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Performance Characteristics of Pulmonary Function Tests for the Detection of Interstitial Lung Disease in Adults with Early Diffuse Cutaneous Systemic Sclerosis

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Abstract

Objective: Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc). Although pulmonary function tests (PFTs) are commonly used to screen for ILD in patients with SSc, studies have shown that they lack sensitivity for the detection of ILD in general SSc cohorts. The aim of this study was to assess the performance characteristics of PFTs for the detection of ILD in patients with early diffuse cutaneous (dc)SSc, a population at high risk for the development of ILD.

Methods: We performed a retrospective cohort study of patients enrolled in the Prospective Registry of Early Systemic Sclerosis at 11 sites in the U.S. between April 2012 and January 2019. Patients were included if they underwent spirometry and high resolution computed tomography (HRCT) scan of the chest. We calculated the performance characteristics of PFTs for the detection of ILD on HRCT.

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Results: 212 patients were included; 54% had radiographic ILD. For the detection of ILD on HRCT, a forced vital capacity (FVC) < 80% predicted had a sensitivity of 63%. The combination of FVC < 80% predicted or DLCO < 80% predicted improved the sensitivity to 85%. An FVC < 80% predicted had a negative predictive value (NPV) of 61%, while the combination of FVC < 80% predicted or DLCO < 80% predicted had an NPV of 70%.

Conclusion: PFTs alone are an inadequate screening tool for ILD in patients with early dcSSc. HRCT should be part of the ILD screening algorithm in patients with dcSSc.

Interstitial lung disease (ILD) is a prevalent complication of systemic sclerosis (SSc), affecting 40–60% of patients with this disease, and is the leading cause of death in patients with SSc (1–4). SSc patients with severe ILD have the greatest loss of lung volume early in the disease course (1). Scleroderma Lung Study II has demonstrated that SSc patients with early ILD can have improvement in lung function and quantitative ILD score on high resolution computed tomography (HRCT) scan of the chest with aggressive treatment with either mycophenolate mofetil or cyclophosphamide (5). However, there are no screening guidelines for ILD in patients with SSc. Moreover, although HRCT is the gold standard diagnostic test for the detection of ILD, there is no consensus among rheumatologists regarding the use of HRCT to screen for ILD in their SSc patients. For example, in a survey of both general rheumatologists and SSc experts, Bernstein et al. found that only 51% of general rheumatologists and 66% of SSc experts reported routinely ordering HRCTs in their newly diagnosed SSc patients (6).

Although pulmonary function tests (PFTs) are frequently used by rheumatologists as a screening test for ILD in their SSc patients, studies have shown that they lack sensitivity for the detection of ILD in a general population of SSc patients (4, 7). For example, in a cross-sectional study of 102 SSc patients (41% with diffuse cutaneous [dc]SSc), with a median disease duration of 6 years (interquartile range [IQR] 3–12.5 years), a forced vital capacity (FVC) < 80% predicted only had a sensitivity of 37.5% for the detection of ILD on HRCT (4). Having an FVC < 80% predicted or a diffusion capacity for carbon monoxide (DLCO) < 70% predicted only improved the sensitivity to 59% (4). The aim of this study was to assess the performance characteristics of PFTs for the detection of ILD on HRCT in patients with early dcSSc – arguably the SSc patients at greatest risk for ILD.

PATIENTS AND METHODS

The Prospective Registry of Early Systemic Sclerosis (PRESS) is a multi-center, prospective cohort study of adults with early dcSSc (disease duration < 2 years from onset of the first non-Raynaud's symptom) who meet American College of Rheumatology/European League Against Rheumatism 2013 Classification Criteria for SSc (8). Enrollment began in April 2012 and is ongoing. Participants were recruited from 11 academic medical centers in the United States: Columbia University, Georgetown University, George Washington University, Hospital for Special Surgery, Johns Hopkins University, Medical University of South Carolina, Northwestern University, University of Michigan, University of Pittsburgh, University of Texas Health Science Center at Houston, and University of Utah. University of Michigan is the data coordinating center. All participants enrolled in PRESS between April 2012 and January 2019 who underwent spirometry and HRCT were included. This study

was approved by the Institutional Review Boards at each of the 11 participating sites. All participants in the PRESS cohort provided written informed consent.

