Computed Tomography of the Chest to Screen for Interstitial Lung Disease in Patients With Systemic Sclerosis at Expert Scleroderma Centers in the United States

Elana J. Bernstein,1 Shervin Assassi,2 Flavia V. Castelino,3 Lorinda Chung,4 Chase Correia,5,6 Luke B. Evnin,7 Tracy M. Frech,8 Jessica K. Gordon,9 Brian A. Skaug,2 Faye N. Hant,10 Laura K. Hummers,11 Nora Sandorfi,12 Ami A. Shah,11 Victoria K. Shanmugam,13 Virginia D. Steen,14 and Dinesh Khanna15

Objective. Although a high-resolution computed tomography (HRCT) scan of the chest is the gold standard test for the detection of interstitial lung disease (ILD), there is no consensus among rheumatologists regarding the use of HRCT to screen for ILD in their patients with systemic sclerosis (SSc). The aims of this study were to describe the HRCT ordering practices at SSc centers in the United States and to determine which patient characteristics are associated with HRCT performance.

Methods. We performed a prospective cohort study of patients with SSc enrolled in the US-based Collaborative National Quality and Efficacy Registry (CONQUER). We performed univariate logistic regression followed by multivariable logistic regression to determine which patient characteristics were associated with HRCT performance.

Results. Of the 356 patients with SSc enrolled in CONQUER, 286 (80.3%) underwent HRCT at some point during their disease course. On multivariable analyses, missing total lung capacity percent predicted (odds ratio [OR] 3.26, 95% confidence interval [CI]: 1.53-7.41, P = 0.007) was positively associated with ever having undergone HRCT, whereas a positive anti-centromere antibody (OR 0.27, 95% CI: 0.12-0.61, P = 0.008) and missing forced vital capacity percent predicted (OR 0.29, 95% CI: 0.10-0.80, P = 0.005) were negatively associated with ever having undergone HRCT. There was a trend toward a positive association between crackles on pulmonary exam and ever having undergone HRCT (OR 2.28, 95% CI: 0.97-6.05, P = 0.058), although this relationship did not reach statistical significance.

Conclusion. The majority of patients with SSc enrolled in CONQUER underwent HRCT. A positive anti-centromere antibody was the key clinical variable inversely associated with performance of HRCT.

INTRODUCTION

Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc) (1–3). 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 this population (4,5). Moreover, although a high-resolution computed tomography (HRCT) scan

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1Elana J. Bernstein, MD, MSc: Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, New York; 2Shervin Assassi, MD, MS, Brian A. Skaug, MD, PhD: University of Texas Health Science Center at Houston, Houston, Texas; 3Flavia V. Castelino, MD: Massachusetts General Hospital, Boston, Massachusetts; 4Lorinda Chung, MD, MS: Stanford University and Palo Alto VA Healthcare System, Palo Alto, California; 5Chase Correia, MD, MS: Northwestern University, Chicago, Illinois; 6Chase Correia, MD, MS: Riverside Rheumatology Specialists, Hampton, Virginia; 7Chase Correia, MD, MS, Luke B. Evnin, PhD: Scleroderma Research Foundation, San Francisco, California; 8Tracy M. Frech, MD, MS: University of Utah, Salt Lake City, and Vanderbilt University Medical Center, Nashville, Tennessee; 9Jessica K. Gordon, MD, MSc: Hospital for Special Surgery, New York, New York; 10Faye N. Hant, DO: Medical University of South Carolina, Charleston, South Carolina; 11Laura K. Hummers, MD, ScM, Ami A. Shah, MD, MHS: Johns Hopkins University, Baltimore, Maryland; 12Nora Sandorfi, MD: University of Pennsylvania, Philadelphia, Pennsylvania; 13Victoria K. Shanmugam, MD: The George Washington University, Washington, DC; 14Virginia D. Steen, MD: Georgetown University, Washington, DC; 15Dinesh Khanna, MD, MSc: University of Michigan, Ann Arbor, Michigan.

