JSRD Journal of Scleroderma and Related Disorders

*Article*

Journal of Scleroderma and Related Disorders
1–11

DOI: 10.1177/2397198320985377
journals.sagepub.com/home/jso
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# Interstitial lung disease in systemic sclerosis quantification of disease classification and progression with high-resolution computed tomography: An observational study

**Johan Clukers[1], Maarten Lanclus[2], Dennis Belmans[3], Cedric Van Holsbeke[3], Wilfried De Backer[1], Dharshan Vummidi[4], Paul Cronin[4], Ben R Lavon[3], Jan De Backer[2] and Dinesh Khanna[5]**

## Abstract

**Introduction:** Systemic sclerosis–associated interstitial lung disease accounts for up to 20% of mortality in these patients and has a highly variable prognosis. Functional respiratory imaging, a quantitative computed tomography imaging technique which allows mapping of regional information, can provide a detailed view of lung structures. It thereby shows potential to better characterize this disease.

**Purpose:** To evaluate the use of functional respiratory imaging quantitative computed tomography in systemic sclerosis–associated interstitial lung disease staging, as well as the relationship between short-term changes in pulmonary function tests and functional respiratory imaging quantitative computed tomography with respect to disease severity.

**Materials and methods:** An observational cohort of 35 patients with systemic sclerosis was retrospectively studied by comparing serial pulmonary function tests and in- and expiratory high-resolution computed tomography over 1.5-year interval. After classification into moderate to severe lung disease and limited lung disease (using a hybrid method integrating quantitative computed tomography and pulmonary function tests), post hoc analysis was performed using mixed-effects models and estimated marginal means in terms of functional respiratory imaging parameters.

**Results:** At follow-up, relative mean forced vital capacity percentage change was not significantly different in the limited (6.37%; $N = 13$; $p = 0.053$) and moderate to severe disease (−3.54%; $N = 16$; $p = 0.102$) groups, respectively. Specific airway resistance decreased from baseline for both groups. (Least square mean changes −25.11% predicted ($p = 0.006$) and −14.02% predicted ($p = 0.001$) for limited and moderate to severe diseases.) In contrast to limited disease from baseline, specific airway radius increased in moderate to severe disease by 8.57% predicted ($p = 0.011$) with decline of lower lobe volumes of 2.97% predicted ($p = 0.031$).

**Conclusion:** Functional respiratory imaging is able to differentiate moderate to severe disease versus limited disease and to detect disease progression in systemic sclerosis.

## Keywords

Interstitial lung disease, systemic scleroderma, computer-assisted image analysis, multidetector-row computed tomography

Date received: 3 May 2020; accepted: 5 December 2020

[1]Faculty of medicine and health sciences, University of Antwerp, Antwerp, Belgium
[2]FLUIDDA Inc, Los Angeles, CA, USA
[3]FLUIDDA NV, Kontich, Belgium
[4]Division of Radiology, University of Michigan, Ann Arbor, MI, USA
[5]Division of Rheumatology, Department of Internal Medicine, University of Michigan Scleroderma Program, Ann Arbor, MI, USA

**Corresponding author:**
Dinesh Khanna, University of Michigan Scleroderma Program, Division of Rheumatology, Department of Internal Medicine, Suite 7C27, 300 North Ingalls Street, SPC 5422, Ann Arbor, MI 48109, USA.
Email: khannad@med.umich.edu

## Introduction

Systemic sclerosis (SSc) is a chronic multisystem autoimmune disease characterized by vascular and immune dysfunction, which leads to skin and internal organ fibrosis.[1,2] Systemic sclerosis–associated interstitial lung disease (SSc-ILD) is responsible for up to 20% of mortality in patients with SSc.[3] Although the prognosis of SSc-ILD is highly variable,[4] the presence of SSc-ILD has a great impact on health-related quality of life. High-resolution computed tomography (HRCT) is the most commonly used screening tool for interstitial lung disease (ILD) in patients with newly diagnosed SSc, as well as in those with unexplained decline in pulmonary function.[2] While 80%–90% of these SSc patients will display interstitial lung abnormalities on computed tomography (CT),[2,5] only 30%–40% will go on to develop clinically significant ILD.[2] Thus, while HRCT remains a vital part of SSc-ILD diagnosis, its optimal role of HRCT findings in diagnosis, monitoring, and prognosis remains to be determined.

