophagus is a frequent but poorly understood incidental finding on high-resolution computed tomography (HRCT) of the thorax in patients with systemic sclerosis (SSc) (Fig. 1) [1,2]. Previous studies have established a relationship between a dilated esophagus and esophageal dysmotility in patients with SSc [2,3]. A study of 1043 subjects demonstrated that SSc patients with more gastrointestinal (GI) involvement/symptoms had a lower forced vital capacity (FVC) % predicted on pulmonary function tests (PFT), supporting the hypothesis that SSc GI and lung disease are associated [4]. Because microaspiration of refluxed gastric contents may play a central role in the initiation and progression of other forms of interstitial lung disease (ILD) including idiopathic ILD [5–8], we hypothesized that a dilated esophagus on HRCT may be associated with ILD in patients with SSc.

Prior studies that examined the association between a patulous esophagus on HRCT and SSc ILD have yielded conflicting results [1,2,9,10]. Small sample sizes and/or treatment of esophageal dilatation as a dichotomous outcome based upon a threshold (≥ 9 mm in the infra-aortic esophagus) limit the conclusions that can be drawn from previous reports [1,2,9,10]. The present study includes a large cohort of clinically well-characterized patients with SSc and utilizes published ILD and state-of-the-art widest esophageal diameter (WED) scoring protocols. Because ILD is a leading cause of death in SSc, and esophageal dysmotility may contribute to ILD progression via microaspiration [5–8], it is important to characterize fully the association between esophageal dilation and both radiographic ILD and pulmonary function in SSc patients.

Methods

Patient selection

Clinical data from Northwestern Scleroderma Program Registry patients were utilized for this cross-sectional study in accordance with Northwestern University Institutional Review Board policy. Only subjects with diffuse cutaneous systemic sclerosis (dcSSc) or limited

cutaneous systemic sclerosis (lcSSc) were included [11]. Subjects met American College of Rheumatology (ACR) 1980 SSc or three out of five CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) criteria [12]. A retrospective chart review was conducted to determine the number of subjects that fulfilled the new 2013 SSc criteria [13]. Patients who were diagnosed with achalasia or who had undergone endoscopic esophageal dilatation, esophageal resection, fundoplication or other gastrointestinal surgeries, pneumonectomy or lobectomy, or other lung surgeries were excluded. If multiple HRCT exams were available, the first HRCT was used.

Clinical and laboratory data

Baseline clinical data were collected from rheumatology clinic notes within one year of the first HRCT. Disease duration was defined as the time between first non-Raynaud symptom attributed to SSc and the baseline HRCT date. A history of scleroderma renal crisis (SRC) was based on clinician documentation of SRC in the medical record. Pulmonary hypertension was considered present based on right heart catheterization with a mean pulmonary artery pressure ≥ 25 mm Hg and a pulmonary capillary wedge pressure < 15 mm Hg [14]. A smoking history was considered positive if the subject was a current or previous smoker, based on the assumption that any smoking exposure may contribute to ILD. Alcohol use was defined as present or absent based upon whether the patient reported current alcohol use at the baseline visit. Myositis was defined as a creatine kinase $> 2 \times$ the upper limit of normal or electromyography consistent with myopathy. Any current use or history of exposure to prednisone, cyclophosphamide, mycophenolate mofetil, or methotrexate was recorded.