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of the chest is the gold standard test for the detection of ILD, there is no consensus among rheumatologists regarding the use of HRCT to screen for ILD in their patients with SSc (6). The aims of this study were to describe the HRCT ordering practices at expert SSc centers in the United States and to determine which patient characteristics are associated with HRCT performance.

PATIENTS AND METHODS

We performed a prospective cohort study of patients with SSc enrolled in the Collaborative National Quality and Efficacy Registry (CONQUER) at 13 sites in the United States between June 6, 2018, and February 1, 2020. CONQUER is a US-based, prospective, multicenter cohort of adults 18 years of age or older with SSc who meet 2013 American College of Rheumatology/European League Against Rheumatism Classification Criteria for SSc (7) and have a disease duration of 5 years or less from the first non-Raynaud’s symptom at enrollment (8,9). Participants’ medical records were reviewed to determine whether HRCT was ever performed, either at a CONQUER baseline or follow-up visit or prior to enrolling in CONQUER. If studies, such as PFTs, are performed external to the CONQUER site but available to the treating rheumatologist, they are entered into the CONQUER database. All study results that are available to the treating rheumatologist are included in the CONQUER database, regardless of where the studies were performed. This study was approved by the institutional review boards at each of the 13 participating sites and complies with the ethical guidelines of the 1975 Declaration of Helsinki. All participants in CONQUER provided written informed consent.

We used the Student’s t-test, χ2 test, and Fisher’s exact test, as appropriate, to compare baseline characteristics between participants who did and did not ever undergo HRCT. We also reported the proportion of participants with certain SSc disease characteristics who ever underwent HRCT.

For modeling purposes, we created informative missing categories for autoantibodies and PFT percentage of predicted values. We performed univariate logistic regression followed by multivariable logistic regression to determine which patient characteristics were associated with ever having undergone HRCT. Each variable that attained a P value of less than 0.1 in the univariate analysis and had fewer than 10% missing observations was included in the final multivariable logistic regression model, as were age and sex. Multicollinearity of the final model was assessed using variance inflation factors.

Likelihood ratio tests were used to calculate P values for the univariate and multivariable logistic regression analyses. Statistical significance was defined as a two-sided P value of less than 0.05. Analyses were performed in SAS version 9.4 (SAS Institute Inc), and R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 356 subjects were enrolled in CONQUER during the study period. The median age at enrollment was 53.8 (interquartile range [IQR] 42.3-62.7) years. Eighty-two percent were female; 78.4% self-identified as White and 12.7% as African American. The median disease duration from the first non-Raynaud’s symptom was 2.6 (IQR 1.3-3.8) years. Two-hundred seventeen (61%) participants had diffuse cutaneous SSc. One hundred (28.1%) participants were anti-topoisomerase I antibody positive, 85 (23.9%) were anti-RNA polymerase III antibody positive, and 43 (12.1%) were anti-centromere antibody positive. A total of 286 (80.3%) participants underwent HRCT at some point during their SSc disease course. The median time between first non-Raynaud’s symptom and HRCT was 1.6 (IQR 0.6-2.8) years and between SSc diagnosis and HRCT was 0.55 (IQR 0.1-1.85) years. The median time between HRCT and CONQUER enrollment was 0.4 (IQR 0-1.2) years. Among those who underwent HRCT compared with those who did not, a smaller proportion were anti-centromere antibody positive (9.4% vs. 22.9%, P = 0.005), and a greater proportion had crackles on exam (24.8% vs. 10.0%, P = 0.007). Subjects with SSc who underwent HRCT had lower percent predicted forced vital capacity (FVC; 82.0% [IQR 70.0%-93.0%] predicted vs. 92.0% [IQR 81.0%-114.0%] predicted, P < 0.001), lower percent predicted forced expiratory volume in 1 second (FEV1; 84.0% [IQR 69.0%-93.0%] predicted vs. 97.0% [IQR 82.0%-110.0%] predicted, P < 0.001), and lower percent predicted diffusion capacity for carbon monoxide (DLCO; 68.0% [IQR 50.5%-85.0%] predicted vs. 75.5% [IQR 63.0%-91.5%] predicted, P = 0.01) than those who did not (Table 1).

