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ORIGINAL ARTICLE

Baseline characteristics of systemic sclerosis patients with restrictive lung disease in a multi-center US-based longitudinal registry

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Abstract

Aim: Interstitial lung disease (ILD) is the leading cause of disease-related death in systemic sclerosis (SSc). Here, we assess baseline characteristics of SSc subjects with and without restrictive lung disease (RLD) in a multi-center, US-based registry.

Methods: SSc patients within 5 years of disease onset were enrolled in the Collaborative National Quality and Efficacy Registry (CONQUER), a multi-center US-based registry of SSc study participants (age ≥ 18 years) enrolled at 13 expert centers. All subjects met 2013 American College of Rheumatology / European League Against Rheumatism criteria. Subjects with a pulmonary function test (PFT) at baseline before April 1, 2020 were included. High-resolution computed tomography scan of the chest was not available to characterize ILD for all subjects. RLD was defined as forced vital capacity (FVC) <80% or total lung capacity (TLC) <80% predicted.

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Results: There were 160 (45%) SSc subjects characterized as having RLD. There was no significant difference in age, gender or disease duration. RLD subjects had a mean disease duration from date of first non-Raynaud's symptom of 2.6 years and a mean FVC% predicted of 67% at baseline. In multivariable analysis, non-White race, higher physician global health assessment and modified Medical Research Council (mMRC) dyspnea scores, were independently associated with RLD. In the subgroup of RLD subjects with ILD, ILD had a negative correlation with RNA polymerase III antibody.
Conclusion: CONQUER is the largest, multi-center, prospective cohort of early SSc patients in the US. Non-White race was independently associated with RLD. In addition, 45% of CONQUER subjects already had RLD, highlighting the importance of screening for SSc-ILD at initial diagnosis.

KEYWORDS
interstitial lung disease, registry, restrictive lung disease, scleroderma, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease affecting multiple organ systems and is characterized by autoimmunity, vasculopathy and fibrosis. Interstitial lung disease (ILD) is the leading cause of death in SSc.[1] Due to disease heterogeneity, evaluation and treatment of SSc is a major clinical challenge. ILD occurs in 40%-60% of patients with SSc and accounts for 35%-60% of mortality.[2,3] The risk of developing ILD is greatest early in the course of SSc and identifying factors associated with restrictive lung disease (RLD) or ILD are important in the care and evaluation of SSc patients.[4]

Several international studies have evaluated SSc-ILD in their SSc patient populations; however, these studies may not reflect the US SSc population.[2,5-7] The purpose of this study was to assess baseline characteristics of SSc patients with and without RLD in a US-based multi-center registry. As high-resolution computed tomography (HRCT) scan of the chest was not available for all subjects; we first evaluated RLD in our cohort using pulmonary function testing (PFT) and then evaluated the subgroup of subjects with RLD who also had evidence of ILD by HRCT scan.

2 | PATIENTS AND METHODS

The Collaborative National Quality and Efficacy Registry (CONQUER) for SSc is a multi-center US-based registry of adult SSc patients (age ≥ 18 years) who enrolled within 5 years of their first non-Raynaud's symptom.[8] Participants were recruited from 13 academic medical centers in the US: Columbia University, George Washington University, Georgetown University, Hospital for Special Surgery, Johns Hopkins University, Massachusetts General Hospital, Medical University of South Carolina, Northwestern University, Stanford University, University of Michigan, University of Pennsylvania, University of Texas Health Science Center at Houston, and University of Utah. All subjects met 2013 American College of Rheumatology / European League Against Rheumatism classification criteria for SSc. The institutional review boards at each of the 13 participating centers approved the study. All participants in CONQUER provided written informed consent, data were collected at the time of a routine clinic appointment and patients completed study questionnaires and clinical measurements at enrollment.

CONQUER subjects with baseline visits between June 6, 2018 and April 1, 2020 were included in this analysis. Data were locked for analyses on February 26, 2021. Subjects were classified as having RLD based on PFT, defined as forced vital capacity (FVC) <80% predicted or total lung capacity (TLC) <80% predicted. Subjects were classified as having ILD if they had one of the following diagnosed on a HRCT scan of the chest: ground glass opacities (GGOs), reticular changes, traction bronchiectasis or honeycombing. Three population definitions were examined in this analysis: subjects with known RLD, subjects with RLD plus confirmed ILD (based on HRCT), and subjects with ILD regardless of RLD status.

2.1 | Statistical analysis

Subject baseline characteristics were summarized using frequencies and percentages for categorical variables and mean and SD for continuous variables. Summaries are presented overall as well as by diagnosis. Variables were compared between disease diagnoses using a Chi-squared test for categorical variables and *t* tests with unpooled variance estimates for continuous variables. In cases of small cell counts, Fisher's exact tests were used. Medication use was recorded for each subject at baseline.

Stepwise selection was performed to predict RLD and RLD with ILD. Variables with more than 20% missing in univariable analyses and variables with few occurrences were not considered for multivariable modeling. The associations of subject characteristics to RLD

or RLD with ILD at baseline were assessed using stepwise logistic regression with the probability of entry of 0.15 and the probability of removal of 0.20. Multicollinearity of the final model was assessed using variance inflation factors. For all analyses, likelihood ratio tests were used for *P* value calculations. Statistical significance in the models was predefined as a 2-sided *P* value <.05. All analyses were performed using SAS software v9.4.

