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Esophageal Dilation and Other Clinical Factors Associated With Pulmonary Function Decline in Patients With Systemic Sclerosis

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ABSTRACT. ***Objective.*** To identify clinical factors, including esophageal dilation on chest high-resolution computed tomography (HRCT), that are associated with pulmonary function decline in patients with systemic sclerosis (SSc).

Methods. Patients fulfilled 2013 SSc criteria and had ≥ 1 HRCT and ≥ 2 pulmonary function tests (PFTs). According to published methods, widest esophageal diameter (WED) and radiographic interstitial lung disease (ILD) were assessed, and WED was dichotomized as dilated (≥ 19 mm) vs not dilated (< 19 mm). Clinically meaningful PFT decline was defined as % predicted change in forced vital capacity (FVC) ≥ 5 and/or diffusion capacity for carbon monoxide (DLCO) ≥ 15. Linear mixed effects models were used to model PFT change over time.

Results. One hundred thirty-eight patients with SSc met the study criteria: 100 (72%) had radiographic ILD; 49 (35%) demonstrated FVC decline (median follow-up 2.9 yrs). Patients with antitopoisomerase I (Scl-70) autoantibodies had 5-year FVC% predicted decline (−6.33, 95% CI −9.87 to −2.79), whereas patients without Scl-70 demonstrated 5-year FVC stability (+1.78, 95% CI −0.59 to 4.15). Esophageal diameter did not distinguish between those with vs without FVC decline. Patients with esophageal dilation had statistically significant 5-year DLCO% predicted decline (−5.58, 95% CI −10.00 to −1.15), but this decline was unlikely clinically significant. Similar results were observed in the subanalysis of patients with radiographic ILD.

Conclusion. In patients with SSc, Scl-70 positivity is a risk factor for FVC% predicted decline at 5 years. Esophageal dilation on HRCT was associated with a minimal, nonclinically significant decline in DLCO and no change in FVC during the 5-year follow-up. These results have prognostic implications for SSc-ILD patients with esophageal dilation.

Key Indexing Terms: biomarkers, gastrointestinal disease, interstitial lung disease, systemic sclerosis

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Interstitial lung disease (ILD) is a leading cause of death in patients with systemic sclerosis (SSc).[1,2] Known risk factors for prevalent SSc-ILD include positive antitopoisomerase I (Scl-70) serum autoantibody status, diagnosis of diffuse cutaneous (dc)-SSc, Black race, male sex, and genetic polymorphisms including certain major histocompatibility complex (MHC) class II human leukocyte alleles (MHC-II HLA-DRB1*11 and HLA-DPB*1301), and non-MHC genes including those for interleukin (IL)-1α, and IL-1β.[2] However, less is known regarding risk factors for SSc-ILD progression. A systematic review of 20 studies between 1994 and 2012 (1524 patients with SSc) found that greater chest high-resolution computed tomography (HRCT) fibrosis severity and shorter SSc disease duration were predictors of ILD progression.[3] Subsequently, Liu, *et al* showed that baseline elevation in C-reactive protein predicted SSc-ILD progression, measured by change in % predicted forced vital capacity (FVC), over a mean time-in-study of 4.4 years.[4] Assassi, *et al* demonstrated that positive Scl-70 autoantibody status was associated with short-term (3-yr) FVC% predicted decline (regression coefficient = −2.49, 95% CI −4.62 to −0.36, P = 0.02) in an SSc cohort where 58% had baseline FVC% predicted > 80. However, beyond 3 years, autoantibody status was not associated with progression, as assessed by FVC% predicted change.[5]

Symptomatic esophageal disease is present in > 50% of patients with SSc, and abnormal esophageal motility of uncertain significance on manometric testing is present in up to 90% of patients with SSc.[6] Esophageal dilation (defined as > 10-mm diameter on coronal HRCT images) in patients with SSc is associated with esophageal dysmotility, as assessed by esophageal transit scintigraphy;[7] further, esophageal dysmotility may be associated with SSc-ILD progression.[1,8] Specifically, Marie, *et al* reported that in 43 patients with SSc-ILD, those with severe vs mild-to-moderate esophageal dysmotility on manometry demonstrated greater 2-year decline in % predicted diffusion capacity for carbon monoxide (DLCO; −16.04% vs 1.47%, P = 0.02), but not FVC% predicted (−3.65% vs 0.09%, P = 0.39).[8] We previously showed in a cross-sectional study that esophageal diameter on axial HRCT images correlated positively with the presence of radiographic ILD and negatively with baseline FVC% and DLCO% predicted in patients with SSc.[9] Moreover, an esophageal diameter ≥ 19 mm had the best combined sensitivity and specificity for associated radiographic SSc-ILD.[10]

Mechanistically, a dilated esophagus may act as a gastric content reservoir allowing for microaspiration that induces lung parenchymal damage.[1,8,11,12] Gastroesophageal reflux disease is associated with idiopathic pulmonary fibrosis, and its treatment has been shown to stabilize lung function, supporting the hypothesis that esophageal dysfunction may also play an important role in SSc-ILD pathogenesis and progression.[13,14] The present study was undertaken to determine if radiographic esophageal dilation is an independent risk factor for pulmonary function decline during 1, 2, and 5 years of follow-up in patients with SSc. We also sought to identify other important patient factors associated with SSc-ILD progression using our large cohort of clinically well-characterized patients with SSc.