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Address correspondence to Elana J. Bernstein, MD, MSc, Columbia University Irving Medical Center, 630 West 168th Street, Suite 3-450, New York, NY 10032. Email: ejb2153@columbia.edu.

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The percentage of CONQUER participants at each site who ever underwent HRCT ranged from 31.3% to 100%. Eighty-four percent and 80% of participants who were anti-topoisomerase I antibody positive and anti-RNA polymerase III antibody positive, respectively, underwent HRCT, whereas only 62.8% of those who were anti-centromere antibody positive underwent HRCT.

### Table 1. Baseline characteristics of CONQUER participants

| HRCT ever performed |
|----------------------|
| Overall (N = 356)    |
| Yes (n = 286)        |
| No (n = 70)          |
| P value              |
|----------------------|
| Age at baseline visit (y) 53.8 (42.3, 62.7) 53.7 (42.5, 63.1) 55.1 (40.5, 61.1) 0.938 |
| Female sex 292 (82.0%) 235 (82.2%) 57 (81.4%) 0.885 |
| Race 0.117 |
| White 272 (78.4%) 212 (76.3%) 60 (87.0%) |
| Black or African American 44 (12.7%) 40 (14.4%) 4 (5.8%) |
| Other 31 (8.9%) 26 (9.4%) 5 (7.2%) |
| Hispanic or Latinx ethnicity 39 (11.2%) 29 (10.3%) 10 (15.2%) 0.259 |
| Ever smoker 119 (33.4%) 96 (33.6%) 23 (32.9%) 0.910 |
| Disease duration (y) 2.6 (1.3, 3.8) 2.6 (1.4, 3.8) 2.6 (1.1, 3.8) 0.787 |
| Antinuclear antibody positive 315 (88.5%) 258 (90.2%) 57 (81.4%) 0.052 |
| Anti-centromere antibody positive 43 (12.1%) 27 (9.4%) 16 (22.9%) 0.005 |
| Anti-Scl-70 antibody positive 100 (28.1%) 84 (29.4%) 16 (22.9%) 0.550 |
| Anti-RNA polymerase III antibody positive 85 (23.9%) 68 (23.8%) 17 (24.3%) 0.205 |
| Supplemental oxygen use 16 (4.5%) 14 (4.9%) 2 (2.9%) 0.748 |
| Crackles on exam 78 (22.0%) 71 (24.9%) 7 (10.0%) 0.007 |
| Diffuse cutaneous subtype 217 (61.0%) 179 (62.6%) 38 (54.3%) 0.202 |
| Modified Rodnan skin score 9.0 (4.0, 19.5) 10.0 (5.0, 22.0) 8.0 (3.0, 15.0) 0.280 |
| New York Heart Association functional class 0.484 |
| Class I or II 321 (90.7%) 256 (90.1%) 65 (92.9%) |
| Class III or IV 33 (9.3%) 28 (9.9%) 5 (7.1%) |
| Participant global health 0.117 |
| 4.0 (2.0, 6.0) 4.0 (2.0, 6.0) 4.0 (2.0, 6.0) 4.0 (2.0, 6.0) 3.0 (2.0, 6.0) 0.199 |
| Physician global health 0.087 |
| 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 0.087 |
| Physician global damage 0.068 |