3 | RESULTS

Three hundred and fifty-seven adult subjects with SSc were enrolled in the CONQUER registry from June 2018 and April 2020. The characteristics of subjects are summarized in Table 1. There were 160 (45%) SSc subjects defined as having RLD at baseline and 122 (76.3%) had baseline HRCT imaging available. More subjects with RLD were Black or African American (35 subjects [21.9%]) and had diffuse cutaneous disease (112 subjects [70%]) with a mean modified Rodnan skin score (mRSS) of 15. There were no significant differences in disease duration between groups. Although there were more subjects in CONQUER with a positive Scl-70 antibody compared to centromere antibody, the frequency of Scl-70 antibodies was not different in subjects with and without RLD. Subjects with RLD were less likely to have a positive centromere antibody (7.5% vs 15.2%, $P = .016$), and more likely to have digital pitting scars (28.8% vs 18.3%, $P = .018$) compared to subjects without RLD.

Mean % predicted FVC was 67% in the RLD group compared to 97% in the non-RLD group. Subjects with RLD had worse New York Heart Association (NYHA) functional class (II or higher) compared to those without RLD. There were 122/160 (76.3%) subjects with RLD and 117/197 (59.4%) subjects without RLD who had a HRCT scan. Of those subjects with RLD who underwent HRCT, 43 (35.2%) subjects had a patulous esophagus (increased esophageal diameter as defined by the radiologist) on HRCT scan compared to 12 (10.3%) subjects without RLD. Importantly, 45 (38.5%) subjects without RLD had evidence of GGOs on HRCT scan and 28 (23.9%) subjects had reticular changes, suggesting the importance of the HRCT in defining ILD. However, these subjects may have had additional risk factors for ILD prompting further evaluation by HRCT.

With regard to physician and patient assessments, the physician global assessment was worse in RLD subjects, with a mean score of 4.1 vs 2.9 in subjects without RLD. Dyspnea measures, including the scleroderma health assessment questionnaire (SHAQ) breathlessness scores, modified Medical Research Council (mMRC) dyspnea scale and Functional Assessment of Chronic Illness Therapy (FACIT) dyspnea scores were significantly worse in subjects with RLD, as expected. In terms of medication usage, 101 (63.1%) subjects with RLD were treated with mycophenolate mofetil compared to 85 (43.1%) subjects without RLD. Six (3.8%) RLD subjects were treated with nintedanib and 1 (0.6%) RLD subject was treated with tocilizumab. There were 108 (67.5%) subjects with RLD who were treated with a proton pump inhibitor (PPI) compared to 106 (53.8%) without RLD.

Univariate analyses of characteristics associated with RLD are summarized in Table 2. After stepwise model selection, the final multivariable model (Table 3), contained the following 5 variables: race, gastrointestinal tract, crackles on exam, physician global health assessment and the mMRC dyspnea scale. Non-White race, higher physician global health assessment scores and mMRC dyspnea scale were associated with RLD at baseline. Gastrointestinal tract involvement was not significantly associated with RLD.

To better understand those subjects with RLD who had radiographic evidence of ILD, we evaluated RLD subjects who also had a HRCT scan performed at baseline. Table 4 summarizes the demographics and characteristics of this subgroup of RLD subjects with and without ILD. Overall, there were no significant differences in age, gender, disease duration, smoking history, physician and patient assessments between those with and without ILD. Medication usage was similar between the subject groups. There were 82 (67%) subjects who had evidence of ILD, defined as having one of the following features on HRCT scan, GGOs, honeycombing, reticular changes or traction bronchiectasis. There were 43 (52%) subjects who had traction bronchiectasis, suggesting more advanced ILD. Of these 43 subjects, 29 subjects had diffuse SSc, 19 subjects had a positive Scl-70 antibody and 1 had a positive centromere antibody. Mean disease duration from date of first non-Raynaud's symptom was 2.95 years and mean mRSS was 12. Additionally, 40 (33%) subjects did not have ILD, suggesting other potential etiologies for RLD including extrinsic causes such as limitations in chest wall movement, or neuromuscular involvement affecting the respiratory muscles. Further evaluation of all subjects with and without ILD (regardless of RLD status), did not reveal any statistically significant differences in body mass index (BMI), mRSS or creatine kinase (CK) (Table S1).

Univariate analyses of RLD subjects with and without ILD are summarized in Table 5. In multivariable modeling (Table 6), a positive RNA polymerase III antibody was negatively associated with ILD. Further evaluation of the skin score (mRSS) of subjects with a positive RNA polymerase III antibody and no evidence of ILD were not significantly different between subjects with and without RLD (RLD positive 20.6 vs RLD negative 21.3, $P = .89$, Wilcoxon rank-sum test).

4 | DISCUSSION

In this study, we describe the baseline characteristics of SSc subjects with RLD enrolled in the first 22 months of CONQUER, a multi-center prospective registry of US SSc subjects within 5 years of SSc onset. We found that 45% of subjects already had RLD with a mean FVC of 67% predicted at entry into the registry, highlighting the importance of screening for ILD at SSc diagnosis. RLD also independently correlated with non-White (African American, Asian or other) race, higher physician global health assessment

TABLE 1 Patient characteristics by restrictive lung disease (RLD)