METHODS

This retrospective study was approved by the Northwestern University Institutional Review Board (STU00066807). Patient consent was obtained through the Northwestern Scleroderma Patient Registry (STU00002669). Patients with sine scleroderma, limited cutaneous (lc-), or dcSSc who fulfilled American College of Rheumatology 2013 SSc classification criteria and had at least 1 HRCT and 2 pulmonary function tests (PFTs) were included.[15] SSc disease duration was defined as the duration between first non-Raynaud SSc symptom and the baseline HRCT date. Follow-up time was defined as time from baseline PFT to last PFT date between April 2008 and August 2016. Patients with prior pulmonary or gastrointestinal (GI) procedures that would independently affect esophageal diameter or PFT measurements, including lung transplant, lobectomy, or esophageal dilatation procedures, were excluded. Important baseline clinical data were obtained by manual review of rheumatology clinic notes within 1 year of HRCT date. Collected data include proton pump inhibitor (PPI) use, prednisone use (any), tobacco use (current or former), digital ulcer (DU) history, pulmonary and GI symptoms, and erythrocyte sedimentation rate. Pulmonary arterial hypertension (PAH) was defined as mean pulmonary arterial pressure ≥ 25 mmHg on right heart catheterization.[16]

An experienced thoracic radiologist (RA), blinded to clinical data, manually reviewed HRCT exams to determine widest esophageal diameter (WED) and the presence or absence of ILD. The WED was defined as the largest of 3 esophageal diameters (mucosa to mucosa) at the level of the mid-arch of the aorta, the carina, and the diaphragmatic hiatus on axial HRCT images.[9] Patients were dichotomized by WED ≥ 19 mm or < 19 mm because our previous results showed that a WED cutpoint of 19 mm had the highest combined sensitivity and specificity for prevalent radiographic SSc-ILD.[10] The presence or absence of radiographic ILD was determined based upon methods described by Kazerooni, *et al*.[9,17] PFT change was analyzed in the full cohort (regardless of ILD status), and subanalysis was performed in patients with baseline radiographic ILD. We evaluated interrater reliability (between 2 radiologists) and intrarater reliability (2 ratings of 1 radiologist) for WED using intraclass correlation coefficient (ICC) for 2-way random effects model and for ILD presence using Cohen κ coefficient and % agreement for a subset of 60 HRCT scans. The sample size of 60 was calculated expecting the estimated ICC to be ≥ 0.90 compared to the null ICC of 0.80 with at least 80% power and α of 0.05.

Baseline PFT was defined as the test closest to, and within 12 months of, the first available HRCT. Subsequent longitudinal PFT data were recorded in months from baseline HRCT. Using National Health and Nutrition Examination Survey III reference populations, predicted FVC was determined by age, sex, and race, and predicted DLCO was determined by age and sex, and adjusted for hemoglobin.[18] The DLCO value was excluded from analysis in patients without an available hemoglobin result within 6 months of PFT or where inspiratory vital capacity (IVC):FVC ratio was < 0.85 (indicating poor test quality).[19]

We performed parallel analyses for FVC and DLCO change. For FVC analyses, we included 138 patients with FVC results and measured change in FVC% predicted to determine patient factors associated with longitudinal FVC decline. For DLCO analyses, we included 99 patients with DLCO results, and measured change in DLCO% predicted to determine patient factors associated with longitudinal DLCO decline. Both change in FVC% and DLCO% predicted were used as surrogates for worsening ILD.[20,21] Clinically meaningful PFT worsening was defined as a ≥ 5-point decrease in FVC% predicted and/or a 15-point decrease in DLCO% predicted.[8,21–26]

Spaghetti plots were used to visualize FVC% and DLCO% predicted change over time between Scl-70–positive vs –negative groups and WED ≥ 19 mm vs WED < 19 mm groups. We tested for baseline differences between those with vs without ILD progression using chi-square tests for categorical variables, and 2-sample t tests with unequal variance for continuous variables. We used linear mixed effects models with random intercepts and an unstructured covariance structure to examine between-group

differences in FVC% and DLCO% predicted change over time. Time since baseline PFT was modeled with a linear term. We tested for group differences by including group*time interaction terms. We analyzed possible differences in FVC% and DLCO% predicted change by WED groups within Scl-70–positive patients by including a 3-way interaction. We presented means adjusted estimates from models adjusted for sex, SSc disease subtype, Scl-70 positivity, SSc disease duration, PPI use, prednisone use, and smoking history. All analyses were conducted using SAS version 9.4 (SAS Institute) and R version 3.5.3 (cran.r-project.org).

RESULTS

The cohort included 138 patients who fulfilled study criteria with a median (range) follow-up of 2.9 (0.3–7.2) years (Figure 1). Fifteen patients (11%) with baseline HRCT died. The median (range) time between last PFT and death was 1.4 (0.2–3.9) years. Baseline characteristics for the full cohort and for patients with baseline radiographic ILD are described in Table 1. Most patients were female (84%), White (75%), and nonsmokers (62%). The mean (SD) age was 50 (11.1) years, and modified Rodnan skin score was 11 (9). Scl-70 was positive in 50 of 138 (36%) patients, and 64 (46%) patients had dcSSc. Radiographic ILD was present in 100 out of 138 (72%) patients, of whom 48% had positive Scl-70 and 54% had dcSSc. The mean (SD) baseline FVC% predicted was 78 (16.7) and DLCO was 60 (20.4) in the full cohort. Among patients with baseline ILD, mean FVC% predicted was 75 (17.3) and DLCO was 57 (19.9). The mean (SD) WED was 17.6 (8.2) mm in the full cohort and 18.6 (7.8) mm among patients with radiographic ILD. The median (IQR) number of PFTs per patient was 3 (2–4).