| 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 3.0 (2.0, 5.0) 0.068 |
| SHAQ breathlessness score 0.016 |
| 1.0 (0.0, 3.0) 1.0 (0.0, 3.0) 1.0 (0.0, 3.0) 1.0 (0.0, 3.0) 1.0 (0.0, 3.0) 1.0 (0.0, 3.0) 0.016 |
| mMRC dyspnea scale score 0.187 |
| 0 30 40 119 (38.6%) 91 (36.5%) 28 (47.5%) |
| 1 125 (40.6%) 107 (43.0%) 18 (30.5%) |
| 2-4 64 (20.8%) 51 (20.5%) 13 (22.0%) |
| FACIT dyspnea score 0.667 |
| 4.0 (1.4, 10.0) 5.0 (1.4, 10.0) 5.0 (1.4, 10.0) 4.0 (1.4, 10.0) 3.0 (1.0, 9.0) 0.667 |
| FVC (L) 0.010 |
| 2.8 (2.4, 3.5) 2.8 (2.3, 3.4) 3.3 (2.6, 3.9) |
| FVC % predicted <0.001 |
| 84.0 (71.0, 96.0) 82.0 (70.0, 93.0) 92.0 (81.0, 114.0) 92.0 (81.0, 114.0) |
| FEV1 (L) 0.003 |
| 2.3 (1.9, 2.8) 2.2 (1.8, 2.7) 2.6 (2.1, 3.2) 2.6 (2.1, 3.2) 0.003 |
| FEV1 % predicted <0.001 |
| 85.0 (72.0, 97.0) 84.0 (69.0, 93.0) 97.0 (82.0, 110.0) 97.0 (82.0, 110.0) |
| FEV1/FVC category 0.004 |
| <80% 114 (32.0%) 103 (36.0%) 11 (15.7%) 11 (15.7%) |
| ≥80% 193 (54.2%) 147 (51.4%) 46 (65.7%) |
| Missing 49 (13.8%) 36 (12.6%) 13 (18.6%) |
| FEV1/FVC (actual) 0.268 |
| 82.0 (78.0, 88.0) 82.0 (78.0, 88.0) 82.0 (78.0, 88.0) 82.0 (78.0, 88.0) |
| FEV1/FVC % predicted 0.319 |
| <80% 114 (32.0%) 93 (32.5%) 21 (30.0%) |
| ≥80% 191 (53.7%) 156 (54.5%) 35 (50.0%) |
| Missing 51 (14.3%) 37 (12.9%) 14 (20.0%) |
| TLC (L) 0.198 |
| 4.5 (3.8, 5.4) 4.5 (3.8, 5.2) 4.5 (3.8, 5.2) 4.8 (4.2, 5.6) |
| TLC % predicted 0.015 |
| 85.0 (74.0, 97.0) 84.0 (71.0, 95.0) 93.0 (80.0, 108.0) 93.0 (80.0, 108.0) |
| TLC % predicted 0.009 |
| <80% 75 (21.1%) 66 (23.1%) 9 (12.9%) |
| ≥80% 133 (37.4%) 96 (33.6%) |
| Missing 148 (41.6%) 124 (43.4%) |
| DLCO (ml/min/mmHg) 0.017 |
| 16.7 (12.3, 21.5) 16.4 (11.9, 21.1) 18.8 (14.1, 24.5) |
| DLCO % predicted 0.010 |
| 70.0 (52.0, 88.0) 68.0 (50.5, 85.0) 75.5 (63.0, 91.5) 75.5 (63.0, 91.5) |
Of the 217 subjects with diffuse cutaneous SSc, 82.5% underwent HRCT. Ninety-one percent (71 out of 78) of participants with crackles on auscultation of the lungs underwent HRCT. Of the 128 subjects with an FVC below 80% predicted, 115 (89.8%) underwent HRCT. Ninety-six out of the 119 (80.7%) ever smokers underwent HRCT. Ninety-one percent (71 out of 78) of participants with diffuse cutaneous SSc underwent HRCT. Ninety-three percent (78 out of 85) of anti-Scl-70 antibody positive patients underwent HRCT. Ninety-three percent (77 out of 84) of patients with a mMRC dyspnea scale score of 4 underwent HRCT.