HRCT exams

The primary outcome was ILD on HRCT. Patients with a new diagnosis of SSc or long-standing SSc with pulmonary complaints evaluated at the Northwestern Scleroderma Program routinely undergo a baseline HRCT exam of the thorax. These studies or digital images of studies performed at outside institutions were obtained. An experienced thoracic radiologist who was blinded to clinical and laboratory data scored HRCT exams using a method adapted from Kazerooni et al. [15] that assesses fibrosis and ground glass opacities. This method is a semi-quantitative scoring system that has been used in previous studies of SSc ILD [9,10,16]. Five lung lobes are scored from 0–5 for degree of fibrosis and ground glass opacities, where 0 = none, 1 = 1–5%, 2 = 6–25%, 3 = 26–50%, 4 = 51–75%, and 5 = $> 75\%$ of lobe demonstrating involvement. Fibrosis is defined as the presence of traction bronchiectasis, honeycombing, and/or reticulation; ground glass opacity is defined as any alveolar opacity preserving the underlying lung architecture. Fibrosis and ground glass opacity scores are summed for all lobes to provide composite fibrosis and ground glass scores. The total ILD score is the sum of the fibrosis and ground glass scores (range of 0–50).

The primary predictor was widest esophageal diameter (WED) that was defined as the largest distance (mm) between internal esophageal mucosal limits for three esophageal diameter measurements on supine axial HRCT images—above the aortic arch, between the right inferior pulmonary vein and the aortic arch, and between the diaphragmatic hiatus and

the right inferior pulmonary vein. Similar methods have been used in previous SSc ILD studies with good inter-observer agreement [9,10,16].

Pulmonary function tests

Pulmonary function test results closest to, and within one year of the HRCT date were identified. Forced vital capacity, total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO) % predicted corrected for hemoglobin were recorded. The majority of PFT tests were performed at Northwestern Memorial Hospital according to American Thoracic Society guidelines [17]. Reference values were based on age, sex, and race for FVC (National Health and Nutrition Examination Survey/NHANES III) [18] and on age and sex for TLC and DLCO % predicted.

Statistical analysis

Descriptive statistics were assessed for the cohort. Multiple linear regression models were used to examine the relationship between WED and primary and secondary outcomes. Variables known to influence lung function (smoking, sex, ethnicity, and body mass index (BMI; kg/m²), variables thought to be potentially important in SSc esophageal and/or pulmonary disease risk (SSc disease subtype, disease duration, and serum autoantibodies; proton pump inhibitor use, and immune suppressive treatment exposure); and markers of SSc disease severity (erythrocyte sedimentation rate and modified Rodnan skin score) were included in the multiple regression models. Estimated regression coefficients and standard errors for the main predictor WED along with *t*-value and significance level were reported. Larger absolute *t*-values imply smaller *p*-values. A *p* < 0.05 was considered significant. SAS version 9.4 (Cary, NC) was used for all analyses.

Results

A total of 450 subjects with lcSSc or dcSSc were identified (Fig. 2). Of these, 276 subjects had HRCT images available. Overall, 174 subjects lacked available HRCT images. Of these, 110 had undergone HRCT scans at outside facilities, and the images were not available for review, and 64 had not undergone HRCT scans. The 64 patients without HRCT testing had a greater mean FVC % predicted (95.6 vs. 76.6; *p* < 0.0001) and a greater mean DLCO % predicted (79.8 vs. 59.9; *p* < 0.0001). In all, 6 subjects were excluded based on a history of gastrointestinal or pulmonary surgery—one had Nissen fundoplication, two had endoscopic esophageal dilatation, two subjects had pulmonary lobectomy, and one had esophagectomy. Thus, 270 subjects were included in the analysis. Overall, 266 subjects had available PFT data, of which 93% PFT were performed at our institution. Incidentally, of these 270 who fulfilled 1980 SSc criteria or the criteria for CREST, 263 (97%) also fulfilled 2013 SSc criteria[13].