Reliability. Because the presence of ILD is based upon clinical judgment, 2 independent assessors reviewed a subset of chest HRCT exams. The interrater reliability κ was 0.96 (95% CI 0.88–1.00) for ILD presence, and ICC was 0.97 (95% CI 0.94–0.98) for WED. The intrarater reliability κ was 0.83 (95% CI 0.67–0.99) for ILD, and ICC was 0.97 (95% CI 0.95–0.98) for WED.

Baseline characteristics and clinically meaningful pulmonary

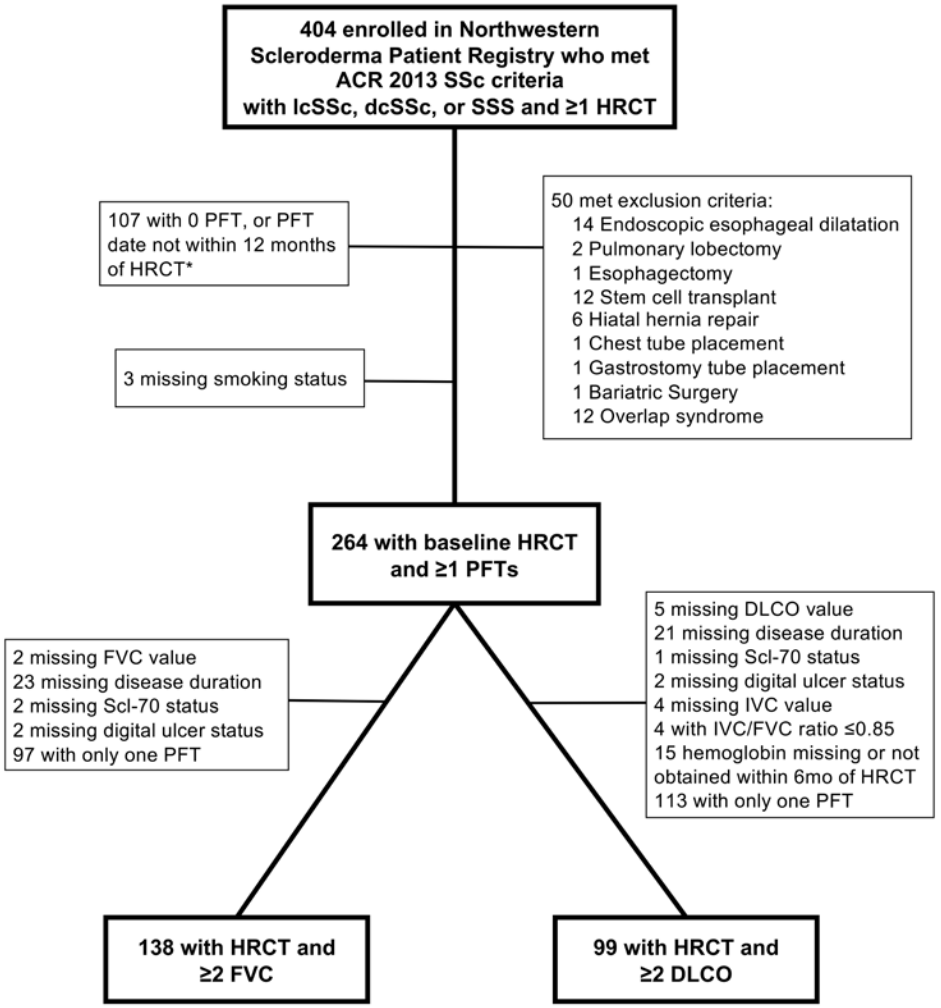

Figure 1. Derivation of analysis sample. * Patients excluded for missing PFTs may have met multiple exclusion criteria. ACR: American College of Rheumatology; dcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography; IVC: inspiratory vital capacity; lcSSc: limited cutaneous systemic sclerosis; PFT: pulmonary function test; SSS: scleroderma sine scleroderma.

Table 1. Baseline characteristics of full study cohort and patients with baseline radiographic SSc-associated ILD.

	Total Cohort, n = 138	Patients With Radiographic SSc-ILD, n = 100
Age at time of HRCT, yrs	50.0 (± 11.1)	49.5 (± 11.6)
Sex, women	116 (84.1)	82 (82.0)
Race, White	104 (75.4)	70 (70.0)
Smoker, current or former	52 (37.7)	37 (37.0)
GI symptoms[a], present	102 (73.9)	74 (74.0)
Pulmonary symptoms[a], present	83 (60.1)	66 (66.0)
PPI use, current	81 (58.7)	60 (60.0)
dcSSc subtype	64 (46.4)	54 (54.0)
SSc disease duration[b], yrs	5.7 (± 7.7)	4.7 (± 5.9)
SSc-specific autoantibodies, positive (n = 136)	107 (78.7)	77 (77.8)
Scl-70	50 (36.2)	48 (48.0)
Anticentromere	24 (17.4)	6 (6.0)
Anti-RNAP3 (n = 135)	34 (25.2)	24 (24.2)
ESR, mm/h	24 (± 22.7)	22 (± 18.6)
mRSS	11 (± 9.0)	13 (± 9.4)
Medications, any use	64 (46.4)	52 (52.0)
Cyclophosphamide	6 (4.3)	6 (6.0)
Mycophenolate mofetil	31 (22.5)	27 (27.0)
Prednisone	35 (25.4)	27 (27.0)
PAH present among those with RHC (n = 56)	19 (33.9)	17 (38.6)
Radiographic ILD, present	100 (72.5)	100 (100.0)
FVC% predicted, baseline	78 (± 16.7)	75 (± 17.3)
DLCO% predicted, baseline	60 (± 20.4)	57 (± 19.9)
Digital ulcers, present	52 (37.7)	40 (40.0)
WED, mm	17.6 (± 8.2)	18.6 (± 7.8)