		SSc RLD at baseline		
	Overall (N = 357)	Yes (n = 160)	No (n = 197)	*P* value
Age, y, at baseline visit: n, mean (SD)	357, 51.7 (13.75)	160, 50.5 (14.15)	197, 52.8 (13.37)	.128[a]
Gender: female	293 (82.1%)	126 (78.8%)	167 (84.8%)	.140[b]
Body mass index, kg/m^2: n, mean (SD)	323, 26.4 (5.54)	148, 26.7 (5.71)	175, 26.0 (5.39)	.273[a]
Race				
White	283 (79.3%)	106 (66.3%)	177 (89.8%)	<.001[c]
Black or African American	41 (11.5%)	35 (21.9%)	6 (3.0%)	
Other	29 (8.1%)	18 (11.3%)	11 (5.6%)	
Ethnicity: Hispanic or Latino	41 (11.5%)	19 (11.9%)	22 (11.2%)	.856[b]
Employment status[d]				
Full-time	166 (46.5%)	73 (45.6%)	93 (47.2%)	.014[b]
Retired	72 (20.2%)	30 (18.8%)	42 (21.3%)	
Disabled	46 (12.9%)	30 (18.8%)	16 (8.1%)	
Other	58 (16.2%)	20 (12.5%)	38 (19.3%)	
Smoking status				
Never	234 (65.5%)	111 (69.4%)	123 (62.4%)	.173[c]
Former	110 (30.8%)	46 (28.8%)	64 (32.5%)	
Current	13 (3.6%)	3 (1.9%)	10 (5.1%)	
Disease duration, y, from date of first non-Raynaud's symptom to baseline visit: n, mean (SD)	357, 2.6 (1.39)	160, 2.6 (1.33)	197, 2.6 (1.44)	.939[a]
Disease duration, y, from date of first Raynaud's symptom to baseline visit: n, mean (SD)	345, 4.7 (6.88)	155, 4.7 (6.94)	190, 4.7 (6.85)	.939[a]
Systemic Sclerosis (SSc) subtype at baseline				
Limited cutaneous	142 (39.8%)	48 (30.0%)	94 (47.7%)	<.001[b]
Diffuse cutaneous	215 (60.2%)	112 (70.0%)	103 (52.3%)	
ANA positive	319 (89.4%)	142 (88.8%)	177 (89.8%)	.384[c]
ANA pattern[e]				
Centromere	54 (15.1%)	14 (8.8%)	40 (20.3%)	.009[b]
Nucleolar	56 (15.7%)	30 (18.8%)	26 (13.2%)	
Other	184 (51.5%)	84 (52.5%)	100 (50.8%)	
Anti-centromere positive	42 (11.8%)	12 (7.5%)	30 (15.2%)	.016[b]
Anti-Scl-70 positive	104 (29.1%)	50 (31.3%)	54 (27.4%)	.728[b]
Anti-RNA polymerase III positive	90 (25.2%)	38 (23.8%)	52 (26.4%)	.133[b]
Anti-U1-ribonucleoprotein positive	27 (7.6%)	17 (10.6%)	10 (5.1%)	.032[c]
Creatine kinase: n, mean (SD)	242, 182.5 (510.94)	113, 190.9 (283.52)	129, 175.2 (648.91)	.804[a]
Modified Rodnan skin score at baseline: n, mean (SD)	357, 12.8 (10.82)	160, 15.0 (11.28)	197, 11.0 (10.11)	<.001[a]
Digital pitting scars	82 (23.0%)	46 (28.8%)	36 (18.3%)	.018[b]
Digital ulcers	18 (5.0%)	11 (6.9%)	7 (3.6%)	.223[c]
Gastric antral vascular ectasia[f]	33 (9.2%)	21 (13.1%)	12 (6.1%)	.023[b]
GI tract: not normal[g]	262 (73.4%)	127 (79.4%)	135 (68.5%)	.023[b]
Crackles on exam	76 (21.3%)	54 (33.8%)	22 (11.2%)	<.001[b]
New York Heart Association functional class at baseline				
Class I	208 (58.3%)	78 (48.8%)	130 (66.0%)	<.001[c]
Class II	116 (32.5%)	59 (36.9%)	57 (28.9%)	
Class III, IV	31 (8.7%)	23 (14.4%)	8 (4.1%)	
Pulmonary and cardiac testing				
FVC% predicted: n, mean (SD)	357, 83.6 (20.17)	160, 67.0 (15.26)	197, 97.0 (11.98)	
Forced expiratory volume in 1 s (EV_1)% predicted: n, mean (SD)	352, 84.3 (19.38)	156, 69.3 (15.47)	196, 96.1 (12.89)	<.001[a]
FEV_1/FVC, actual: n, mean (SD)	349, 82.3 (11.18)	154, 84.7 (9.40)	195, 80.4 (12.10)	<.001[a]
TLC% predicted: n, mean (SD)	244, 86.7 (21.80)	116, 72.1 (18.67)	128, 99.9 (14.93)	

TABLE 1 (Continued)