Table 1. HRCT ever performed by selected clinical characteristics

| Characteristic                      | Overall (N = 356) | Yes (N = 286) | No (N = 70) | P value |
|-------------------------------------|-------------------|---------------|-------------|---------|
| Crackles on exam                    | 78 (21.9%)        | 64 (22.3%)    | 14 (19.7%)  | 0.450   |
| Anti-Scl-70 antibody positive       | 100 (28.2%)       | 85 (30.1%)    | 15 (21.4%)  | 0.180   |
| Anti-nuclear antibody positive      | 315 (88.9%)       | 258 (90.9%)   | 57 (78.6%)  | 0.140   |
| Antinuclear antibody positive in a nucleolar pattern | 56 (15.9%) | 52 (19.1%) | 4 (5.7%) | 0.070   |
| Anti-centromere antibody positive   | 43 (12.2%)        | 27 (9.9%)     | 16 (22.9%)  | 0.008   |
| Anti-DLCO % predicted              | 183 (51.4%)       | 155 (54.2%)   | 28 (40.0%)  | 0.101   |
| ≥80%                                | 101 (28.4%)       | 77 (26.9%)    | 24 (34.3%)  |         |
| Missing                             | 72 (20.2%)        | 54 (18.9%)    | 18 (25.7%)  |         |

Of the 217 subjects with diffuse cutaneous SSc, 82.5% underwent HRCT. Ninety-one percent (71 out of 78) of participants with crackles on auscultation of the lungs underwent HRCT. Of the 128 subjects with an FVC below 80% predicted, 115 (89.8%) underwent HRCT. Ninety-six out of the 119 (80.7%) ever smokers underwent HRCT. Ninety-one percent (71 out of 78) of participants with diffuse cutaneous SSc underwent HRCT. Ninety-three percent (78 out of 85) of anti-Scl-70 antibody positive patients underwent HRCT. Ninety-three percent (77 out of 84) of patients with a mMRC dyspnea scale score of 4 underwent HRCT.

Table 2. HRCT ever performed by selected clinical characteristics

| Characteristic                      | N with characteristic | N (%) with characteristic who underwent HRCT |
|-------------------------------------|-----------------------|---------------------------------------------|
| Total N in CONQUER                 | 356                   | 286 (80.3%)                                |
| Antinuclear antibody positive       | 315                   | 258 (81.9%)                                |
| Antinuclear antibody positive in a nucleolar pattern | 56 | 52 (92.9%) | |
| Anti-centromere antibody positive   | 43                    | 27 (62.8%)                                 |
| Anti-DLCO % predicted              | 183                   | 155 (89.8%)                                |
| ≥80%                                | 101                   | 77 (76.2%)                                 |
| Missing                             | 72                    | 54 (75%)                                   |

Abbreviations: CONQUER, Collaborative National Quality and Efficacy Registry; DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography of the chest; mMRC, Modified Medical Research Council; SHAQ, Scleroderma Health Assessment Questionnaire; TLC, total lung capacity.
undergone HRCT whereas a positive anti-centromere antibody (OR 0.27; 95% CI: 0.12-0.61; \(P=0.008\)) and missing FVC percent predicted (OR 0.29; 95% CI: 0.10-0.80; \(P=0.005\)) were negatively associated with ever having undergone HRCT (Table 4).

There was a trend toward a positive association between crackles on pulmonary exam and ever having undergone HRCT (OR 2.28; 95% CI: 0.97-6.05; \(P=0.058\)), although this relationship did not reach statistical significance.

The 70 participants who did not undergo HRCT at any time during their disease course did not have one for the following reasons: the treating rheumatologist did not think it was clinically indicated (n = 25, 35.7%); the patient did not have insurance or insurance did not cover the cost of the HRCT (n = 2, 2.9%); HRCT was ordered but the patient did not have it done (n = 9, 12.9%); or the reason HRCT was not performed was unable to be determined (n = 34, 48.6%). Of the 25 participants (median disease duration 2.8 [IQR 1.1-3.8] years) in whom the treating rheumatologist thought HRCT was not clinically indicated, 72% were never smokers and 28% were ever smokers; 36% were anti-centromere antibody positive, 20% were anti-topoisomerase I antibody positive, and 20% were anti-RNA polymerase III antibody positive; 64% had the limited cutaneous subtype and 36% had the diffuse cutaneous subtype; 80% had an FVC 80% or more predicted and 8% had an FVC 80% or less predicted; and 48% had a DLCO 80% or more predicted and 24% had a DLCO less than 80% predicted. None of these 25 participants had crackles on auscultation of the lungs.