Values are expressed as mean (± SD) or n (%). [a] Pulmonary and GI symptoms defined as positive pulmonary and/or GI review of systems in an outpatient rheumatology clinic note within 1 year of HRCT date. [b] SSc disease duration defined as the interval between first non-Raynaud SSc symptom and baseline HRCT date. dcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing capacity for carbon monoxide (adjusted for hemoglobin); ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; GI: gastrointestinal; HRCT: high-resolution computed tomography of the chest; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; PAH: pulmonary arterial hypertension; PPI: proton pump inhibitor; RHC: right heart catheterization; RNAP3: RNA polymerase III; Scl-70: antitopoisomerase I; SSc: systemic sclerosis; WED: widest esophageal diameter.

function change. We compared baseline characteristics between patients with and without meaningful change in FVC (≥ 5-point change) and DLCO (≥ 15-point change; Table 2 and Table 3). In both the full study cohort and among patients with baseline radiographic SSc-ILD, positive Scl-70 status was more common in patients with vs without FVC worsening (full cohort: 51% vs 28%, $P = 0.01$; radiographic ILD only: 62% vs 39%, $P = 0.05$). Among patients with baseline radiographic ILD, those with meaningful FVC change less commonly had DUs present (26% vs 49%, $P = 0.03$). Baseline FVC% predicted was lower in those who demonstrated significant DLCO decline (full cohort: 67 vs 78, $P = 0.03$; radiographic ILD only: 64 vs 76, $P = 0.04$). There was no difference in the presence of PAH in those with vs without longitudinal DLCO decline.

Longitudinal pulmonary function change by Scl-70 status. In the full cohort, baseline FVC% predicted was lower in those with positive vs negative Scl-70 status (72, 95% CI 68–77 vs 82, 95% CI 79–86, respectively; $P < 0.01$). There was a statistically significant decline in FVC% predicted at 1, 2, 3, and 5 years in patients with positive Scl-70 status (5-yr change: –6.33, 95% CI –9.87 to –2.79, $P < 0.01$), adjusted for sex, PPI use, prednisone use, SSc disease subtype, SSc disease duration, smoking history (current or former), and WED (Table 4, Figure 2). In those lacking Scl-70, there was no significant change in FVC% predicted in the adjusted model (1.78, 95% CI –0.59 to 4.15, $P = 0.14$). The reverse was observed for DLCO% predicted change where patients lacking Scl-70 demonstrated a statistically significant modeled change in DLCO% predicted from baseline to 1, 2, 3, and 5 years (5-yr change: –3.31, 95% CI –6.57 to –0.05) that did not meet the prespecified clinical threshold for significance. Patients with positive Scl-70 lacked significant change in DLCO% predicted over time (5-yr change: –4.65, 95% CI –10.96 to 1.65; Table 4, Figure 2). Similar findings were observed when restricting the analysis to only those with radiographic ILD at baseline (Figure 2B; Supplementary Table 1, available with the online version of this article).

Longitudinal pulmonary function change by WED. Baseline characteristics for patients with a WED ≥ 19 vs < 19 mm are shown in Supplementary Table 2 (available with the online version of this article). At baseline, radiographic ILD was more common

Table 2. Baseline characteristics of patients with systemic sclerosis with vs. without clinically meaningful %-predicted FVC worsening.

	Full Analytic Cohort, n = 138			Radiographic ILD Present, n = 100		
	No FVC Decline, n = 89	FVC Decline ≥ 5, n = 49	*P*	No FVC Decline, n = 61	FVC Decline ≥ 5, n = 39	*P*
Age at time of HRCT, yrs	49.2 (± 11.9)	51.7 (± 9.4)	0.18	48.6 (± 12.4)	51.0 (± 10.1)	0.28
Sex, women	78 (87.6)	38 (77.6)	0.19	52 (85.2)	30 (76.9)	0.43
Race, White	67 (75.3)	37 (75.5)	> 0.99	42 (68.9)	28 (71.8)	0.93
Smoker, current or former	32 (36.0)	20 (40.8)	0.70	20 (32.8)	17 (43.6)	0.38
GI symptoms[a], present	66 (74.2)	36 (73.5)	> 0.99	44 (72.1)	30 (76.9)	0.77
Pulmonary symptoms[a], present	53 (59.6)	30 (61.2)	0.99	38 (62.3)	28 (71.8)	0.45
PPI use, current	53 (59.6)	28 (57.1)	0.93	36 (59.0)	24 (61.5)	0.97
dcSSc subtype	42 (47.2)	22 (44.9)	0.94	36 (59.0)	18 (46.2)	0.29
SSc disease duration[b], yrs	5.6 (± 7.5)	5.8 (± 8.1)	0.89	4.1 (± 5.1)	5.5 (± 6.9)	0.27
Scl-70, positive	25 (28.1)	25 (51.0)	0.01	24 (39.3)	24 (61.5)	0.05
Anticentromere, positive	17 (19.1)	7 (14.3)	0.63	4 (6.6)	2 (5.1)	> 0.99
Anti-RNAP3, positive	26 (29.9)	8 (16.7)	0.14	19 (31.7)	5 (12.8)	0.06
ESR	24 (± 25.1)	23 (± 17.8)	0.82	20 (± 18.1)	25 (± 19.2)	0.24
mRSS	11.9 (± 9.7)	10.5 (± 7.5)	0.34	13.8 (± 10.1)	10.9 (± 7.8)	0.12
Medications, any use	41 (46.1)	23 (46.9)	> 0.99	32 (52.5)	20 (51.3)	> 0.99
Cyclophosphamide	4 (4.5)	2 (4.1)	> 0.99	4 (6.6)	2 (5.1)	> 0.99
Mycophenolate mofetil	18 (20.2)	13 (26.5)	0.53	15 (24.6)	12 (30.8)	0.65
Prednisone	24 (27.0)	11 (22.4)	0.71	18 (29.5)	9 (23.1)	0.63
PAH present among those with RHC (N = 56)	8 (26.7)	11 (42.3)	0.34	6 (28.6)	11 (47.8)	0.32
Radiographic ILD, present	61 (68.5)	39 (79.6)	0.23	61 (100.0)	39 (100.0)	NA
FVC% predicted, baseline	77 (± 16.8)	79 (± 16.8)	0.71	74 (± 17.9)	75 (± 16.6)	0.79
DLCO% predicted, baseline	60 (± 19.6)	59 (± 21.8)	0.74	59 (± 20.2)	54 (± 19.3)	0.20
Digital ulcers, present	38 (42.7)	14 (28.6)	0.15	30 (49.2)	10 (25.6)	0.03
WED, mm	17.2 (± 7.9)	18.3 (± 8.6)	0.43	18.6 (± 7.6)	18.6 (± 8.3)	0.99