	Overall (N = 357)	SSc RLD at baseline		*P* value
		Yes (n = 160)	No (n = 197)	
Diffusion capacity of carbon monoxide % predicted: n, mean (SD)	323, 71.2 (23.87)	144, 57.8 (21.39)	179, 82.0 (20.05)	<.001[a]
Baseline supplemental oxygen use	15 (4.2%)	11 (6.9%)	4 (2.0%)	.031[c]
Six minute walk test distance, m[h]	423.5 (197.42)	373.6 (139.78)	497.3 (245.72)	.036[a]
High-resolution computed tomography performed at baseline	239 (66.9%)	122 (76.3%)	117 (59.4%)	<.001[b]
Ground glass opacity	107 (44.8%)	62 (50.8%)	45 (38.5%)	.116[b]
Reticular changes	69 (28.9%)	41 (33.6%)	28 (23.9%)	.127[b]
Honeycombing	17 (7.1%)	14 (11.5%)	3 (2.6%)	.010[c]
Traction bronchiectasis	62 (25.9%)	43 (35.2%)	19 (16.2%)	.001[b]
Patulous esophagus	55 (23.0%)	43 (35.2%)	12 (10.3%)	<.001[b]
Assessments[i]				
Participant global health at baseline	4.0 (2.58)	4.3 (2.47)	3.7 (2.63)	.026[a]
Physician global health at baseline	3.4 (2.03)	4.1 (2.09)	2.9 (1.80)	<.001[a]
Physician global damage at baseline	3.9 (6.96)	4.3 (2.18)	3.7 (9.16)	.389[a]
SHAQ breathlessness score at baseline	3.3 (11.37)	5.1 (15.01)	1.9 (7.03)	.017[a]
Modified Medical Research Council dyspnea scale at baseline				
0	126 (35.3%)	34 (21.3%)	92 (46.7%)	<.001[b]
1	122 (34.2%)	58 (36.3%)	64 (32.5%)	
2-4	66 (18.5%)	44 (27.5%)	22 (11.2%)	
FACIT dyspnea score at baseline	6.5 (6.81)	8.4 (7.52)	5.0 (5.79)	<.001[a]
Medications				
Azathioprine[j]	5 (1.4%)	2 (1.3%)	3 (1.5%)	1.000[c]
Cyclophosphamide	2 (0.6%)	2 (1.3%)	0 (0.0%)	.200[c]
Hydroxychloroquine	75 (21.0%)	33 (20.6%)	42 (21.3%)	.873[b]
Methotrexate	32 (9.0%)	13 (8.1%)	19 (9.6%)	.617[b]
Mycophenolate mofetil	186 (52.1%)	101 (63.1%)	85 (43.1%)	<.001[b]
Nintedanib	7 (2.0%)	6 (3.8%)	1 (0.5%)	.048[c]
Prednisone[j]	72 (20.2%)	40 (25.0%)	32 (16.2%)	.040[b]
Rituximab[k]	6 (1.7%)	4 (2.5%)	2 (1.0%)	.414[c]
Tocilizumab	3 (0.8%)	1 (0.6%)	2 (1.0%)	1.000[c]
PPI[l]	214 (59.9%)	108 (67.5%)	106 (53.8%)	.009[b]

Note: Restrictive lung disease (RLD) is defined by forced vital capacity (FVC) or total lung capacity (TLC) <80% predicted. Sample contains subjects with baseline pulmonary function test (PFT) before April 1, 2020 with non-missing FVC or TLC predicted values.

All *P* values for categorical variables exclude missings, except where the missingness is informative which is the case for the following variables: antinuclear antibodies (ANA), antibodies, and gastric antral vascular ectasia (GAVE).

[a]*t* test with unpooled variance estimates.

[b]Chi-squared test.

[c]Fisher's exact test.

[d]Employment status of 'Other' includes part-time, homemaker, student or unemployed.

[e]ANA pattern of 'Other' includes speckled, homogenous and mixed pattern.

[f]GAVE displays counts and percent of Yes out of No/Missing with missings assuming no GAVE.

[g]Gastrointestinal (GI) tract not normal: distal esophageal hypoperistalsis; small bowel abnormal (eg reflux, bloating, distension) or antibiotics required for bacterial overgrowth or malabsorption syndrome; episodes of pseudo-obstruction or hyperalimentation required.

[h]6 minute walk test n = 57 (16%); RLD 34 (21%); no RLD 23 (12%).

[i]Participant global assessment n = 323 (142 RLD, 181 no RLD). Physician global health n = 355 (159 RLD, 196 no RLD). Physician global damage n = 355 (159 RLD, 196 no RLD). Scleroderma health assessment questionnaire (SHAQ) breathlessness score n = 326 (144 RLD, 182 no RLD). Functional Assessment of Chronic Illness Therapy (FACIT) dyspnea score n = 318 (139 RLD, 179 no RLD).

[j]Indications for azathioprine, prednisone: skin, myositis, arthritis, ILD, other.

[k]Indications for rituximab: skin, arthritis, ILD, other.

[l]PPI (proton pump inhibitor) includes omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, dexlansoprazole.

TABLE 2 Univariable analyses for restrictive lung disease (RLD)