PFTs were performed at each PRESS site in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (9–11), as clinically indicated. The lower limit of normal for FVC, total lung capacity (TLC), and DLCO was defined as 80% predicted. HRCTs were ordered at the discretion of the treating physician, and were interpreted by expert thoracic radiologists at each PRESS site according to ATS/ERS standards (12, 13) for the presence or absence of ILD. The local expert thoracic radiologists visually inspected participants' HRCTs for the presence of features of ILD, including ground glass opacities, reticular changes, honeycombing, and traction bronchiectasis. For each participant, the first set of PFTs and the first HRCT were used in the analyses.

Statistical analysis

The following test characteristics of single PFT parameters and combinations of PFT parameters for the detection of ILD on HRCT were calculated: sensitivity, specificity, positive predictive value, negative predictive value (NPV), positive likelihood ratio (LR), negative LR, false positive rate, and false negative rate (FNR). Analyses were performed in R, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Two-hundred eighty-three adults with dcSSc were enrolled in PRESS between April 2012 and January 2019, of whom 212 (75%) underwent spirometry and HRCT, had available HRCT interpretations, and were included in the analyses. The mean disease duration was 1.2 (standard deviation [SD] 0.7) years from the first non-Raynaud's symptom attributable to SSc at PRESS cohort entry. The mean age of participants was 51.7 (SD 13.8) years and the majority were female (67.9%). The mean modified Rodnan skin score was 20.8 (SD 10.3), 32.2% were positive for the anti-topoisomerase I antibody, and 49.4% were positive for the anti-RNA polymerase III antibody. The mean FVC was 80.4 (SD 18.8) % predicted, mean TLC 86.7 (SD 20.4) % predicted, and mean DLCO 68.4 (SD 24.4) % predicted (Table 1). Fifty-four percent of participants had radiographic evidence of ILD, including ground glass opacities (77%, 85/110), reticular changes (62%, 60/97), and/or honeycombing (7.5%, 8/106). Of the 115 participants with radiographic ILD, only 63% had an FVC < 80% predicted. The median absolute time between PFTs and HRCT was 0.1 years (IQR 0–0.4 years).

Among participants with ILD, those with an FVC ≥ 80% predicted (i.e., "false negatives") had a shorter disease duration than those with an FVC < 80% predicted (i.e., "true positives") (1.0 ± 0.6 vs. 1.4 ± 0.8 years; Table 2). Among participants with ILD, a greater proportion of those with an FVC ≥ 80% predicted were female and white than those with an FVC < 80% predicted (76.7% vs. 56.9%; 83.7% vs. 63.9%, respectively; Table 2). Conversely, a greater proportion of those with an FVC < 80% predicted were black than those with an FVC ≥ 80% predicted (27.8% vs. 2.3%; Table 2).

For the detection of ILD on HRCT, an FVC < 80% predicted had a sensitivity of 63%, a TLC < 80% predicted had a sensitivity of 46%, and a DLCO < 80% predicted had a sensitivity of 80%. The combination of FVC < 80% predicted or DLCO < 80% predicted improved the sensitivity to 85%. Adding a TLC < 80% predicted to this combination (i.e., FVC < 80% predicted or TLC < 80% predicted or DLCO < 80% predicted) did not further improve the sensitivity (Table 3).

An FVC < 80% predicted had an NPV of 61% in this early dcSSc patient population with an ILD prevalence of 54%. A DLCO < 80% predicted had an NPV of 68%, while the combination of FVC < 80% predicted or DLCO < 80% predicted had an NPV of 70%. An FVC < 80% predicted had a negative LR of 0.5 and an FNR of 37%, while a DLCO < 80% predicted had a negative LR of 0.4 and an FNR of 20%. The combination of FVC < 80% predicted or DLCO < 80% predicted had a negative LR of 0.4 and an FNR of 15% (Table 3).

