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BRIEF REPORT

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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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. This study was undertaken to assess the performance characteristics of PFTs for the detection of ILD in patients with early diffuse cutaneous SSc (dcSSc), 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 US between April 2012 and January 2019. Patients were included if they underwent spirometry and high-resolution computed tomography (HRCT) of the chest. We calculated the performance characteristics of PFTs for the detection of ILD on HRCT.

Results. The study included 212 patients, 54% of whom had radiographic ILD. For the detection of ILD on HRCT imaging, a forced vital capacity (FVC) <80% predicted had a sensitivity of 63%. The combination of FVC <80% predicted or diffusing capacity for carbon monoxide (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 the diagnosis of ILD in patients with early dcSSc. HRCT should be part of the ILD screening algorithm in patients with dcSSc.

INTRODUCTION

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 experience

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improvement in lung function and quantitative ILD score on high-resolution computed tomography (HRCT) of the chest when receiving 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 HRCT scans 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 patients with SSc, studies have shown that they lack sensitivity for the detection of ILD in a general population of patients

Table 1. Baseline characteristics at PRESS enrollment*

	Overall (n = 212)	ILD (n = 115)	No ILD (n = 97)
Age years	51.7 ± 13.8	53.1 ± 13.0	50.1 ± 14.5
Female sex, no. (%)	144 (67.9)	74 (64.3)	70 (72.2)
Race, no. (%)			
White	161 (75.9)	82 (71.3)	79 (81.4)
African American	31 (14.6)	21 (18.3)	10 (10.3)
Asian	9 (4.2)	6 (5.2)	3 (3.1)
Hispanic	23 (10.8)	13 (11.3)	10 (10.3)
Smoking status, no. (%)			
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 first non-Raynaud's symptom, years	1.2 ± 0.7	1.3 ± 0.7	1.2 ± 0.6
Modified Rodnan skin thickness score	20.8 ± 10.3 (207)	20 ± 9.9 (113)	21.8 ± 10.7 (94)
Antibody positivity, no./no. assessed (%)			
Antinuclear antibody positive	169/183 (92.3)	89/98 (90.8)	80/85 (94.1)
Anti-topoisomerase I antibody positive	57/177 (32.2)	40/97 (41.2)	17/80 (21.2)
Anti-RNA polymerase III antibody positive	79/160 (49.4)	37/85 (43.5)	42/75 (56.0)
Anticentromere antibody positive	3/150 (2)	1/85 (1.2)	2/65 (3.1)
Antifibrillarin antibody positive	1/46 (2.2)	0/22 (0)	1/24 (4.2)
Anti-Th/To antibody positive	5/44 (11.4)	2/23 (8.7)	3/21 (14.3)
PFTs			
FVC, liters	3.1 ± 1.6 (211)	2.9 ± 0.9 (114)	3.4 ± 2.1 (97)
FVC, % predicted	80.4 ± 18.8 (212)	76.1 ± 18.7 (115)	85.5 ± 17.8 (97)
FEV_1, liters	2.8 ± 5.8 (209)	3.1 ± 7.8 (113)	2.6 ± 0.7 (96)
FEV_1, % predicted	83.4 ± 19.8 (210)	79.4 ± 18.9 (114)	88.2 ± 19.7 (96)
FEV_1/FVC ratio	84.3 ± 10.9 (194)	85.3 ± 11.3 (107)	83 ± 10.3 (87)
TLC, liters	5 ± 3.2 (148)	4.6 ± 1.2 (85)	5.7 ± 4.7 (63)
TLC, % predicted	86.7 ± 20.4 (146)	83.6 ± 20.3 (85)	91.1 ± 20.0 (61)
DLco, % predicted	68.4 ± 24.4 (199)	60.5 ± 22.2 (109)	78 ± 23.5 (90)
Absolute time between PFTs and HRCT imaging, years	0.3 ± 0.4 (211)	0.3 ± 0.4 (115)	0.3 ± 0.4 (96)
Absolute time between PFTs and HRCT imaging, median (IQR) years (no. assessed)	0.1 (0–0.4) (211)	0.1 (0–0.4) (115)	0.1 (0–0.4) (96)
Treatments			
Mycophenolate mofetil, no. (%)	83 (39.2)	50 (43.5)	33 (34.0)
Prednisone, no. (%)	68 (32.1)	33 (28.7)	35 (36.1)
Methotrexate, no. (%)	28 (13.2)	13 (11.3)	15 (15.5)
Hydroxychloroquine, no. (%)	27 (12.7)	15 (13)	12 (12.4)
Cyclophosphamide, no. (%)	6 (2.8)	4 (3.5)	2 (2.1)
D-penicillamine, no. (%)	5 (2.4)	2 (1.7)	3 (3.1)
Azathioprine, no. (%)	4 (1.9)	4 (3.5)	0 (0)
Investigational drug, no./no. assessed (%)	6/211 (2.8)	2/114 (1.8)	4/97 (4.1)
Supplemental oxygen use, no./no. assessed (%)	4/211 (1.9)	3/114 (2.6)	1/97 (1)
New York Heart Association Functional Class, no./no. assessed (%)			
I	88/195 (45.1)	43/107 (40.2)	45/88 (51.1)
II	73/195 (37.4)	44/107 (41.1)	29/88 (33)
III	34/195 (17.4)	20/107 (18.7)	14/88 (15.9)
IV	0/195 (0)	0/107 (0)	0/88 (0)
SHAQ breathlessness score	2.2 ± 2.8 (175)	2.5 ± 3 (94)	1.8 ± 2.5 (81)