Quantifying the extent of fibrosis on CT has demonstrated clinical significance in the context of ILD generally, including prediction of pulmonary function decline[6] and mortality risk.[7–9] Following advances in quantitative measurements of fibrosis,[10] quantitative computed tomography (qCT) has been shown promise as a tool for detecting treatment effects. Analysis of patients treated with cyclophosphamide in the Scleroderma Lung Study-I demonstrated stabilization in the extent of fibrosis, and correlated this with improvements in forced vital capacity (FVC), $D_{LCO}$, and breathlessness (as measured by the transition Dyspnea Index).[6,11]

Most of the available qCT methods make use of densitometric (high-attenuation areas) measurements or histogram signature mapping techniques (trained by an expert radiologist).[12] Functional respiratory imaging (FRI) is a novel qCT methodology which performs volumetric structural analysis of the lungs by segmentation of airway and vascular structures in addition to pure attenuation-based schemes.[13,14] This segmentation process also permits endpoints to be computed on a lobar level, intended to allow analysis of heterogeneity of findings. In addition, fluid flow simulations may be performed within these three-dimensional (3D) models of the airways, allowing for calculation of so-called "functional" endpoints (e.g. airway resistance).

In past studies with idiopathic pulmonary fibrosis (IPF) patients, airway changes detected by FRI were shown to be predictive of functional decline in patients with preserved FVC.[15] This suggests that regionalized structural quantification may be able to detect disease processes which lung-averaged densitometric endpoints fail to capture. Thus, the purpose of this observational study is to evaluate the use of FRI qCT endpoints in detecting changes in the airways and lung parenchyma associated with progressing disease in SSc-ILD patients, and observing the association between these changes and changes in pulmonary function tests (PFTs).

## Methods

### Study design

Participants were recruited from a specialized scleroderma clinic (single-site tertiary referral academic center). Patients at this clinic are invited to volunteer for an observational cohort for research purposes. This retrospective observational study selected patients from this longitudinal cohort, with data collection thus determined a priori. Participants were selected at random from this larger cohort by D.K. without background on the FRI method. No prior power calculation was conducted for statistical purpose. Study parameters for each patient were extracted from data collected via case report forms and housed in the REDCap database. This data extraction was performed by D.K.

### Patients

All 35 study participants (18 years of age or older) signed an Institutional Review Board (IRB)–approved informed consent (to participate in the above-mentioned database). They met the 2013 ACR/EULAR criteria for SSc,[16] and were chosen with or without the presence of ILD on HRCT, defined by the presence of bilateral, subpleural, lower lobe predominant distribution of either: (1) reticular and/or ground glass opacity, with or without traction bronchiectasis or (2) honeycombing (absence of a pattern that is predominantly nodular, cystic, peribronchovascular/central or upper lung predominant, mosaic attenuation, or consolidation). Patients were excluded if forced expiratory volume in 1 s (FEV1)/FVC was $<0.70$, suggestive of obstructive lung disease (Figure 1).

Patients included in this study were recruited from 21 October 2014 through 25 September 2017, and the minimum clinical follow-up of the selected patients in the observational cohort was 12 months. We captured PFTs and both inspiratory and expiratory thin-slice CT studies performed within a 1-month interval (maximum) during the initial visit at the clinic (i.e. start of clinical follow-up within the observational cohort). Scleroderma-associated serologies were assessed. For participants, the serology and HRCT data were captured based on chart review; PFTs were performed in the clinic at every visit. HRCT was performed in routine clinical care (i.e. follow-up or indication of worsening of disease), not on standard time points. We refer to the Supplementary material for CT settings and modalities.