DISCUSSION

We found that DLCO < 80% predicted had better sensitivity than FVC < 80% predicted or TLC < 80% predicted for the detection of ILD on HRCT in patients with early dcSSc. The combination of FVC < 80% predicted or DLCO < 80% predicted performed better than any individual parameter, with a sensitivity of 85% for the detection of ILD on HRCT in this population. We demonstrated that spirometry alone is an insufficient screening tool for ILD in patients with dcSSc, as evidenced by a sensitivity of 63% and FNR of 37% for an FVC < 80% predicted. Although a decreased DLCO in patients with longer disease duration is likely to reflect pulmonary vascular disease, this is an unlikely etiology for a decreased DLCO in this group of patients with early dcSSc. Thus, when employing PFTs as a screening tool for early ILD in patients with dcSSc, it is important to check the DLCO in addition to spirometry. Moreover, although a sensitivity of 85% is reasonable, it is inadequate for an ILD screening test as it results in an FNR of 15%, thereby falsely reassuring 15% of patients that they do not have ILD when in fact they do. The NPV is, arguably, an even more important screening test characteristic than sensitivity because it is affected by disease prevalence (14). We found that an FVC < 80% predicted had an NPV of 61%, while the combination of FVC < 80% predicted or DLCO <80% predicted only improved the NPV to 70%. Thus, patients with early dcSSc who have “normal” PFTs only have a 70% probability of not having ILD on HRCT.

A recent study of all 815 resident SSc patients in Norway (80% of whom had baseline HRCTs and 86% of whom had baseline PFTs) – only 18% of whom had dcSSc – from 2000 to 2012 found that at baseline, 50% of the SSc patients had radiographic evidence of ILD on HRCT (15). Moreover, the mean FVC of the 77 patients with radiographic ILD extent > 10% was 78 (SD 19) % predicted, approximately 17% had an FVC > 100% predicted, and approximately 43% had an FVC of 70–100% predicted (15). The mean FVC of the 249 patients with radiographic ILD extent < 10% was 91 (SD 21) % predicted, approximately 40% had an FVC > 100% predicted, and approximately 50% had an FVC of 70–100% predicted (15). In addition, among patients with an FVC in the “normal” range of 80–100% predicted, those with radiographic ILD extent < 10% and > 10% on baseline HRCT had significantly diminished survival compared to those without fibrosis on HRCT (63% and

62%, respectively, versus 82%, p-value=0.01) (15). Thus, baseline HRCT has important prognostic value, even among patients with FVCs in the “normal” range (15). The mere presence of SSc-ILD on baseline HRCT is associated with increased mortality.

There are some limitations of this study. HRCTs and PFTs were not performed in all PRESS patients and were instead ordered at the discretion of their treating physicians. Notably, however, 92% and 93% of patients in the PRESS cohort underwent HRCT and PFTs, respectively, as part of clinical care. The prevalence of ILD in other dcSSc patient populations is likely similar to the prevalence of ILD in ours, thus our results are generalizable to other dcSSc patients who undergo both PFTs and HRCT. Centralized reads of participants’ HRCTs were not performed. However, HRCTs were interpreted by expert thoracic radiologists at each PRESS site according to ATS/ERS standards (12, 13). ILD extent was not quantified, thus we were unable to categorize and analyze patients according to disease extent.

There are several strengths of this study. To our knowledge, PRESS is the largest cohort comprised solely of, and therefore focused specifically on, patients with early dcSSc. We were therefore able to address an important question – i.e., the predictive value of PFTs for the radiographic detection of ILD – in a group at high risk for the development of ILD. The PRESS investigators are all experienced in the conduct of observational studies and clinical trials in patients with SSc and were therefore able to collect – prospectively – robust phenotypic data.

In conclusion, we demonstrated that PFTs lack sufficient sensitivity and NPV for the detection of ILD on HRCT in patients with early dcSSc. We therefore recommend that all patients with dcSSc undergo baseline HRCT, in addition to PFTs, to screen for ILD.

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Table 1:

Baseline Characteristics at PRESS Enrollment

	Overall N = 212	ILD N = 115	No ILD N = 97
Age, mean ± SD years	51.7 ± 13.8	53.1 ± 13.0	50.1 ± 14.5
Female sex, n (%)	144 (67.9)	74 (64.3)	70 (72.2)
Race, n (%)			
White	161 (75.9)	82 (71.3)	79 (81.4)
Black	31 (14.6)	21 (18.3)	10 (10.3)
Asian	9 (4.2)	6 (5.2)	3 (3.1)
Hispanic ethnicity, n (%)	23 (10.8)	13 (11.3)	10 (10.3)
Smoking status, n (%)			
Never	128 (60.4)	70 (60.9)	58 (59.8)
Former	70 (33)	37 (32.2)	33 (34.0)
Current	14 (6.6)	8 (7.0)	6 (6.2)
Disease duration from 1st non-Raynaud's symptom, mean ± SD years	1.2 ± 0.7	1.3 ± 0.7	1.2 ± 0.6
Modified Rodnan skin score, mean ± SD	20.8 ± 10.3 N = 207	20 ± 9.9 N = 113	21.8 ± 10.7 N = 94
Antinuclear antibody (ANA) positive, n (%)	169 (92.3) N = 183	89 (90.8) N = 98	80 (94.1) N = 85
Anti-topoisomerase I positive, n (%)	57 (32.2) N = 177	40 (41.2) N = 97	17 (21.2) N = 80
Anti-RNA polymerase III positive, n (%)	79 (49.4) N = 160	37 (43.5) N = 85	42 (56.0) N = 75
Anti-centromere positive, n (%)	3 (2) N = 150	1 (1.2) N = 85	2 (3.1) N = 65
Anti-fibrillarin positive, n (%)	1 (2.2) N = 46	0 (0) N = 22	1 (4.2) N = 24
Anti-Th/To positive, n (%)	5 (11.4) N = 44	2 (8.7) N = 23	3 (14.3) N = 21
FVC, mean ± SD liters	3.1 ± 1.6 N = 211	2.9 ± 0.9 N = 114	3.4 ± 2.1
FVC, mean ± SD % predicted	80.4 ± 18.8	76.1 ± 18.7	85.5 ± 17.8
FEV1, mean ± SD liters	2.8 ± 5.8 N = 209	3.1 ± 7.8 N = 113	2.6 ± 0.7 N = 96
FEV1, mean ± SD % predicted	83.4 ± 19.8 N = 210	79.4 ± 18.9 N = 114	88.2 ± 19.7 N = 96
FEV1/FVC ratio, mean ± SD	84.3 ± 10.9 N = 194	85.3 ± 11.3 N = 107	83 ± 10.3 N = 87
TLC, mean ± SD liters	5 ± 3.2 N = 148	4.6 ± 1.2 N = 85	5.7 ± 4.7 N = 63
TLC, mean ± SD % predicted	86.7 ± 20.4 N = 146	83.6 ± 20.3 N = 85	91.1 ± 20.0 N = 61
DLCO, mean ± SD % predicted	68.4 ± 24.4 N = 199	60.5 ± 22.2 N = 109	78 ± 23.5 N = 90
Absolute time between PFTs and HRCT, mean ± SD years	0.3 ± 0.4 N = 211	0.3 ± 0.4	0.3 ± 0.4 N = 96
Absolute time between PFTs and HRCT, median (IQR) years	0.1 (0–0.4) N = 211	0.1 (0–0.4)	0.1 (0–0.4) N = 96

	Overall N = 212	ILD N = 115	No ILD N = 97
Mycophenolate mofetil, n (%)	83 (39.2)	50 (43.5)	33 (34.0)
Prednisone, n (%)	68 (32.1)	33 (28.7)	35 (36.1)
Methotrexate, n (%)	28 (13.2)	13 (11.3)	15 (15.5)
Hydroxychloroquine, n (%)	27 (12.7)	15 (13)	12 (12.4)
Cyclophosphamide, n (%)	6 (2.8)	4 (3.5)	2 (2.1)
D-penicillamine, n (%)	5 (2.4)	2 (1.7)	3 (3.1)
Azathioprine, n (%)	4 (1.9)	4 (3.5)	0 (0)
Investigational drug, n (%)	6 (2.8) N = 211	2 (1.8) N = 114	4 (4.1)
Supplemental oxygen use, n (%)	4 (1.9) N = 211	3 (2.6) N = 114	1 (1)
New York Heart Association Functional Class, n (%)	N = 195	N = 107	N = 88
I	88 (45.1)	43 (40.2)	45 (51.1)
II	73 (37.4)	44 (41.1)	29 (33)
III	34 (17.4)	20 (18.7)	14 (15.9)
IV	0 (0)	0 (0)	0 (0)
SHAQ breathlessness score, mean ± SD	2.2 ± 2.8 N = 175	2.5 ± 3 N = 94	1.8 ± 2.5 N = 81