Values are expressed as mean (SD) or n (%). [a] Pulmonary and GI symptoms defined as positive pulmonary and/or GI review of systems in an outpatient rheumatology clinic note within 1 year of HRCT date. [b] SSc disease duration defined as the interval between first non-Raynaud SSc symptom and baseline HRCT date. dcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing capacity for carbon monoxide (adjusted for hemoglobin); ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; GI: gastrointestinal; HRCT: high-resolution computed tomography of the chest; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; NA: not applicable; PAH: pulmonary arterial hypertension; PPI: proton pump inhibitor; RHC: right heart catheterization; RNAP3: RNA polymerase III; Scl-70: antitopoisomerase I; SSc: systemic sclerosis; WED: widest esophageal diameter.

in patients with WED ≥ 19 vs < 19 mm (52 of 64 [81%] vs 48 of 74 [65%], $P = 0.03$). The baseline mean FVC% predicted was lower in WED ≥ 19 compared to those with WED < 19 mm (73 vs 82, $P < 0.01$). Similarly, the baseline mean DLCO% predicted was lower in the wider (vs narrower) WED group (57 vs 64, $P = 0.05$). The mean follow-up time was similar for individuals with WED ≥ 19 vs < 19 (3.1 and 3.0 yrs, respectively).

Longitudinally, patients with WED ≥ 19 mm demonstrated a small, statistically significant DLCO% predicted change from baseline to 5 years (−5.58, 95% CI −10.00 to −1.15; Table 4, Figure 2), adjusted for sex, PPI use, prednisone use, SSc disease subtype, SSc disease duration, smoking history (current or former), and Scl-70 status. There was no statistically significant difference in FVC% predicted change in patients dichotomized by esophageal diameter (Table 4, Figure 2). Similar findings were observed when restricting the analysis to only patients with baseline radiographic ILD (Figure 2; Supplementary Table 3, available with the online version of this article). Testing the 3-way interaction of Scl-70 status, WED, and time showed there was no significant difference in FVC decline among patients with positive Scl-70 status comparing WED ≥ 19 vs < 19 mm (difference in change from baseline to 5 yrs = −3.17, 95% CI −11.14 to 4.79).

DISCUSSION

To determine the effect of esophageal dilation on SSc-ILD progression, we examined a large cohort of 138 well-characterized patients with SSc who had undergone HRCT and serial PFT. We showed that esophageal dilation on axial chest HRCT images was associated with a minimal, nonclinically significant decline in DLCO and no change in FVC during the 5-year follow-up, and Scl-70 is associated with SSc-ILD worsening as assessed by FVC and/or DLCO decline. In patients with SSc, Savarino, *et al* reported an association between greater number of proximal reflux episodes on pH impedance testing and pulmonary fibrosis on HRCT, supporting the hypothesis that esophageal dysfunction is related to SSc-ILD.[27] Similarly, in a previous study, we showed that a larger WED was associated with prevalent radiographic SSc-ILD and lower FVC% and DLCO% predicted.[9,10] However, in the present study, a dilated esophagus on HRCT did not predict longitudinal FVC worsening. Winstone, *et al*,[28] who studied 145 patients with SSc (median follow-up 4 yrs),

Table 3. Baseline characteristics of patients with systemic sclerosis with vs without clinically meaningful DLCO% predicted worsening.