Baseline study cohort characteristics are shown in Tables 1 and 2. Subjects' mean $\pm$ SD age was 51 ± 12 years and 82% were women. 42% had dcSSc, and the mean $\pm$ SD mRSS was 13 ± 11 . The mean $\pm$ SD SSc disease duration was 6.3 ± 7.8 years, and the mean $\pm$ SD BMI was 26 ± 6 kg/m². The median esophageal diameter was 18 mm with a range of 4–44 mm. To identify which patient factors are associated with wider esophageal diameters, we divided

patients based upon whether their esophageal diameter was < or the median esophageal diameter of 18 mm (Supplementary Table 1). Subjects with greater esophageal diameters were more likely to be Scl-70 positive (34% vs. 24%, $p = 0.002$), have dcSSc (46% vs. 39%, $p = 0.23$), and longer disease duration (6.7 years vs. 5.7 years, $p = 0.29$). They were also more likely to be men (25% vs. 10%, $p = 0.001$) and older (52 vs. 50 y, $p = 0.31$). Subjects with greater esophageal diameters were also more likely to be taking proton pump inhibitors (74% vs. 50%, $p < 0.0001$) and to have taken mycophenolate mofetil (24% vs. 11%, $p = 0.004$). Mean erythrocyte sedimentation rate was greater in the subjects with greater esophageal diameters (26.4 vs. 18.4, $p = 0.02$). Mean body mass index and a history of scleroderma renal crisis, myositis and pulmonary hypertension were equally distributed between groups and were not adjusted for.

Results of analyses assessing the association between WED and ILD are shown in Table 3 and Figure 3. Estimated regression coefficients demonstrated positive associations between WED and total ILD score ($\beta = 0.27$, 95% CI: 0.09–0.41), fibrosis ($\beta = 0.15$, 95% CI: 0.07–0.23), and ground glass opacities ($\beta = 0.12$, 95% CI: 0.04–0.20) after adjusting for age, sex, race/ethnicity, BMI, disease subtype, smoking, disease duration, serum autoantibodies, erythrocyte sedimentation rate, modified Rodnan skin score, and proton pump inhibitor and immune suppressive medication use (Table 3). We observed a high correlation between TLC and FVC % predicted ($r = 0.84$, $p < 0.0001$, data not shown). Therefore, we included FVC rather than TLC % predicted in subsequent analyses. Figure 3 shows the association between WED with ILD score, FVC and DLCO % predicted. There was a positive correlation between total ILD score and WED and negative associations in the adjusted analyses between WED and FVC% predicted ($\beta = -0.42$, 95% CI: -0.69 to -0.13) and adjusted DLCO % predicted ($\beta = -0.45$, 95% CI: -0.80 to -0.09) (Table 3 and Figure 3). These data demonstrate that SSc patients with larger esophageal diameters have more lung fibrosis and worse pulmonary function independent of age, sex, race/ethnicity, BMI, disease subtype, smoking, disease duration, serum autoantibodies, erythrocyte sedimentation rate, modified Rodnan skin score, and proton pump inhibitor and immune suppressive medication use.

Discussion

Our study results demonstrate that a larger esophageal diameter on HRCT is associated with more extensive radiographic ILD as well as lower PFT parameters in patients with SSc. This association holds true even after adjustment for age, sex, race/ethnicity, body mass index, and smoking; SSc disease duration, subtype, and serum autoantibodies; markers of disease severity (erythrocyte sedimentation rate and modified Rodnan skin score); and proton pump inhibitor and immune suppressant medication use. Although a review of the medical literature revealed no articles that have found an association between sex and esophageal diameter, we included sex in our model because men with SSc are known to be at increased risk for worse SSc.

Prior studies designed to assess the association between a patulous esophagus and SSc ILD yielded conflicting results. In 2008, Vonk et al. [2] studied 105 consecutive patients with SSc and 107 controls and concluded that the prevalence of pulmonary fibrosis on HRCT chest was not increased in patients with esophageal diameters > 10 mm as compared to subjects