Participants with ILD were retrospectively divided into two categories (i.e. disease severity classification), according to a prognostic algorithm integrating qCT fibrosis scores and PFTs. The classification method we applied is

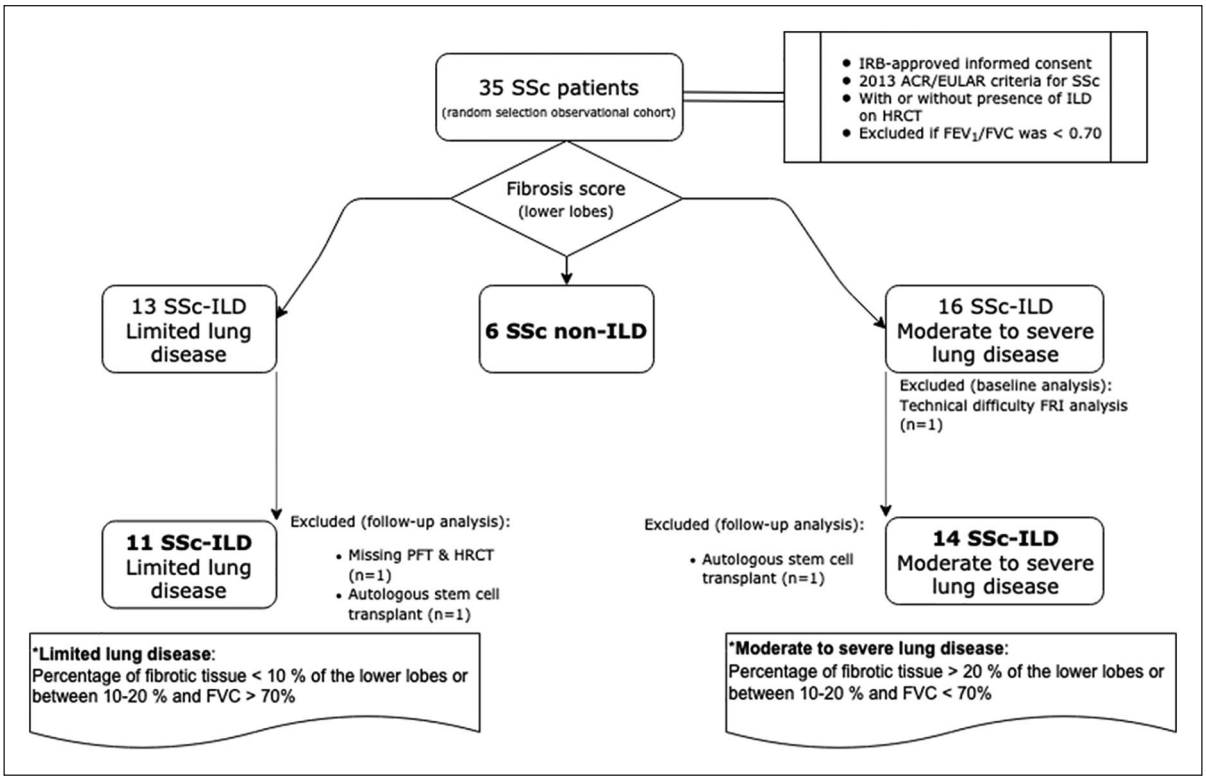


**Figure 1.** In- and exclusion criteria: flow diagram.

similar to that proposed by Goh et al.[7,17] Our algorithm determined extent of fibrosis using an automated computer program, and different cut-off points for ILD extent, to measure up to the differences in visual scoring and qCT-determined fibrosis (of the lower lobes only).

The first category was patients with moderate to severe lung disease (FRI percentage of fibrotic tissue (at total lung capacity (TLC)) >20% of the lower lobes or between 10% and 20% and FVC <70%). The second category of patients had limited lung disease defined as FRI percentage of fibrotic tissue (at TLC) <10% of the lower lobes or between 10% and 20% and FVC >70%.[7,17,18]

In addition, all HRCT scans were interpreted by fellowship-trained thoracic radiologists (D.V. and P.C.) who assigned the degree of total ILD extent on visual read as <10%, 10%–20%, and >20% without the knowledge of FRI classification. We assessed concordance for disease classification between visual read and FRI.