	Full Analytic Cohort, n = 99			Radiographic ILD present, n = 73		
	No Significant Decline in DLCO, n = 88	Decline in DLCO% Predicted ≥ 15 (n = 11)	*P*	No Significant Decline in DLCO, n = 64	Decline in DLCO% Predicted ≥ 15, n = 9	*P*
Age at time of HRCT, yrs	49.9 (± 10.6)	47.3 (± 12.6)	0.53	49.0 (± 10.5)	46.1 (± 13.7)	0.56
Sex, women	72 (81.8)	9 (81.8)	> 0.99	52 (81.2)	7 (77.8)	> 0.99
Race, White	66 (75.0)	9 (81.8)	0.90	45 (70.3)	7 (77.8)	0.94
Smoker, current or former	30 (34.1)	4 (36.4)	> 0.99	22 (34.4)	3 (33.3)	> 0.99
GI symptoms[a], present	65 (73.9)	8 (72.7)	> 0.99	47 (73.4)	7 (77.8)	> 0.99
Pulmonary symptoms[a], present	56 (63.6)	8 (72.7)	0.80	44 (68.8)	8 (88.9)	0.39
PPI use, current	49 (55.7)	6 (54.5)	> 0.99	38 (59.4)	5 (55.6)	> 0.99
dcSSc subtype	38 (43.2)	8 (72.7)	0.13	31 (48.4)	7 (77.8)	0.20
SSc disease duration, yrs*	5.9 (± 8.4)	3.4 (± 4.6)	0.14	4.6 (± 5.8)	3.9 (± 5.0)	0.71
Scl-70, positive	32 (36.4)	3 (27.3)	0.80	30 (46.9)	3 (33.3)	0.68
Anticentromere, positive	16 (18.2)	0 (0.0)	0.27	3 (4.7)	0 (0.0)	> 0.99
Anti-RNAP3, positive	24 (27.3)	4 (40.0)	0.64	17 (26.6)	3 (33.3)	0.98
ESR	24 (± 22.0)	23 (± 20.2)	0.91	23 (± 18.4)	26 (± 19.9)	0.72
mRSS	11.0 (± 9.4)	16.2 (± 8.6)	0.08	11.8 (± 10.1)	15.4 (± 9.2)	0.29
Medications, any use	42 (47.7)	7 (63.6)	0.50	33 (51.6)	6 (66.7)	0.62
Cyclophosphamide	5 (5.7)	0 (0.0)	0.94	5 (7.8)	0 (0.0)	0.87
Mycophenolate mofetil	21 (23.9)	2 (18.2)	0.97	19 (29.7)	2 (22.2)	0.94
Prednisone	24 (27.3)	3 (27.3)	> 0.99	18 (28.1)	2 (22.2)	> 0.99
PAH present among those with RHC (n = 56)	9 (25.0)	4 (44.4)	0.46	8 (30.8)	4 (50.0)	0.57
Radiographic ILD, present	64 (72.7)	9 (81.8)	0.78	64 (100.0)	9 (100.0)	NA
FVC% predicted, baseline	78 (± 16.6)	67 (± 14.1)	0.03	76 (± 17.5)	64 (± 13.6)	0.04
DLCO% predicted, baseline	58 (± 18.3)	69 (± 19.3)	0.10	56 (± 18.4)	62 (± 12.9)	0.18
Digital ulcers, present	33 (37.5)	6 (54.5)	0.45	26 (40.6)	4 (44.4)	> 0.99
WED, mm	17.2 (± 8.6)	19.5 (± 8.9)	0.44	18.1 (± 8.1)	20.0 (± 9.6)	0.58

Values are expressed as mean (SD) or n (%). [a] Pulmonary and GI symptoms defined as positive pulmonary and/or GI review of systems in an outpatient rheumatology clinic note within 1 year of HRCT date. [b] SSc disease duration defined as the interval between first non-Raynaud SSc symptom and baseline HRCT date. dcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing capacity for carbon monoxide (adjusted for hemoglobin); ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; GI: gastrointestinal; HRCT: high-resolution computed tomography of the chest; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; NA: not applicable; PAH: pulmonary arterial hypertension; PPI: proton pump inhibitor; RHC: right heart catheterization; RNAP3: RNA polymerase III; Scl-70: antitopoisomerase I; SSc: systemic sclerosis; WED: widest esophageal diameter.

Table 4. Model-based estimates for change over time in FVC% (n = 138) and DLCO% predicted (n = 99) in patients with SSc by Scl-70 and WED (95% CI)[a].

Change From Baseline, yrs	FVC% Predicted				DLCO% Predicted			
	Negative Scl-70		Positive Scl-70		Negative Scl-70		Positive Scl-70	
1	0.36	(−0.12, 0.83)	−1.27	(−1.97, −0.56)	−0.66	(−1.31, −0.01)	−0.93	(−2.19, 0.33)
2	0.71	(−0.24, 1.66)	−2.53	(−3.95, −1.12)	−1.32	(−2.63, −0.02)	−1.86	(−4.38, 0.66)
3	1.07	(−0.36, 2.49)	−3.80	(−5.92, −1.67)	−1.99	(−3.94, −0.03)	−2.79	(−6.57, 0.99)
5	1.78	(−0.59, 4.15)	−6.33	(−9.87, −2.79)	−3.31	(−6.57, −0.05)	−4.65	(−10.96, 1.65)
	WED < 19 mm		WED ≥ 19 mm		WED < 19 mm		WED ≥ 19 mm	
1	0.14	(−0.41, 0.68)	−0.49	(−1.08, 0.11)	−0.43	(−1.19, 0.34)	−1.12	(−2.00, −0.23)
2	0.27	(−0.81, 1.35)	−0.97	(−2.16, 0.22)	−0.85	(−2.37, 0.67)	−2.23	(−4.00, −0.46)
3	0.41	(−1.22, 2.03)	−1.46	(−3.24, 0.33)	−1.28	(−3.56, 1.01)	−3.35	(−6.00, −0.69)
5	0.68	(−2.03, 3.38)	−2.43	(−5.40, 0.55)	−2.13	(−5.93, 1.68)	−5.58	(−10.00, −1.15)

PFT results shown as % predicted. [a] PFT means for Scl-70 analysis adjusted for sex, PPI use, prednisone use, SSc disease subtype, duration since first non-Raynaud (yrs), smoking history (current or former), and WED. PFT means for WED analysis adjusted for sex, PPI use, prednisone use, SSc disease subtype, duration since first non-Raynaud (yrs), smoking history (current or former), and Scl-70 autoantibody status. DLCO: diffusing capacity for carbon monoxide (adjusted for hemoglobin); ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; PFT: pulmonary function test; PPI: proton pump inhibitor; RHC: right heart catheterization; Scl-70: antitopoisomerase I; SSc: systemic sclerosis; WED: widest esophageal diameter.