with esophageal diameters ≥ 10 mm. This study, however, did not examine the relationship between ground glass changes on HRCT and esophageal diameter. In 2011, Pandey et al. [9] published results of a retrospective study of 50 patients with SSc and found no significant differences in HRCT-based weighted scores (adjusting for lung lobe size) for ground glass, fibrosis, honeycombing, and overall ILD burden between patients with esophageal diameters > 9 mm compared to those with esophageal diameters ≤ 9 mm. Although the authors concluded that there was no association between esophageal dilatation and ILD, it is possible that the size of the cohort or the cut point of 9 mm may account for the lack of association. Interestingly, the authors did note of a statistically significant reduction in DLCO and a non-significant trend toward reduction in TLC in those with esophageal diameters > 9 mm. This suggests that DLCO may be a more sensitive marker of lung injury related to silent aspiration as has been shown in other forms of lung injury [19]. Finally, in 2012, Patiwetwitoon et al published results from another study involving 71 patients with SSc and showed a significant correlation between the extent of honeycombing on HRCT and esophageal diameter [10]. The authors did not report pulmonary function test results. Our results in a larger cohort using HRCT to assess ILD and esophageal diameter demonstrate an association between WED, and lung fibrosis and ground glass opacities. Additionally, we find an association between WED and reductions in FVC and DLCO % predicted that underscores the functional implication of a higher ILD score on HRCT. Thus, our study is the largest to date and the first to demonstrate a clear association between the extent of esophageal dilatation and increased ILD as well as PFT reductions in SSc patients.

Due to limited cohort sizes, the three studies cited above treated esophageal dilatation as a dichotomous rather than as a continuous variable. The method used to define the presence of esophageal dilatation in these studies was based upon a previous study by Pitrez et al. [3] who conducted receiver operating characteristic (ROC) curves to demonstrate that supra-aortic ≥ 4 mm and an infra-aortic ≥ 9 mm esophageal luminal diameters on coronal HRCT had good discriminatory capacity for esophageal dysfunction as assessed by esophageal scintigraphy. The use of coronal measurements to measure esophageal diameter has a tendency to underestimate the WED, particularly if the dilatation is predominantly in the anterior-posterior dimension. Additionally, the long axis of the esophagus is orthogonal to the axial plane, thus axial views likely provide the most accurate WED measurements. Our study is the first to assess the degree of esophageal dilation using axial HRCT measurements in a large number of patients that fulfill the new 2013 SSc criteria.

We show that esophageal dilatation was significantly more common in patients with Scl-70 serum autoantibodies. Vonk et al. [2] found that esophageal dilatation was more prevalent in patients with longer SSc disease duration (defined as the interval between the first non-Raynaud symptom and HRCT date), but the results were not statistically significant. Further, no association between esophageal dilatation and SSc subset, SSc-specific serum autoantibodies, or sex were identified [2]. The small cohorts in the Pandey et al. [9] and Patiwetwitoon et al. [15] studies precluded any assessment of associations between esophageal dilatation patient factors including sex, SSc disease duration and subset, and serum autoantibodies. Future longitudinal studies to determine whether a patulous esophagus is a risk factor for ILD progression should be designed to include careful assessment of SSc disease duration, subset, and serum autoantibodies.

We speculate that SSc patients with increased WED have significant esophageal dysfunction that leads to increased pulmonary aspiration and resultant lung injury from either acid or particulate matter aspiration. Aspiration might have a role in both driving existing lung inflammation or be an independent cause of lung injury. Although our study does not prove a causal relationship between esophageal diameter and SSc ILD, our results are consistent with the findings of previous studies suggesting that microaspiration may be a significant mechanism in the development and/or progression of ILD in SSc. For example, Lock et al. [20] found that SSc patients with hypomotility or aperistalsis on esophageal manometry had lower lung volumes and lower DLCO values. In addition, Marie et al. [21] demonstrated that more severe esophageal motor abnormalities in SSc patients were not only associated with a greater prevalence of ILD on HRCT scan and lower baseline DLCO values, but also they were associated with a greater deterioration of DLCO at a follow-up interval of 2 years. Supporting the hypothesis that microaspiration may mediate the relationship between esophageal dysmotility and ILD in SSc, Savarino et al. [22] showed that the presence of pulmonary fibrosis on HRCT was associated with a greater number of proximal reflux episodes on pH-impedance monitoring in patients with SSc.