* Except where indicated otherwise, values are the mean ± SD (no. assessed). PRESS = Prospective Registry of Early Systemic Sclerosis; ILD = interstitial lung disease; PFTs = pulmonary function tests; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; TLC = total lung capacity; DLco = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography; IQR = interquartile range; SHAQ = Scleroderma Health Assessment Questionnaire.

with SSc (4,7). For example, in a cross-sectional study of 102 patients with SSc (41% with diffuse cutaneous SSc [dcSSc]) with a median disease duration of 6 years (interquartile range [IQR] 3–12.5 years), a forced vital capacity (FVC) <80% predicted had a sensitivity of only 37.5% for the detection of ILD on HRCT imaging (4). Having an FVC <80% predicted or a diffusing capacity for carbon monoxide (DL_{CO}) <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

Study population. The Prospective Registry of Early Systemic Sclerosis (PRESS) is a multicenter, prospective cohort study of adults with early dcSSc (disease duration <2 years from the onset of the first non–Raynaud's phenomenon [RP] symptom) who met the 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 US: 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. The 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 and HRCT. 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 DL_{CO} was defined as 80% predicted. HRCT scans 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' HRCT scans for the presence of ILD characteristics, including ground glass opacities, reticular changes, honeycombing, and traction bronchiectasis. For each participant, the first set of PFTs and the first HRCT image were used in the analyses.

Statistical analysis. The following test characteristics of single PFT parameters and combinations of PFT parameters to detect 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 using R, version 3.5.2 (R Foundation for Statistical Computing).

RESULTS

Two hundred eighty-three adults with dcSSc were enrolled in the PRESS study 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 ± SD disease duration was 1.2 ± 0.7 years from the first non–RP symptom attributable to SSc at PRESS cohort entry. The mean ± SD age of the participants was 51.7 ± 13.8 years, and the majority were female (67.9%). Patients had a mean ± SD modified Rodnan skin thickness score of 20.8 ± 10.3. Of the patients included, 32.2% were positive for the anti–topoisomerase I antibody, and 49.4% were positive for the anti–RNA polymerase III antibody. The mean ± SD FVC was 80.4 ± 18.8 % predicted, the mean ± SD TLC was 86.7 ± 20.4 % predicted, and the mean ± SD DL_{CO} was 68.4 ± 24.4 % predicted (Table 1). Fifty-four percent of the participants had radiographic evidence of ILD, including ground glass opacities (85 of 110 [77%]), reticular changes (60 of 97 [62%]), and/or honeycombing (8 of 106 [7.5%]). 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) (mean ± SD 1.0 ± 0.6 versus 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 compared to those with an FVC <80% predicted (76.7% versus 56.9%; and 83.7% versus 63.9%, respectively) (Table 2). Conversely, a greater proportion of those with an FVC <80% predicted than those with an FVC ≥80% predicted were African American (27.8% versus 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 DL_{CO} <80% predicted had a sensitivity of 80%. The combination of FVC <80% predicted or DL_{CO} <80% predicted improved the sensitivity to 85%. Adding a TLC <80% predicted to this combination (i.e., FVC <80% predicted, TLC <80% predicted, or DL_{CO} <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 DL_{CO} <80% predicted had an NPV of 68%, while the combination of FVC <80% predicted or DL_{CO} <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 DL_{CO} <80% predicted had a negative LR of 0.4 and an FNR of 20%. The combination of FVC <80% predicted or DL_{CO} <80% predicted had a negative LR of 0.4 and an FNR of 15% (Table 3).