## *FRI analysis and statistics*

Two groups of patients were selected for analysis: patients with limited lung disease (one patient with missing follow-up PFT and HRCT) and patients with moderate to severe lung disease (one patient excluded due to technical difficulties with the FRI analysis). In addition, one patient in each group was treated with an autologous stem cell transplant, which has been shown to significantly influence disease progression on HRCT,[19] and was therefore excluded for follow-up analysis (in terms of both qCT and PFTs; Figure 1).

A detailed explanation of FRI methodology[15] is provided in the Supplementary material. Descriptive statistics were calculated as appropriate: mean and standard deviation, or median and interquartile range (IQR) for continuous measurements. Changes and difference in FVC for each group were assessed by (repeated measures) analysis of variance (ANOVA). Analysis of qCT measures was performed using linear mixed-effects models. Post hoc contrast assessments (baseline and follow-up) between different covariates were performed using estimated marginal means.

The following qCT parameters were computed with FRI for analysis: lobar volume (iVlobe) at TLC, image-based airway resistance (iRaw), specific image-based airway resistance (siRaw), image-based airway radius (iRADaw), specific image-based airway radius (siRADaw), image-based airway volume (iVaw), specific image-based airway volume (siVaw), image-based blood vessel volume (iVbV), and percentage of fibrotic tissue at TLC. In previous research in fibrotic lung disease using FRI, the parameters most sensitive to disease progression were lobe volumes, siRADaw, and percentage of fibrotic tissue at TLC and predicted lobe volume(s) at TLC[15] (Figure 2).

These parameters were determined for the whole lung, the lower lung zones (right and left lower lobes), and the