Table 3. Univariate associations with performance of HRCT

|                             | HRCT ever performed |            |            |
|-----------------------------|---------------------|------------|------------|
|                             | Odds ratio (95% CI) | \(P\) value |
| Age at baseline visit (y)   | 1.00 (0.98, 1.02)   | 0.937      |
| Sex                         |                     |            |            |
| Male                        | Reference           |            |            |
| Female                      | 1.05 (0.52, 2.01)   |            |            |
| Race                        |                     |            |            |
| White                       | Reference           |            |            |
| Black or African American   | 2.83 (1.09, 7.70)   |            |            |
| Other                       | 1.47 (0.58, 4.49)   |            |            |
| Ethnicity                   |                     |            |            |
| Not Hispanic or Latinx      | Reference           |            |            |
| Hispanic or Latinx          | 0.64 (0.30, 1.45)   |            |            |
| Ever smoker                 |                     |            |            |
| No                          | Reference           |            |            |
| Yes                         | 1.03 (0.60, 1.82)   |            |            |
| Disease duration (y)        | 1.03 (0.85, 1.23)   | 0.780      |
| Antinuclear antibody        |                     |            |            |
| Negative                    | Reference           |            |            |
| Positive                    | 1.51 (0.53, 3.78)   |            |            |
| Missing                     | 0.48 (0.12, 1.81)   |            |            |
| Anti-centromere antibody    |                     |            |            |
| Negative                    | Reference           |            |            |
| Positive                    | 0.32 (0.16, 0.65)   |            |            |
| Missing                     | 0.70 (0.38, 1.33)   |            |            |
| Anti-Scl-70 antibody        |                     |            |            |
| Negative                    | Reference           |            |            |
| Positive                    | 1.41 (0.77, 2.72)   |            |            |
| Missing                     | 0.95 (0.49, 2.46)   |            |            |
| Anti-RNA polymerase III antibody |                 |            |            |
| Negative                    | Reference           |            |            |
| Positive                    | 0.77 (0.40, 1.53)   |            |            |
| Missing                     | 0.58 (0.32, 1.06)   |            |            |
| Supplemental oxygen use     |                     |            |            |
| No                          | Reference           |            |            |
| Yes                         | 1.77 (0.48, 11.44)  |            |            |
| Crackles on exam            |                     |            |            |
| No                          | Reference           |            |            |
| Yes                         | 2.99 (1.39, 7.43)   |            |            |
| SSc subtype                 |                     |            |            |
| Limited cutaneous           | Reference           |            |            |
| Diffuse cutaneous           | 1.41 (0.83, 2.39)   |            |            |
| Modified Rodnan skin score  | 1.02 (0.99, 1.04)   | 0.242      |
| New York Heart Association  |                     |            |            |
| functional class            |                     |            |            |
| Class I, II                 | Reference           |            |            |
| Class III, IV               | 1.42 (0.57, 3.41)   |            |            |
| Participant global health   | 1.08 (0.97, 1.21)   | 0.163      |
| Physician global health     | 1.12 (0.99, 1.27)   | 0.081      |
| Physician global damage     | 1.11 (0.99, 1.26)   | 0.080      |
| SHAQ breathlessness score   | 1.06 (1.00, 1.19)   | 0.091      |
| mMRC dyspnea scale score    |                     |            |            |
| 0                           | Reference           |            |            |
| 1                           | 1.83 (0.96, 3.57)   |            |            |
| 2-4                         | 1.21 (0.58, 2.60)   |            |            |
| FACIT dyspnea score         | 1.01 (0.97, 1.06)   | 0.647      |
| FVC % predicted             |                     |            |            |
| ≥80%                        | Reference           |            |            |
| <80%                        | 2.82 (1.49, 5.69)   |            |            |
| Missing                     | 0.81 (0.40, 1.72)   |            |            |