The strengths of this study include a large, clinically well- characterized SSc study population. In addition, we treated esophageal dilatation and ILD as continuous variables that increased our power to detect meaningful differences. Study limitations include a retrospective design that lessened our ability to assess esophageal motility, as invasive esophageal studies were not performed routinely in our cohort. Also, more detailed descriptions of some baseline variables, such as pack-years of tobacco exposure or duration of disease-modifying anti-rheumatic drug therapy were not available. In addition, this study was not designed to determine the temporal association between esophageal dilatation and ILD. Finally, the retrospective design of this study resulted in the exclusion of patients in whom HRCT testing was not performed. Patients with long-standing SSc who lack pulmonary complaints are not referred for HRCT exams. Thus, it is possible that our study results over-estimate the prevalence of esophageal dilation in patients with SSc.

Given the substantial morbidity and mortality burden of ILD in SSc, there is a pressing need to elucidate factors that contribute to the development and progression of SSc ILD. Because SSc patients routinely undergo HRCT lung testing, demonstrating that WED predicts ILD progression would be useful clinically. Patients with esophageal dilatation might benefit from more aggressive reflux control and/or the development of better measures to correct esophageal dilatation. Furthermore, understanding the role of esophageal abnormalities in the pathogenesis of SSc ILD may help with the risk assessment of patients with SSc ILD who are undergoing evaluation for lung transplantation. Based upon our results, longitudinal studies are needed to determine if esophageal dilatation predicts ILD progression.

Conclusions

Our article presents two main findings. First, we show that a wider esophageal diameter on HRCT is associated with higher total interstitial lung disease, higher fibrosis, and higher ground opacities scores. Second, we show that a wider esophageal diameter is associated with a lower forced vital capacity and diffusion for carbon monoxide % predicted. Thus, a

dilated esophagus is associated with worse radiographic lung disease and pulmonary function in SSc patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.semarthrit.2016.02.004>.

Abbreviations

HRCT	high-resolution computed tomography
SSc	systemic sclerosis
GI	gastrointestinal
FVC	forced vital capacity
PFT	pulmonary function tests
ILD	interstitial lung disease
WED	widest esophageal diameter
dcSSc	diffuse cutaneous systemic sclerosis
lcSSc	limited cutaneous systemic sclerosis
ACR	American College of Rheumatology
CREST	calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias
SRC	scleroderma renal crisis
TLC	total lung capacity
DLCO	diffusing capacity for carbon monoxide
NHANES	National Health and Nutrition Examination Survey
BMI	body mass index
ROC	receiver operating characteristic

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Fig. 1. Esophageal diameter variation on HRCT in patients with systemic sclerosis. Axial high-resolution computed tomography chest images show (A) a normal-caliber esophagus (arrow) in a healthy control and (B) a patulous esophagus with an air fluid level (arrow) in a patient with systemic sclerosis.

Fig. 2.

Study cohort. lcSSc, limited cutaneous systemic sclerosis, dcSSc, diffuse cutaneous systemic sclerosis, HRCT, high-resolution computed tomography of the thorax, and PFT, pulmonary function tests.

Fig. 3. Association between WED with lung fibrosis score and pulmonary function test parameters. Scatter plot with linear fitted line between WED with (A) total ILD score, (B) FVC % predicted, and (C) DLCO adjusted % predicted. WED, widest esophageal diameter, ILD, interstitial lung disease, FVC, forced vital capacity, DLCO, diffusion capacity for carbon monoxide adjusted for hemoglobin.