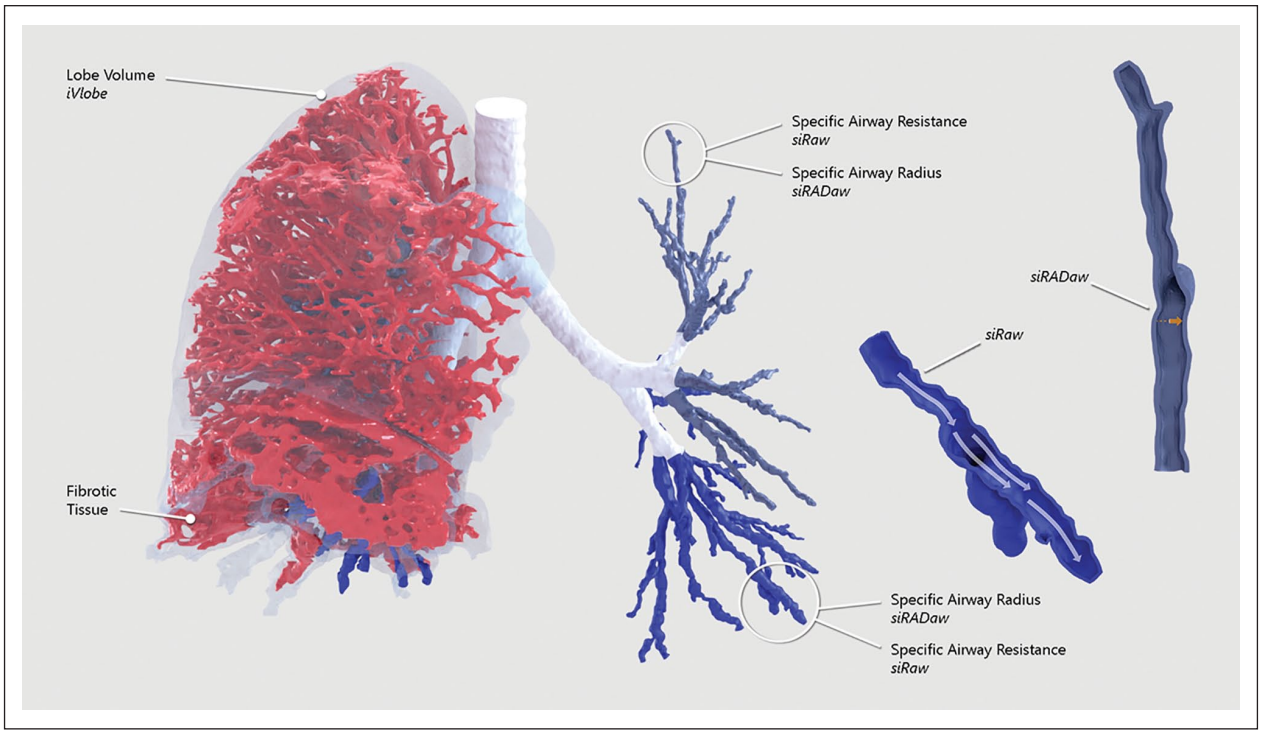


**Figure 2.** FRI measurements pictured on a patient case from the study cohort.

upper lung zones (right upper and middle lobe; left upper lobe). All analyses were performed using the open-source statistical environment R version 3.2.5 or higher (The R Foundation for Statistical Computing, Vienna, Austria). A part of the results of this study was presented in the form of an abstract/thematic poster session at the European Respiratory Society 2019 annual congress.[20]

## Results

Participants included 35 patients with SSc who had mean age of 51.6 years, 31 (88.6%) had diffuse cutaneous SSc, and mean disease duration of 3.7 years. In those with ILD ($n=29$), mean age was 52.7 years, 25 (86.2%) had diffuse cutaneous SSc, and mean disease duration was 4 years (Figure 1 and Table 1).

Population characteristics were similar between ILD groups. Mainstay of treatment consisted of daily oral mycophenolate mofetil in approximately 50% of participants (Table 2).

One patient (moderate to severe disease group) died during follow-up, but was included in the FVC and FRI analysis. Six participants who, after expert radiological and FRI assessment, did not have ILD on HRCT, were included in the baseline analysis as a reference for our SSc-ILD cohort. The interobserver agreement for disease classification (between FRI fibrosis score and visual read by an expert radiologist) was moderate (Cohen's weighted κ coefficient 0.59).

Subjects with ILD had HRCT at baseline and a second HRCT scan after approximately 1.5 years of follow-up ($n=25$; median time: 18 months (IQR 12–33)). There was no difference in follow-up time between groups in terms of HRCT (limited disease: median time is 18 months (IQR 13.75–35.25); moderate to severe disease: median time is 19 months (IQR 11.75–29.25), $p=0.81$).

A significant correlation was observed between FVC and lobar volumes at TLC in a mixed-effects model of all available HRCT studies ($n=55$; $R^2=0.43$, $p<0.001$). A positive correlation was shown between FVC and siRaw ($R^2=0.07$, $p=0.046$) and a negative correlation between FVC and siRADaw ($R^2=0.24$, $p<0.001$; Figure S1 in the Supplementary material).

In terms of disease severity (moderate to severe vs limited), relative mean FVC% change on PFT ($n=26$) showed trends toward a decline between baseline and follow-up in moderate to severe disease ($-3.54\% \pm 7.83\%$; $p=0.102$) and an increase in limited disease ($6.37\% \pm 9.64\%$; $p=0.053$), respectively. The relative mean FVC% change between groups differed significantly ($p=0.008$; Figure 3).

With regard to the SSc-non-ILD patients, a difference in total lobe volumes at TLC was observed from both limited and moderate severe diseases at baseline (least square mean difference 13.55% predicted; $p=0.028$ and 30.19% predicted; $p=<0.001$, respectively; Figure 4).