		SSc RLD at baseline	
	% Missing[a]	Odds ratio (95% CI)	*P* value
Age, y, at baseline visit	0%	0.99 (0.97, 1.00)	.125
Gender (female vs male)	0%	0.67 (0.39, 1.14)	.141
Race (non-White vs White)	1%	5.21 (2.92, 9.70)	<.001
Ethnicity (Hispanic or Latino vs not Hispanic or Latino)	2%	1.06 (0.55, 2.04)	.856
Employment status (not full-time vs full-time)	4%	1.06 (0.69, 1.63)	.783
Ever smoked (yes vs no)	0%	0.73 (0.47, 1.14)	.169
Disease duration, y, from date of first non-Raynaud's symptom to baseline visit	0%	1.01 (0.87, 1.17)	.939
Systemic sclerosis (SSc) subtype (diffuse cutaneous vs limited cutaneous)	0%	2.13 (1.38, 3.32)	<.001
Antinuclear antibodies			
Positive vs negative	0%	0.60 (0.24, 1.46)	.381
Not assessed vs negative		0.41 (0.10, 1.49)	
Centromere			
Positive vs negative	0%	0.38 (0.20, 0.70)	.006
Not assessed vs negative		0.70 (0.41, 1.20)	
Anti-Scl-70			
Positive vs negative	0%	1.21 (0.75, 1.94)	.729
Not assessed vs negative		1.02 (0.52, 2.00)	
Anti-RNA polymerase III			
Positive vs negative	0%	0.72 (0.43, 1.21)	.132
Not assessed vs negative		0.61 (0.37, 1.01)	
Modified Rodnan skin score (mRSS)	0%	1.04 (1.02, 1.06)	<.001
Digital pitting scars (yes vs no)	1%	1.81 (1.10, 3.00)	.019
Digital ulcers (yes vs. no)	0%	1.99 (0.77, 5.53)	.158
Gastric antral vascular ectasia (yes vs no/missing)	0%	2.33 (1.12, 5.03)	.023
Gastrointestinal tract (not normal vs normal)	1%	1.76 (1.08, 2.91)	.022
Crackles on exam (yes vs no)	0%	4.09 (2.39, 7.22)	<.001
New York Heart Association functional class	1%		<.001
Class II vs class I		1.73 (1.09, 2.74)	
Class III, IV vs class I		4.79 (2.12, 11.91)	
Baseline supplemental oxygen use (yes vs no)	1%	3.61 (1.21, 13.23)	.021
6 minute walk test distance (every 50 m)	84%	0.78 (0.60, 0.95)	.010
Participant global health	10%	1.10 (1.01, 1.20)	.027
Physician global health	1%	1.38 (1.23, 1.56)	<.001
Physician global damage	1%	1.01 (0.98, 1.06)	.428
Scleroderma health assessment questionnaire breathlessness score	9%	1.04 (1.01, 1.12)	.005
Modified Medical Research Council dyspnea scale			
1 vs 0	12%	2.45 (1.45, 4.20)	<.001
2-4 vs 0		5.41 (2.87, 10.48)	
Functional Assessment of Chronic Illness Therapy dyspnea score	11%	1.08 (1.04, 1.12)	<.001

Note: Results are based on univariable models.

[a]Rates of missingness are calculated out of the records with a non-missing value for the outcome (RLD). Note that ANA and antibody variables have 0% missing because this missing is informative and thus included in the model. All variables in this table are considered for multivariable modeling with stepwise regression except 6 min walk test due to missings.

TABLE 3 Multivariable model for restrictive lung disease (RLD)

	SSc RLD at baseline	
	Odds ratio (95% CI)	***P* value**
Race		
White	Reference	<.001
Non-White	4.29 (2.13, 9.07)	
Gastrointestinal tract		
Normal	Reference	.112
Not normal	1.65 (0.89, 3.12)	
Crackles on exam		
No	Reference	<.001
Yes	3.31 (1.76, 6.39)	
Physician global health	1.19 (1.04, 1.38)	.013
Modified Medical Research Council dyspnea scale		
0	Reference	.021
1	1.91 (1.05, 3.47)	
2-4	2.65 (1.26, 5.61)	

Note: N = 306.

Results are based on a multivariable model, adjusting for each of the predictors in this table.

and mMRC dyspnea scores. Not all subjects with RLD had a HRCT scan at baseline to evaluate ILD, which resulted in a smaller ILD subgroup for analysis. Here, ILD had a negative correlation with RNA polymerase III antibody, similar to other studies where a positive anti-RNA polymerase III is reported to be less likely associated with SSc ILD.[9]

Prior observational studies have demonstrated that race, particularly African American race in SSc is associated with more severe RLD.[10-12] While our study evaluated "non-White" race as a group, the majority were African American and the findings here are similar to those in other studies. As we continue to enroll subjects in CONQUER, further study into racial disparities and its impact on SSc-ILD are warranted.

In our cohort, a higher proportion of RLD subjects who underwent HRCT had a patulous esophagus (35.2% vs 10.3%, $P < .001$) compared to subjects without RLD. Prior studies have demonstrated that SSc subjects with more gastrointestinal symptoms had a lower FVC% predicted on PFTs; additionally, increased esophageal diameter on HRCT scan is associated with more severe radiographic ILD and lower lung volumes in SSc subjects.[13,14] There were 43 (52.4%) RLD subjects with ILD who had evidence of traction bronchiectasis, suggesting more advanced ILD. These patients were primarily of the diffuse SSc subtype (n = 29, 67%). The extent of traction bronchiectasis is a strong determinant of mortality in connective tissue disease-related ILD.[15]

In those subjects without RLD, a sizable percentage (23.9%-38.5%) of subjects had evidence of ILD on HRCT scan. Prior studies have shown considerable variability in ordering HRCTs in screening for SSc-ILD, and PFTs alone are inadequate for assessment of ILD in SSc.[16-18] Our findings do emphasize the need for careful review of HRCT scans and utilizing both HRCT and PFTs in the assessment of ILD in SSc subjects, consistent with prior consensus statements recommending all SSc subjects be screened with HRCT.[19] However, we should note that this subset of subjects without RLD who had evidence of ILD on HRCT scan may have had other risk factors for ILD (ie diffuse skin disease, African American race, positive Scl-70 antibodies) thereby impacting the decision to order a HRCT scan. Our study also found that 33% of RLD subjects did not have ILD on HRCT scan, suggesting other potential extrinsic etiologies for RLD that will need to be explored further. Prior studies have found that SSc subjects can exhibit respiratory muscle weakness, contributing to reductions in FVC and TLC; overlap conditions such as myositis can additionally contribute to RLD.[19-21] Evaluation of all subjects with and without ILD, regardless of RLD did not show any differences in CK (Table S1).

Of the patient reported outcomes collected, higher mMRC dyspnea scores were independently associated with RLD. The mMRC dyspnea scale queries dyspnea on 5 scaled statements of dyspnea in relation to life activities, similar to the NYHA classification.[22] The mMRC is validated in idiopathic pulmonary fibrosis but not in SSc ILD.[23] RLD subjects in our cohort demonstrated difficulty with breathlessness as expected compared to those without RLD.