Table 2. Comparison of baseline characteristics between patients with SSc-ILD with FVC ≥80% predicted and FVC <80% predicted*

	FVC ≥80% and ILD (n = 43)	FVC <80% and ILD (n = 72)
Age, years	54.7 ± 11.7	52.1 ± 13.7
Female sex, no. (%)	33 (76.7)	41 (56.9)
Race, no. (%)		
White	36 (83.7)	46 (63.9)
African American	1 (2.3)	20 (27.8)
Asian	4 (9.3)	2 (2.8)
Hispanic	3 (7.0)	10 (13.9)
Smoking status, no. (%)		
Never	25 (58.1)	45 (62.5)
Former	16 (37.2)	21 (29.2)
Current	2 (4.7)	6 (8.3)
Disease duration from first non-Raynaud's symptom, years	1.0 ± 0.6	1.4 ± 0.8
Modified Rodnan skin score	19.1 ± 9.7 (43)	20.5 ± 10.0 (70)
Antinuclear antibody positive, no./no. assessed (%)	32/36 (88.9)	57/62 (91.9)
Anti-topoisomerase I antibody positive, no./no. assessed (%)	13/35 (37.1)	27/62 (43.5)
Anti-RNA polymerase III antibody positive, no./no. assessed (%)	17/32 (53.1)	20/53 (37.7)
Anticentromere antibody positive, no./no. assessed (%)	0/32 (0)	1/53 (1.9)
FVC, liters	3.4 ± 0.8 (43)	2.6 ± 0.7 (71)
FVC, % predicted	96.8 ± 9.6	63.7 ± 9.6
FEV_1, liters	4.6 ± 12.6 (43)	2.1 ± 0.6 (70)
FEV_1, % predicted	95.2 ± 17.9 (43)	69.7 ± 11.8 (71)
FEV_1/FVC ratio	80.1 ± 8.5 (41)	88.5 ± 11.7 (66)
TLC, liters	5.3 ± 1.0 (36)	4.1 ± 1.0 (49)
TLC, % predicted	102.0 ± 12.3 (36)	70.1 ± 13.0 (49)
DLco, % predicted	74.8 ± 20.3 (42)	51.5 ± 18.4 (67)
New York Heart Association Functional Class, no. (%)	41	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)
SHAQ breathlessness score	1.6 ± 2.2 (35)	3.1 ± 3.3 (59)

* Except where indicated otherwise, values are the mean ± SD (no. assessed). SSc = systemic sclerosis; ILD = interstitial lung disease; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; TLC = total lung capacity; DLco = diffusing capacity for carbon monoxide; SHAQ = Scleroderma Health Assessment Questionnaire.

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 scans 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 an FNR of 37% for an FVC <80% predicted. Although a decreased DLco in patients with a 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 the detection of 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

Table 3. Performance characteristics of pulmonary function tests for the detection of interstitial lung disease*

PFT parameter	No. of patients	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; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; FPR = false-positive rate; FNR = false-negative rate; FVC = forced vital capacity; TLC = total lung capacity; DLco = diffusing capacity for carbon monoxide.

FVC <80% predicted had an NPV of 61%, while the combination of FVC <80% predicted or DL_{CO} <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 (of whom 80% had baseline HRCT scans and 86% had baseline PFTs)—only 18% of whom had dcSSc—from 2000 to 2012 found that at baseline, 50% of the patients with SSc had radiographic evidence of ILD on HRCT (15). Moreover, for the 77 patients who had a radiographic ILD extent of >10%, the mean ± SD FVC was 78 ± 19% predicted. Of these 77 patients, ~17% had an FVC >100% predicted, and ~43% had an FVC of 70–100% predicted (15). For the 249 patients who had a radiographic ILD extent of <10%, the mean ± SD FVC was 91 ± 21% predicted, ~40% had an FVC >100% predicted, and ~50% had an FVC of 70–100% predicted (15). In addition, among patients with an FVC in the normal range of 80–100% predicted, both those with a radiographic ILD extent of <10% and those with a radiographic ILD extent of >10% on baseline HRCT had significantly diminished survival compared to those without fibrosis on HRCT (63% and 62%, respectively, versus 82%; $P = 0.01$) (15). Thus, baseline HRCT imaging has important prognostic value, even among patients with FVCs in the normal range (15). The mere presence of SSc-related ILD on baseline HRCT is associated with increased mortality.

There are some limitations of this study. HRCT scans 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 our study population; thus, our results are generalizable to other dcSSc patients who undergo both PFTs and HRCT. Centralized reading of participants' HRCT scans was not performed. However, HRCT images 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.

The present study has several strengths. 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.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bernstein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bernstein, Khanna.
Acquisition of data. Bernstein, Jaafar, Assassi, Domsic, Frech, Gordon, Broderick, Hant, Hinchcliff, Shah, Shanmugam, Steen, Khanna.
Analysis and interpretation of data. Bernstein, Khanna.

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