reported that for every 1-cm increase in esophageal diameter on chest HRCT at baseline, there was a 1.8% higher lung fibrosis score and 5.5% lower FVC% predicted ($P < 0.001$) after adjustment for age, sex, weight, and BMI. However, there was no association between esophageal diameter and change in FVC% predicted at 1-year follow-up when adjusting for baseline fibrosis

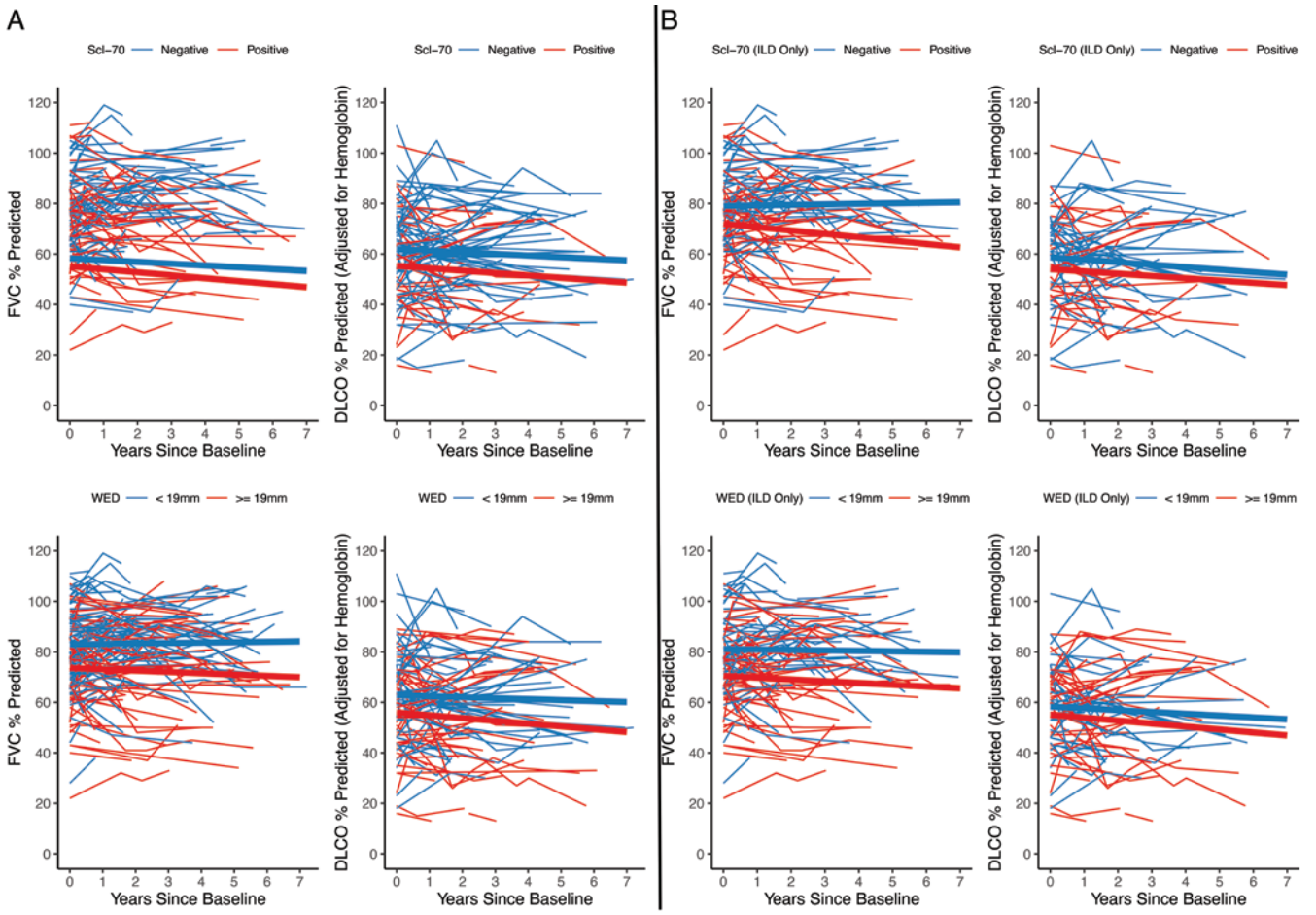

Figure 2. Change in pulmonary function by Scl-70 autoantibody status and WED. (A) Analysis of the full cohort (n = 138). (B) Analysis of the subset of patients with interstitial lung disease on baseline high-resolution computed tomography scan (n = 100). Spaghetti plot depicting change in FVC% (n = 138) and DLCO% predicted (n = 99) over time in patients with SSc. Thick lines represent estimated FVC% and DLCO% predicted from statistical model using data from all patients. DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; Scl-70: antitopoisomerase I; SSc: systemic sclerosis; WED: widest esophageal diameter.

score.[28] Our study included DLCO% predicted, which some consider to better estimate ILD extent, as discussed below, and we tested a proposed WED threshold of 19 mm as an esophageal dilation cutpoint that could be important to include in chest HRCT reports in patients with SSc.