Medication usage in CONQUER was generally similar between subjects with and without RLD, although mycophenolate mofetil and PPIs were used more frequently in RLD subjects. While 2 new drugs, nintedanib and tocilizumab, were recently Food and Drug Administration-approved for the treatment of SSc ILD, only a few subjects with RLD were treated with these medications at the time of our data collection.[24-26]

Our study has some limitations. First, due to available PFT data we were primarily able to assess RLD. Historically, FVC has been used to monitor SSc ILD progression; however, there is debate on its utility as a surrogate marker for ILD.[27,28] We defined RLD based on FVC or TLC <80% predicted, similar to many other studies in SSc ILD but different from American Thoracic Society guidelines which define RLD solely as TLC <80% predicted.[4,29,30] Second, CONQUER is a prospective multicenter registry of patients seen at specialized SSc centers and may be subject to referral bias with potentially sicker SSc patients being captured within 5 years of their disease onset and hence a significant proportion having RLD. All tests and clinical assessments were performed at the discretion of the individual clinician, and PFT or HRCT testing is not an absolute requirement for entry into the registry, nor is the cost of these studies covered by the study. Third, as HRCT results were not available for all participants in CONQUER, we were only able to evaluate ILD in a subgroup of RLD subjects. For subjects in the ILD subgroup, centralized reading of HRCT scans was not performed and ILD extent in subgroups could not be quantified.

There are notable strengths to our study. CONQUER is the largest, multi-center, prospective cohort of early-stage SSc patients in the US and allows for longitudinal collection of data in a multi-center group of SSc subjects seen by scleroderma specialists at expert centers. The criteria for early disease duration of less than 5 years will provide crucial information for the early, active time of the disease.

TABLE 4 Patient characteristics by interstitial lung disease (ILD) status among those with restrictive lung disease (RLD)

		SSc ILD at baseline		
	Overall (N = 122)	Yes (n = 82)	No (n = 40)	*P* value
Age, y, at baseline visit: n, mean (SD)	122, 50.1 (14.07)	82, 51.2 (14.13)	40, 48.0 (13.88)	.244[a]
Gender: female	95 (77.9%)	64 (78.0%)	31 (77.5%)	1.000[c]
Body mass index, kg/m^2: n, mean (SD)	114, 26.4 (5.28)	76, 26.4 (5.11)	38, 26.6 (5.67)	.845[a]
Race				
White	82 (67.2%)	55 (67.1%)	27 (67.5%)	.536[c]
Black or African American	23 (18.9%)	17 (20.7%)	6 (15.0%)	
Other	16 (13.1%)	9 (11.0%)	7 (17.5%)	
Ethnicity: Hispanic or Latino	15 (12.3%)	10 (12.2%)	5 (12.5%)	1.000[c]
Employment status				
Full-time	58 (47.5%)	40 (48.8%)	18 (45.0%)	.017[c]
Retired	21 (17.2%)	18 (22.0%)	3 (7.5%)	
Disabled	22 (18.0%)	9 (11.0%)	13 (32.5%)	
Other	15 (12.3%)	11 (13.4%)	4 (10.0%)	
Smoking status				
Never	86 (70.5%)	57 (69.5%)	29 (72.5%)	1.000[c]
Former	34 (27.9%)	23 (28.0%)	11 (27.5%)	
Current	2 (1.6%)	2 (2.4%)	0 (0.0%)	
Disease duration, y, from date of first non-Raynaud's symptom to baseline visit: n, mean (SD)	122, 2.7 (1.33)	82, 2.7 (1.32)	40, 2.6 (1.36)	.924[a]
Disease duration, y, from date of first Raynaud's symptom to baseline visit: n, mean (SD)	119, 5.3 (7.77)	81, 4.9 (7.09)	38, 6.1 (9.10)	.465[a]
Systemic sclerosis (SSc) subtype at baseline				
Limited cutaneous	36 (29.5%)	24 (29.3%)	12 (30.0%)	.934[b]
Diffuse cutaneous	86 (70.5%)	58 (70.7%)	28 (70.0%)	
ANA positive	108 (88.5%)	72 (87.8%)	36 (90.0%)	.568[c]
ANA pattern				
Centromere	9 (7.4%)	6 (7.3%)	3 (7.5%)	.176[c]
Nucleolar	21 (17.2%)	11 (13.4%)	10 (25.0%)	
Other	64 (52.5%)	47 (57.3%)	17 (42.5%)	
Anti-centromere positive	8 (6.6%)	5 (6.1%)	3 (7.5%)	.887[c]
Anti-Scl-70 positive	41 (33.6%)	33 (40.2%)	8 (20.0%)	.073[c]
Anti-RNA polymerase III positive	29 (23.8%)	14 (17.1%)	15 (37.5%)	.033[c]
Anti-U1-ribonuclear protein positive	14 (11.5%)	10 (12.2%)	4 (10.0%)	.178[c]
Creatine kinase: n, mean (SD)	86, 202.6 (312.03)	63, 213.2 (347.83)	23, 173.5 (184.36)	.498[a]
Modified Rodnan skin score (mRSS) at baseline: n, mean (SD)	122, 14.4 (10.68)	82, 13.7 (10.24)	40, 15.9 (11.52)	.321[a]
Digital pitting scars	37 (30.3%)	24 (29.3%)	13 (32.5%)	.747[b]
Digital ulcers	6 (4.9%)	6 (7.3%)	0 (0.0%)	.176[c]
GAVE	11 (9.0%)	7 (8.5%)	4 (10.0%)	.749[c]
GI tract: not normal	97 (79.5%)	64 (78.0%)	33 (82.5%)	.639[c]
Crackles on exam	47 (38.5%)	45 (54.9%)	2 (5.0%)	<.001[c]
New York Heart Association functional class at baseline				
Class I	59 (48.4%)	35 (42.7%)	24 (60.0%)	.191[c]
Class II	45 (36.9%)	33 (40.2%)	12 (30.0%)	
Class III, IV	18 (14.8%)	14 (17.1%)	4 (10.0%)	
Pulmonary and cardiac testing				
Forced vital capacity (FVC)% predicted: n, mean (SD)	122, 66.2 (15.43)	82, 64.5 (15.55)	40, 69.8 (14.72)	.070[a]
Forced expiratory volume in 1 s (FEV_1)% predicted: n, mean (SD)	119, 68.7 (15.28)	80, 68.2 (14.89)	39, 69.5 (16.22)	.681[a]