At baseline, all typical FRI parameters showed differences between participants with moderate to severe and limited diseases: FRI determined total lobe volumes (least

**Table 1.** Patient characteristics at baseline.

| Variable | All ($n=35$) | ILD ($n=29$) | Moderate to severe ($n=16$) | Limited ($n=13$) | No ILD ($n=6$) |
|---|---|---|---|---|---|
| Age, mean | 51.6 | 52.7 | 50.8 | 55 | 46.6 |
| Female sex, *n* (%) | 22 (62.9) | 19 (65.5) | 11 (68.8) | 8 (61.5) | 3 (50.0) |
| Race, *n* (%) | | | | | |
| White | 32 (91.4) | 27 (93.1) | 16 (100.0) | 11 (84.6) | 5 (83.3) |
| Black | 1 (2.9) | 0 (0) | 0 (0) | 0 (0) | 1 (16.7) |
| Other | 2 (5.7) | 2 (6.9) | 0 (0) | 2 (15.4) | 0 (0) |
| Ethnicity | | | | | |
| Hispanic | 3 (8.6) | 3 (10.3) | 1 (6.2) | 2 (15.4) | 0 (0) |
| Non-Hispanic | 31 (88.6) | 25 (86.2) | 15 (93.8) | 10 (76.9) | 6 (100) |
| Unknown | 1 (2.9) | 1 (3.4) | 0 (0) | 1 (7.7) | 0 (0) |
| Systemic sclerosis (%) | | | | | |
| Limited (%) | 4 (11.4) | 4 (13.8) | 2 (12.5) | 2 (15.4) | 0 (0) |
| Diffuse[a] (%) | 31 (88.6) | 25 (86.2) | 14 (87.5) | 11 (84.6)[a] | 6 (100) |
| Disease duration, mean ± SD (years) | | | | | |
| After first non-Raynaud's symptoms | 3.7 (3.2) | 4.0 (3.3) | 3.1 (1.7) | 5.1 (4.4) | 1.0 (0.2) |
| After first Raynaud's symptoms[b] | 3.9 (3.7) | 4.2 (3.9) | 4.1 (2.4) | 4.3 (5.3) | 1.0 (0.3) |
| After ILD diagnosis | 1.4 (1.3) | 1.4 (1.3) | 1.5 (1) | 1.2 (1.0) | NA |
| Modified Rodnan skin score, mean ± SD | 15 (11) | 15 (11) | 17.0 (9.5) | 12 (11.8) | 16.5 (14.6) |
| Autoantibodies (%) | | | | | |
| Anitnuclear Antibody | 33 (94.3) | 27 (93.1) | 15 (93.8) | 12 (92.3) | 6 (100) |
| Anti-centromere | 3 (8.6) | 3 (10.3) | 1 (6.3) | 2 (15.4) | 0 (0) |
| Anti-topoisomerase-I | 11 (31.4) | 10 (34.5) | 7 (43.8) | 3 (23.1) | 1 (16.7) |
| Anti-RNA polymerase 3 | 5 (14.3) | 4 (13.8) | 1 (6.3) | 3 (23.1) | 1 (16.7) |
| Anti-Ro | 5 (14.3) | 4 (13.8) | 2 (12.5) | 2 (15.4) | 1 (16.7) |
| Anti-U1 ribonucleoprotein | 3 (8.6) | 3 (10.3) | 1 (6.3) | 2 (15.4) | 0 (0) |
| ILD pattern ($n=29$) | | | | | |
| Non-Specific Interstitial Pneumonia (NSIP) | 26 (74.3) | 26 (89.7) | 13 (81.3) | 13 (100) | NA |
| Usual Interstitial Pneumonia (UIP) | 3 (8.6) | 3 (10.3) | 3 (18.7) | 0 (0) | NA |
| Other | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NA |
| Visual quantification of ILD extent HRCT | | | | | |
| <10% disease extent | 10 (28.6) | 10 (34.4) | 2 (12.5) | 8 (61.6) | NA |
| 10%–20% disease extent | 5 (14.3) | 5 (17.2) | 2 (12.5) | 3 (23.0) | NA |
| >20% disease extent | 14 (40.0) | 14 (48.3) | 12 (75.0) | 2 (15.4) | NA |
| No ILD | 6 (17.1) | NA | NA | NA | 6 (100) |
| PFT values (% predicted), mean ± SD | | | | | |
| FVC, % | 78.4 (21.4) | 75.1 (16.2) | 67.7 (15.5) | 84.2 (12.1) | 94.5 (13.2) |
| TLC, % ($n=13$) | 96.6 (29.4) | 91.2 (10.1) | 84.0 (7.2) | 94.3 (10.0) | 114.7 (13.9) |
| $D_{LCO}$, % ($n=33$) | 69.5 (28.3) | 62.6 (22.5) | 53.7 (22.9) | 73.8 (16.8) | 100.5 (17.6) |