(Continued)
Table 4. Multivariable-adjusted associations with performance of HRCT

| Predictor                          | HRCT ever performed | Odds ratio (95% CI) | P value |
|-----------------------------------|---------------------|---------------------|---------|
| Age at baseline visit (y)         |                      |                     |         |
| Male                              | 1.00 (0.98, 1.03)    | 0.659               |         |
| Female                            | 1.26 (0.57, 2.65)    | 0.560               |         |
| Race                              |                      |                     |         |
| White                             | Reference            |                     |         |
| Black or African American         | 2.51 (0.88, 9.06)    | 0.231               |         |
| Other                             | 1.07 (0.38, 3.59)    | 0.231               |         |
| Antinuclear antibody              |                      |                     |         |
| Negative                          | Reference            |                     |         |
| Positive                          | 1.69 (0.55, 4.66)    | 0.218               |         |
| Missing                           | 0.65 (0.14, 3.03)    | 0.008               |         |
| Anti-centromere antibody          |                      |                     |         |
| Negative                          | Reference            |                     |         |
| Positive                          | 0.27 (0.12, 0.61)    | 0.27                |         |
| Missing                           | 0.72 (0.35, 1.53)    | 0.058               |         |
| Crackles on exam                  |                      |                     |         |
| No                                | Reference            |                     |         |
| Yes                               | 2.28 (0.97, 6.05)    | 0.058               |         |
| Physician global health           | 0.96 (0.78, 1.14)    | 0.675               |         |
| Physician global damage           | 1.05 (0.96, 1.30)    | 0.497               |         |
| ≥80% FVC % predicted              | Reference            |                     |         |
| <80% FVC % predicted              | 1.84 (0.84, 4.25)    | 0.005               |         |
| Missing                           | 0.29 (0.10, 0.80)    | 0.005               |         |
| ≥80% TLC % predicted              | Reference            |                     |         |
| <80% TLC % predicted              | 1.46 (0.57, 3.94)    | 0.007               |         |
| Missing                           | 3.26 (1.53, 7.41)    | 0.007               |         |

Note: N = 343. Results are based on a multivariable model, adjusting for each of the predictors in this table.

Abbreviations: DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography of the chest; TLC, total lung capacity.

DISCUSSION

In this multicenter, observational study of 356 patients with SSc followed by SSc specialists at 13 expert SSc centers in the United States, we found that 80.3% of patients with SSc had undergone HRCT at some point during their disease course. In multivariable analyses, missing TLC percent predicted was positively associated with ever having undergone HRCT, whereas a positive anti-centromere antibody and missing FVC percent predicted were negatively associated with ever having undergone HRCT. The presence of crackles on pulmonary exam was also positively associated with ever having undergone HRCT, although this association did not reach statistical significance.

Our results are similar to those of a population-based study of SSc-ILD in Norway in which 650 out of 815 (80%) patients with SSc underwent HRCT (10). In that study, a statistically significantly greater proportion of patients who underwent HRCT than those who did not had the diffuse cutaneous subtype or were positive for anti-topoisomerase I or anti-RNA polymerase III antibodies (10). In our study, although a greater proportion of patients who underwent HRCT than those who did not had the diffuse cutaneous subtype or were anti-topoisomerase I antibody positive, these differences were not statistically significant.

In a survey of general rheumatologists and SSc experts regarding their HRCT ordering practices in newly diagnosed patients with SSc, Bernstein et al found that a greater proportion of SSc expert respondents than general rheumatologist respondents reported regularly ordering HRCTs in these patients (66% vs. 51%) (6). Although our study reports the proportion of patients with SSc followed at expert SSc centers who have undergone HRCT to screen for ILD, it remains unknown what percentage of patients with SSc followed in community or private practices or at medical centers without SSc centers have undergone HRCT to screen for ILD.