Table 1Baseline characteristics of study subjects ($N = 270$)

	Mean $\pm$ SD or n (%)
Age at time of CT, y	51 (11.7)
Sex, women	222 (82.2%)
BMI, kg/m ²	25.77 (5.66)
Race, white	203 (75.2%)
Smoker, current or former	102 (37.8%)
PPI, current	168 (62.2%)
Alcohol, current	114 (51.1%)
Disease subtype, diffuse cutaneous	114 (42.2%)
Modified Rodnan Skin Score	12.57 (11.00)
Duration since first non-Raynaud, y	6.25 (7.82)
Scleroderma renal crisis, positive	4 (1.6%)
Myositis, present	21 (9.8%)
Pulmonary hypertension, present	28 (14.7%)
Medications	
Mycophenolate mofetil	48 (17.8%)
Cyclophosphamide	17 (6.3%)
Methotrexate	40 (14.8%)
Prednisone	61 (22.6%)

BMI, body mass index (kg/m²), PPI, proton pump inhibitor.

Table 2

Laboratory studies and pulmonary function tests

	Mean $\pm$ SD or <i>n</i> (%)
Laboratory studies (<i>N</i> = 270)	
ANA, positive	258 (97.7%)
Anti-Ro, positive	32 (12.2%)
Anti-La, positive	10 (3.9%)
SSc-specific antibodies, positive	
Scl-70	71 (30.3%)
Anticentromere	49 (22.3%)
RNA pol III	43 (25.3%)
CRP, mg/dL	0.98 $\pm$ 1.73
ESR, mm/h	22.63 $\pm$ 22.26
Hemoglobin, mg/dL	12.65 $\pm$ 1.61
Pulmonary function tests (<i>N</i> = 266): % predicted	
FEV1	78.43 $\pm$ 17.86
FVC	76.71 $\pm$ 17.62
TLC	85.59 $\pm$ 17.97
DLCO corrected for hemoglobin	60.13 $\pm$ 20.92

ANA, antinuclear antibodies, DLCO, diffusion for carbon monoxide, CRP, C-reactive protein, ESR, erythrocyte sedimentation rate FEV1, forced expiratory volume in one second, FVC, forced vital capacity, RNA pol III, RNA polymerase III, Scl-70, anti-topoisomerase I, TLC, total lung capacity.

Table 3

Association between widest esophageal diameter and HRCT findings and pulmonary function test parameters

Outcome variables	Predictor: widest esophageal diameter (WED)					
	Unadjusted models			Adjusted models		
	Estimate	SE	t-value	Estimate	SE	t-value
Total ILD score ^a	0.42 ***	0.07	6.14	0.27 **	0.07	3.77
Total fibrosis score ^a	0.21 ***	0.04	5.55	0.15 **	0.04	3.74
Total ground glass score ^a	0.20 ***	0.04	5.23	0.12 **	0.04	2.85
FVC % predicted ^b	-0.65 **	0.13	-5.09	-0.42 *	0.14	-3.04
DLCO adjusted % predicted ^c	-0.64 **	0.15	-4.16	-0.45 *	0.18	-2.50

DLCO, diffusion capacity for carbon monoxide adjusted for hemoglobin % predicted, FVC, forced vital capacity, HRCT, high-resolution computed tomography, ILD, interstitial lung disease.

^a Adjusted for age, sex, ethnicity, BMI, smoking, proton pump inhibitor, disease subtype, disease duration, erythrocyte sedimentation rate, modified Rodnan skin score, SSc-specific antibody, mycophenolate use, cyclophosphamide use, and prednisone use.^b Adjusted for BMI, smoking, proton pump inhibitor, disease subtype, disease duration, erythrocyte sedimentation rate, modified Rodnan skin score, SSc-specific antibody, mycophenolate use, cyclophosphamide use, and prednisone use.^c Adjusted for race/ethnicity, BMI, smoking, proton pump inhibitor, disease subtype, disease duration, erythrocyte sedimentation rate, modified Rodnan skin score, SSc-specific antibody, mycophenolate use, cyclophosphamide use, and prednisone use.* $p < 0.05$.** $p < 0.001$.*** $p < 0.0001$.