SD: standard deviation; ILD: interstitial lung disease; PFT: pulmonary function test; FVC: forced vital capacity; TLC: total lung capacity; HRCT: high-resolution computed tomography; NA: not available.

[a]One patient had overlap with dcSSc.

[b]Two patients did not have Raynaud's phenomenon, and one patient's date of Raynaud's onset was unknown.

square mean difference −16.64% predicted; $p=0.0007$), siRADaw (least square mean difference 57.66% predicted; $p=0.0001$), and siRaw (least square mean difference −37.01% predicted; $p=0.24$; Figure 4). Patients with moderate to severe disease showed a decline from baseline in lobar volume in the lower lobes (least square mean change −2.97% predicted; $p=0.031$); no significant change from baseline was observed in the limited disease group (mean change −1.62% predicted; $p=0.496$; Figure 5).

Patients in the moderate to severe group showed an increase from baseline in siRADaw (least square mean change 8.57% predicted; $p=0.011$) and decrease in siRaw (change −14.02% predicted; $p=0.001$). In patients with limited disease, there was no change in siRADaw (least square mean change 2.55% predicted; $p=0.237$) and a significant decrease in siRaw (change −25.11% predicted; $p=0.006$) from baseline.

Finally, when considering FRI parameters at TLC (on a lobar level) at baseline and follow-up for both groups, differences were observed in the lower lobes for all FRI parameters of interest (FRI determined lobe volumes, siRaw, and siRADaw; Figure S2 in the Supplementary

**Table 2.** Background treatment according to disease severity.

| | Moderate to severe lung disease ($n=16$)[a] | Limited lung disease ($n=13$) [b] | No ILD ($n=6$) |
|---|---|---|---|
| Prednisone, *n* (%) | 4 (25) | 5 (38.5) | 1 (16.7) |
| Cyclophosphamide, *n* (%) | 3 (18.8) | 1 (7.7) | 0 (0) |
| Mycophenolate mofetil, *n* (%) | 8 (50) | 7 (53.8) | 3 (50) |
| D-penicillamine, *n* (%) | 0 (0) | 0 (0) | 0 (0) |
| Methotrexate, *n* (%) | 3 (18.8) | 0 (0) | 0 (0) |
| Plaquenil, *n* (%) | 0 (0) | 0 (0) | 1 (16.7) |
| Azathioprine, *n* (%) | 0 (0) | 0 (0) | 0 (0) |
| Rituximab, *n* (%) | 0 (0) | 0 (0) | 0 (0) |
| Abatacept, *n* (%) | 0 (0) | 0 (0) | 0 (0) |
| Autologous stem cell transplantation, *n* (%) | 1 (6.3) | 1 (7.7) | 0 (0) |

ILD: interstitial lung disease.
[a]Moderate to severe lung disease is defined as more extensive disease (FRI percentage of fibrotic tissue (at TLC) >20% of the lower lobes or between 10% and 20% of the lower lobes and FVC <70%).
[b]Limited lung disease is defined as FRI percentage of fibrotic tissue (at TLC) <10% of the lower lobes or between 10% and 20% and FVC >70%.