It has long been the practice of many rheumatologists, including SSc specialists, to order HRCTs to screen for ILD only in patients with SSc with certain clinical features associated with a high risk for ILD, such as those who are anti-topoisomerase I antibody positive or anti-centromere antibody negative, or those who have the diffuse cutaneous subtype or a diminished FVC percent predicted. Although there are certain clinical features that are predictive of severe or progressive ILD in patients with SSc, and others that seem to be “protective” against severe or progressive ILD, these features are not absolute. For example, in the population-based study of SSc-ILD in Norway, 114 of the 357 (37%) anti-centromere antibody positive patients who underwent HRCT had ILD (10). Moreover, of the 77 patients in that study with more than 10% fibrosis on HRCT, 10% were anti-centromere antibody positive—a feature that we tend to associate with decreased risk of severe or progressive SSc-ILD (10). Data now suggest that any degree of fibrosis on HRCT is associated with increased mortality: Hoffmann-Vold et al found that, among patients with SSc with normal-range FVCs of 80% to 100% predicted, those with any degree of fibrosis on HRCT may have clinically significant progression, further study is critical to better define the subgroup of patients who are at high risk of ILD progression and therefore warrant early intervention, a key goal of personalized medicine in SSc. Currently, there are two medications—nintedanib (11) and toclizumab (12)—approved by the US Food and Drug Administration (FDA) for the treatment of SSc-ILD. Given the mounting body of evidence about the importance of HRCT screening for SSc-ILD, these newly FDA-approved therapies, in addition to the existing therapeutic armamentarium of mycophenolate mofetil and cyclophosphamide (13,14) and the low radiation exposure associated with undergoing HRCT (ie, 2-4 mSv) (15), we encourage rheumatologists to perform HRCTs (in addition to PFTs) to screen for ILD in their newly diagnosed patients with SSc.
There are some limitations of our study. First, CONQUER participants were recruited from dedicated SSc centers. Therefore, our results may not be generalizable to patients with SSc followed by rheumatologists in other practice settings. Second, we were unable to adjust for site in the multivariable model because at some sites, 100% of participants underwent HRCT. Natural site variability and practices (eg, differences in ordering plethysmography to measure TLC) may therefore account for some of the results observed in the multivariable model. For example, at one of the CONQUER sites, 42 of the 49 (85.7%) participants who underwent HRCT were missing TLC percent predicted. Conversely, participants who did not undergo basic spirometry (eg, FVC) also likely did not undergo HRCT. Third, we do not collect insurance status or cost of HRCT in CONQUER. Finally, although some patients underwent HRCT a few years prior to CONQUER entry, 67% of participants who underwent HRCT did so within 1 year of CONQUER enrollment, and the median time between HRCT and CONQUER enrollment was only 0.4 (IQR 0.1-1.2) years.

There are several strengths of our study. CONQUER is the largest multicenter, prospective cohort of patients with SSc in the United States. Therefore, it provided an excellent platform in which to evaluate the use of HRCT to screen for SSc-ILD. It also enabled us to investigate the clinical characteristics associated with the performance of HRCT and to assess variability across SSc centers. Finally, the CONQUER investigators are all highly experienced in the conduct of clinical trials and observational studies in SSc and therefore were able to collect robust phenotypic data about CONQUER participants.

In summary, the majority of patients with SSc enrolled in CONQUER underwent HRCT to screen for SSc-ILD, although there was variability by site. A positive anti-centromere antibody was the key clinical variable inversely associated with performance of HRCT. Because HRCT is the gold standard diagnostic test for ILD, and PFTs lack sufficient sensitivity for the detection of SSc-ILD (4,5), future research should explore the use of HRCT to screen for ILD in patients with SSc followed in other clinical settings.

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 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.

Acquisition of data. Bernstein, Assassi, Castellino, Chung, Correia, Evin, Frech, Gordon, Skaug, Hant, Hummers, Sandorfi, Shah, Shanmugan, Steen, Khanna.

Analysis and interpretation of data. Bernstein, Khanna.

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