We demonstrate that the presence of Scl-70 autoantibodies was associated with FVC but not DLCO worsening over a 2.9-year median follow-up period. Assassi, *et al* reported that positive Scl-70 status was associated with short-term (3-yr) decline in FVC% predicted in 244 patients with SSc.[5] We found a statistically significant (though not likely clinically meaningful) decline in DLCO% predicted in patients without Scl-70. This finding may be because DLCO decline is less specific for ILD and can be observed in SSc-associated PAH.[29]

We report a 73% ILD prevalence in our cohort that is similar to other tertiary care center rates (36–84%).[30,31,32] Our prevalence on the upper end of this reported range is likely a result of selection bias due to inclusion criteria requiring patients to have an available chest HRCT. Although many patients undergo HRCT at the baseline visit, it is not standard of care for all patients at our center. Thus, HRCT may be obtained more frequently in patients with pulmonary symptoms or abnormal physical exam findings in whom ILD is present. Further, only 51 of 138 (37%) patients we studied demonstrated clinically meaningful FVC worsening. Reasons for FVC stability may be related to high baseline FVC% predicted, reflecting more mild disease or the use of medications including mycophenolate mofetil and cyclophosphamide for ILD in approximately 30% of patients at the time of baseline HRCT scan.[20,33] In this retrospective study, we were unable to assess the longitudinal use of ILD medications that may have stabilized pulmonary function and confounded the relationship with esophageal diameter and ILD. Thus, patients may have received ILD therapies after the baseline HRCT exam. Another possible reason for stability is the interdisciplinary care provided at our SSc program that includes aggressive use of PPIs, lifestyle management counseling including head-of-bed elevation, avoidance of meals before recumbency, and importance of attaining/maintaining ideal body weight (the mean BMI of our group was 26 [SD 5.73]). The control of GI reflux with acid suppressive therapy and counseling may be associated with a slower rate of FVC decline.[34,35] We also did not classify patients by ILD pattern (usual interstitial pneumonia vs

fibrotic nonspecific interstitial pneumonia), which could have affected PFT trajectory.

In this study, we defined clinically meaningful PFT worsening a priori as ≥ 5-point decrease in FVC% predicted or 15-point decrease in DLCO% predicted.[8,21–26] We chose FVC% predicted change ≥ 5 as an intermediate threshold based upon studies using a range of FVC change between 2 and 10 to define meaningful change. Specifically, in idiopathic pulmonary fibrosis, a 2- to 6-point decline in FVC% predicted is defined as clinically meaningful.[24] Based on the Scleroderma Lung Study (SLS)-I and SLS-II, clinically meaningful change in FVC% predicted at 12 months could be considered as low as an FVC decline of 3–3.3%,[25] whereas the Outcomes in Rheumatology (OMERACT) Connective Tissue Disease-ILD Working Group suggest FVC decline ≥ 10% to define progression.[26] Compared to SLS-I and SLS-II and the nintedanib trial[36] that each followed patients for only 1 year, our median follow-up was 2.9 years. Regarding DLCO, some studies suggest that DLCO best estimates SSc-ILD extent, although the potential lack of specificity and reproducibility limits its use as an outcome.[37,38] Future studies may help determine the minimal clinically important differences in FVC and DLCO, specifically in patients with SSc.

Our study has limitations. As an observational study, no conclusions regarding the causality of esophageal dilation and ILD progression can be inferred, and patient follow-up and PFT timing is not uniform. Also, mean SSc disease duration at the time of HRCT is 5.7 years in the full cohort (4.7 yrs among those with baseline radiographic ILD), which limits assessment of early pulmonary function decline and may enrich our cohort for patients with more stable disease. The relatively high mean baseline FVC% predicted of 75 for patients in our cohort limits our ability to identify patient factors that are associated with longitudinal FVC decline in patients with more severe pulmonary disease at baseline. Also, patients did not routinely undergo esophageal manometry, so we are unable to comment on the relationship between esophageal diameter and dysfunction. Additionally, we defined esophageal dilation as ≥ 19 mm, because we previously found that this cutpoint has the best combined sensitivity and specificity for SSc-ILD. Previous studies investigating esophageal dilation effect on pulmonary function defined esophageal dilation as ≥ 10 mm, based on radiographic definitions of "normal," and found no association with esophageal dilation and ILD.[7] Our definition, while more precisely related to SSc-ILD, may misclassify some patients with a more mildly dilated esophagus (10–18 mm) and bias our results toward the null hypothesis (no difference in FVC decline between groups). Only 1 expert radiologist determined if radiographic ILD was present vs absent, which is the standard for clinical care.

Study strengths include examination of FVC% and DLCO% predicted as surrogates for worsening pulmonary disease in a sample of well-characterized patients with SSc. Study coordinators routinely contact outside hospitals to obtain serum autoantibody serologies and PFT records to reduce ascertainment bias. The DLCO measurement accuracy was assured by adjusting for hemoglobin, and by excluding patients for whom a complete blood count was not available in the preceding 6 months and for whom the IVC:FVC ratio was < 0.85, because these features improve DLCO accuracy. Excluding patients with poor-quality DLCO data or lacking hemoglobin values within 6 months may have introduced selection bias; however, inclusion of these patients would introduce error into the DLCO measurement. Other strengths include the large study size and the evaluation of esophageal diameter as a potential novel predictor for SSc-ILD progression. Also, an expert thoracic radiologist performed all esophageal diameter measurements on axial images and identified the largest diameter among 3 locations: mid-arch of the aorta, the carina, and the diaphragmatic hiatus. This allowed us to more accurately classify patients by esophageal diameter.

Scl-70 autoantibody positivity is a risk factor for FVC% predicted decline in patients with SSc. Esophageal dilation on HRCT was associated with a minimal, nonclinically significant 5-year decline in DLCO% predicted and no change in FVC% predicted during follow-up. These results have prognostic implications for SSc-ILD patients with esophageal dilation. Prospective studies that enroll patients with early SSc disease such as the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) and Prospective Registry of Early Systemic Sclerosis (PRESS) registries will enable identification of the relationship between esophageal diameter and early PFT decline and may identify other patient factors and/or biomarkers associated with ILD progression.[39,40]

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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