TABLE 4 (Continued)

	Overall (N = 122)	SSc ILD at baseline		*P* value
		Yes (n = 82)	No (n = 40)	
FEV_1/FVC (actual): n, mean (SD)	117, 85.0 (9.79)	79, 86.0 (9.68)	38, 82.9 (9.83)	.113[a]
Total lung capacity % predicted: n, mean (SD)	87, 71.0 (18.16)	57, 68.4 (18.80)	30, 76.0 (15.99)	.052[a]
Diffusion capacity of carbon monoxide % predicted: n, mean (SD)	110, 56.4 (21.35)	75, 53.1 (20.78)	35, 63.5 (21.09)	.018[a]
Baseline supplemental oxygen use	9 (7.4%)	7 (8.5%)	2 (5.0%)	.716[c]
6 minute walk test distance, m[d]	379.7 (139.29)	381.7 (144.32)	353.5 (40.31)	.523[a]
High-resolution computed tomography performed at baseline[e]	122 (100.0%)	82 (100.0%)	40 (100.0%)	
Ground glass opacity	62 (50.8%)	62 (75.6%)	0 (0.0%)	
Reticular changes	41 (33.6%)	41 (50.0%)	0 (0.0%)	
Honeycombing	14 (11.5%)	14 (17.1%)	0 (0.0%)	
Traction bronchiectasis[f]	43 (35.2%)	43 (52.4%)	0 (0.0%)	
Patulous esophagus	43 (35.2%)	33 (40.2%)	10 (25.0%)	.137[c]
Assessments[g]				
Participant global health at baseline	4.3 (2.49)	4.2 (2.61)	4.6 (2.24)	.444[a]
Physician global health at baseline	4.0 (2.09)	4.1 (2.08)	3.7 (2.11)	.308[a]
Physician global damage at baseline	4.1 (2.12)	4.3 (2.16)	3.7 (1.99)	.143[a]
SHAQ breathlessness score at baseline	5.1 (15.02)	5.3 (15.04)	4.8 (15.19)	.879[a]
Modified Medical Research Council dyspnea scale at baseline				
0	25 (20.5%)	15 (18.3%)	10 (25.0%)	.671[c]
1	45 (36.9%)	28 (34.1%)	17 (42.5%)	
2-4	31 (25.4%)	22 (26.8%)	9 (22.5%)	
FACIT dyspnea score at baseline	8.1 (7.19)	7.7 (6.95)	8.7 (7.70)	.517[a]
Medications				
Azathioprine	1 (0.8%)	1 (1.2%)	0 (0.0%)	1.000[c]
Cyclophosphamide	2 (1.6%)	2 (2.4%)	0 (0.0%)	1.000[c]
Hydroxychloroquine	25 (20.5%)	17 (20.7%)	8 (20.0%)	1.000[c]
Methotrexate	9 (7.4%)	3 (3.7%)	6 (15.0%)	.058[c]
Mycophenolate mofetil	80 (65.6%)	54 (65.9%)	26 (65.0%)	.926[b]
Nintedanib	5 (4.1%)	5 (6.1%)	0 (0.0%)	.171[c]
Prednisone	28 (23.0%)	17 (20.7%)	11 (27.5%)	.404[b]
Rituximab	4 (3.3%)	4 (4.9%)	0 (0.0%)	.302[c]
Tocilizumab	1 (0.8%)	1 (1.2%)	0 (0.0%)	1.000[c]
PPI[h]	87 (71.3%)	58 (70.7%)	29 (72.5%)	.839[b]

Note: ILD is defined by a subject having at least one of the following: ground glass opacity (GGO), honeycombing, reticular changes or traction bronchiectasis. Sample contains subjects with RLD and a baseline high-resolution computed tomography (HRCT) scan recorded.

All *P* values for categorical variables exclude missings, except where the missingness is informative which is the case for the following variables: antinuclear antibodies (ANA), antibodies, and gastric antral vascular ectasia (GAVE).

[a]*t* test with unpooled variance estimates.

[b]Chi-squared test.

[c]Fisher's exact test.

[d]6 minute walk test n = 28 (23%): ILD 26 (32%), no ILD 2 (5%).

[e]*P* values are not calculated for GGO, honeycombing, reticular changes, and traction bronchiectasis because those variables were used to derive ILD.

[f]Traction bronchiectasis: diffuse SSc 29 (67%), anti-Scl-70 positive 19 (44%), anti-centromere positive 1 (2%), anti-RNA polymerase III positive 11 (25%), mRSS, mean (SD) 12 (10.24), disease duration from first non-Raynaud's symptom, mean (SD) 2.95 (1.33).