PRESS = Prospective Registry of Early Systemic Sclerosis; SD = standard deviation; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide; IQR = interquartile range; ILD = interstitial lung disease; HRCT = high resolution computed tomography; SHAQ = Scleroderma Health Assessment Questionnaire

Table 2:

Comparison of Baseline Characteristics between SSc-ILD Patients with FVC ≥ 80% predicted and FVC < 80% predicted

	FVC ≥ 80% & ILD N = 43	**FVC < 80% & ILD N = 72**
Age, mean ± SD years	54.7 ± 11.7	52.1 ± 13.7
Female sex, n (%)	33 (76.7)	41 (56.9)
Race, n (%)		
White	36 (83.7)	46 (63.9)
Black	1 (2.3)	20 (27.8)
Asian	4 (9.3)	2 (2.8)
Hispanic ethnicity, n (%)	3 (7.0)	10 (13.9)
Smoking status, n (%)		
Never	25 (58.1)	45 (62.5)
Former	16 (37.2)	21 (29.2)
Current	2 (4.7)	6 (8.3)
Disease duration from 1st non-Raynaud's symptom, mean ± SD years	1.0 ± 0.6	1.4 ± 0.8
Modified Rodnan skin score, mean ± SD	19.1 ± 9.7	20.5 ± 10.0 N = 70
Antinuclear antibody (ANA) positive, n (%)	32 (88.9) N = 36	57 (91.9) N = 62
Anti-topoisomerase I positive, n (%)	13 (37.1) N = 35	27 (43.5) N = 62
Anti-RNA polymerase III positive, n (%)	17 (53.1) N = 32	20 (37.7) N = 53
Anti-centromere positive, n (%)	0 (0) N = 32	1 (1.9) N = 53
FVC, mean ± SD liters	3.4 ± 0.8	2.6 ± 0.7 N = 71
FVC, mean ± SD % predicted	96.8 ± 9.6	63.7 ± 9.6
FEV1, mean ± SD liters	4.6 ± 12.6	2.1 ± 0.6 N = 70
FEV1, mean ± SD % predicted	95.2 ± 17.9	69.7 ± 11.8 N = 71
FEV1/FVC ratio, mean ± SD	80.1 ± 8.5 N = 41	88.5 ± 11.7 N = 66
TLC, mean ± SD liters	5.3 ± 1.0 N = 36	4.1 ± 1.0 N = 49
TLC, mean ± SD % predicted	102.0 ± 12.3 N = 36	70.1 ± 13.0 N = 49
DLCO, mean ± SD % predicted	74.8 ± 20.3 N = 42	51.5 ± 18.4 N = 67
New York Heart Association Functional Class, n (%)	N = 41	N = 66
I	21 (51.2)	22 (33.3)
II	16 (39.0)	28 (42.4)
III	4 (9.8)	16 (24.2)
IV	0 (0)	0 (0)

	FVC ≥ 80% & ILD N = 43	**FVC < 80% & ILD N = 72**
SHAQ breathlessness score, mean ± SD	1.6 ± 2.2 N = 35	3.1 ± 3.3 N = 59

SSc = systemic sclerosis; ILD = interstitial lung disease; FVC = forced vital capacity; SD = standard deviation; FEV1 = forced expiratory volume in 1 second; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide; SHAQ = Scleroderma Health Assessment Questionnaire

Table 3:

Performance Characteristics of Pulmonary Function Tests for the Detection of Interstitial Lung Disease

PFT Parameters	N	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR	FPR	FNR
FVC < 80%	212	63%	68%	70%	61%	2.0	0.5	0.32	0.37
TLC < 80%	146	46%	77%	74%	51%	2.0	0.7	0.23	0.54
DLCO < 80%	200	80%	51%	66%	68%	1.6	0.4	0.49	0.20
FVC or DLCO < 80%	199	85%	42%	64%	70%	1.5	0.4	0.58	0.15
FVC or TLC or DLCO < 80%	143	85%	42%	68%	66%	1.5	0.4	0.58	0.15

PFT = pulmonary function test; FVC = forced vital capacity; TLC = total lung capacity; DLCO = diffusion capacity for carbon monoxide; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; FPR = false positive rate; FNR = false negative rate