[g]Participant global assessment n = 107 (71 ILD, 36 no ILD). Physician global health n = 121 (82 ILD, 39 no ILD). Physician global damage n = 121 (82 ILD, 39 no ILD). Scleroderma health assessment questionnaire (SHAQ) breathlessness score n = 108 (72 ILD, 36 no ILD). Functional Assessment of Chronic Illness Therapy (FACIT) dyspnea score n = 104 (68 ILD, 36 no ILD).

[h]PPI (proton pump inhibitor) includes omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, dexlansoprazole.

TABLE 5 Univariable analyses for interstitial lung disease (ILD) among patients with restrictive lung disease (RLD)

		SSc ILD at baseline	
	% Missing[a]	Odds ratio (95% CI)	*P* value
Age at baseline visit	0%	1.02 (0.99, 1.04)	.243
Gender (female vs male)	0%	1.03 (0.40, 2.51)	.945
Race (non-White vs White)	1%	0.98 (0.44, 2.25)	.965
Ethnicity (Hispanic or Latino vs not Hispanic or Latino)	1%	0.99 (0.32, 3.37)	.981
Employment status (not full-time vs full-time)	5%	0.86 (0.39, 1.86)	.692
Ever smoked (yes vs no)	0%	1.16 (0.51, 2.75)	.733
Disease duration, y, from date of first non-Raynaud's symptom to baseline visit	0%	1.01 (0.76, 1.35)	.922
SSc subtype (diffuse cutaneous vs limited cutaneous)	0%	1.04 (0.44, 2.34)	.934
Anti-Scl-70			
Positive vs negative	0%	2.65 (1.10, 6.94)	.073
Missing vs negative		0.90 (0.26, 3.31)	
Anti-RNA polymerase III			
Positive vs negative	0%	0.30 (0.12, 0.74)	.035
Missing vs negative		0.64 (0.24, 1.74)	
Modified Rodnan skin score	0%	0.98 (0.95, 1.02)	.299
Digital pitting scars (yes vs no)	1%	0.87 (0.39, 2.01)	.748
Gastrointestinal tract (not normal vs normal)	0%	0.75 (0.27, 1.92)	.563
6 minute walk test distance (every 50 m)	77%	1.08 (0.63, 1.85)	.779
Participant global health	12%	0.94 (0.80, 1.11)	.461
Physician global health	1%	1.10 (0.92, 1.34)	.297
Physician global damage	1%	1.15 (0.95, 1.39)	.147
Scleroderma health assessment questionnaire breathlessness score	11%	1.00 (0.98, 1.04)	.876
Modified Medical Research Council dyspnea scale	17%		.637
1 vs 0		1.10 (0.40, 2.99)	
2-4 vs 0		1.63 (0.53, 5.06)	
Functional Assessment of Chronic Illness Therapy dyspnea score	15%	0.98 (0.93, 1.04)	.500

Note: Results are based on univariable models.

[a]Rates of missingness are calculated out of the records with a non-missing value for the outcome (ILD). Note that antinuclear antibody and antibody variables have 0% missing because this missing is informative and thus included in the model. All variables in this table are considered for multivariable modeling with stepwise regression except 6 min walk test due to missing.

TABLE 6 Multivariable model for interstitial lung disease (ILD) among patients with restrictive lung disease (RLD)

	SSc ILD at baseline	
	Odds ratio (95% CI)	*P* value
Anti-RNA polymerase III		
Negative	Reference	.035
Positive	0.30 (0.12, 0.74)	
Missing	0.64 (0.24, 1.74)	

Note: N = 122.

Results are based on a multivariable model, adjusting for each of the predictors in this table.

Additionally, we anticipate that with the diverse location of scleroderma centers across the US, the findings we obtain from CONQUER will translate to most SSc patients.

In summary, we found that non-White race was independently associated with RLD. Additionally, 45% of subjects in CONQUER with early disease already had RLD, highlighting the importance of screening for ILD at the time of SSc diagnosis. Ultimately, we hope that data from the CONQUER SSc Registry will allow us to refine care for SSc patients and track patient outcomes that will enable more individualized care for patients with SSc.

CONFLICT OF INTEREST

FVC reports consulting fees from Boehringer Ingelheim. SA reports consulting fees from Novartis, Boehringer Ingelheim, and Corbus. EJB has received consulting fees from Boehringer Ingelheim. LC has received consulting fees from Boehringer Ingelheim, Genentech, Mitsubishi Tanabe, and Eicos Sciences and served on the Data Safety Monitoring Board for Reata. LBE is Chairman of the Board of the Scleroderma Research Foundation (a volunteer, uncompensated

position) and is co-founder and co-owner of MPM Capital, which has invested in various biopharmaceutical companies; LBE represents MPM Capital on the Board of Directors for each of Blade Therapeutics, Trishula Therapeutics, Oncorus, Frontier Medicines, Werewolf Therapeutics, TwentyEight-Seven Therapeutics and Umoja Biopharma. LBE owns stock directly in Eicos Sciences, an affiliate of Civi BioPharma. LKH has received consulting fees from Boehringer Ingelheim, Corbus Pharmaceuticals, CSL Behring. DK reports personal fees from Acceleron, Actelion, Amgen, Bayer, Blade Therapeutics, Boehringer Ingelheim, CSL Behring, Corbus, Galapagos, Genentech/Roche, Horizon, Merck, Mitsubishi Tanabe Pharma, Sanofi-Aventis, and United Therapeutics. DK is Chief Medical Officer of Eicos Sciences, Inc, a subsidiary of Civi BioPharma and has stock options. VS has received consulting fees from Boehringer Ingelheim, CSL Behring, Eicos Sciences, Inc. Other authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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