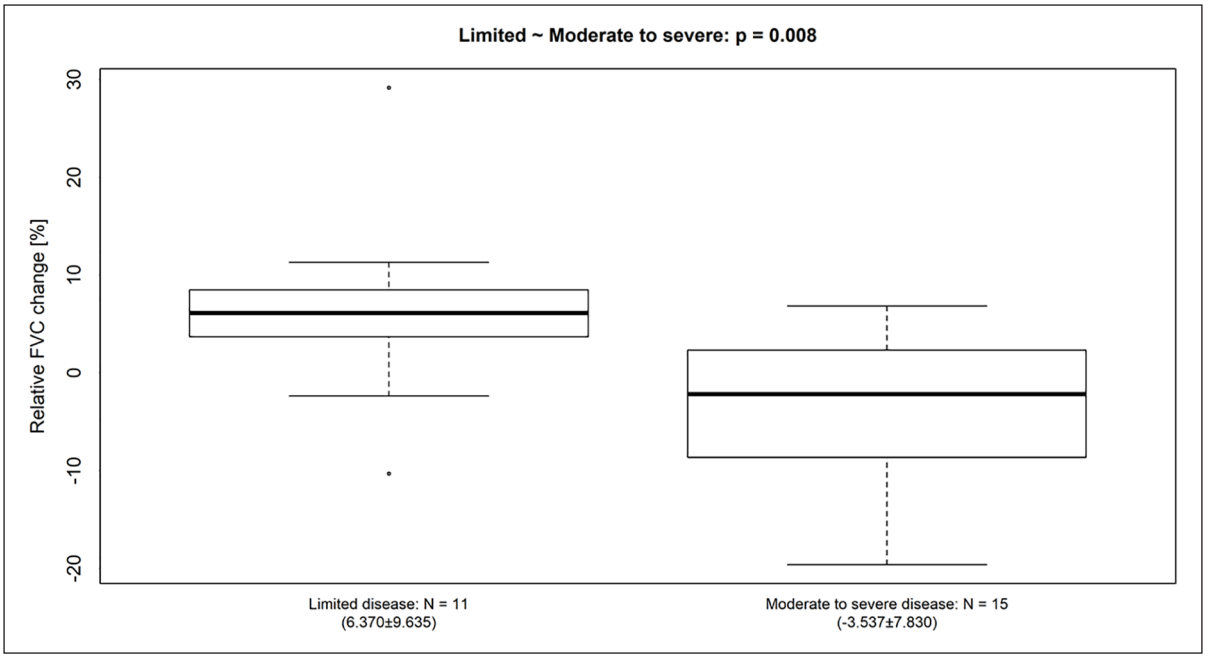


**Figure 3.** Relative change in forced vital capacity (FVC) (% predicted) from baseline to follow-up in limited and moderate to severe diseases.
[a]Moderate to severe disease is defined as more extensive disease (FRI percentage of fibrotic tissue (at TLC) >20% of the lower lobes or between 10% and 20% of the lower lobes and FVC <70%).
[b]Limited lung disease is defined as FRI percentage of fibrotic tissue (at TLC) <10% of the lower lobes or between 10% and 20% and FVC >70%.

material). The lower lobes were characterized by smaller FRI determined lobar volumes, lower siRaw, and larger siRADaw in the moderate to severe disease group.

## Discussion

This study offers preliminary evidence of the power of qCT methods to characterize fibrotic lung disease in patients with SSc.[8,9,21,22] We show that disease staging using a hybrid method incorporating PFTs and qCT quantification of fibrotic extent can differentiate moderate to severe versus limited ILD at baseline. Furthermore, this staging predicts FVC decline, with the severe group experiencing a significantly larger loss in FVC than the limited group, which experienced no decline.

We were able to show a statistically significant change, over a relative short time, in lower lobe volumes and airway diameter (siRADaw) in the moderate to severe lung disease group and a statistically significant change in airway resistance (siRaw) in both groups. This provides additional evidence that functional decline in SSc-ILD is related to changes in the airways which can be quantified using qCT.

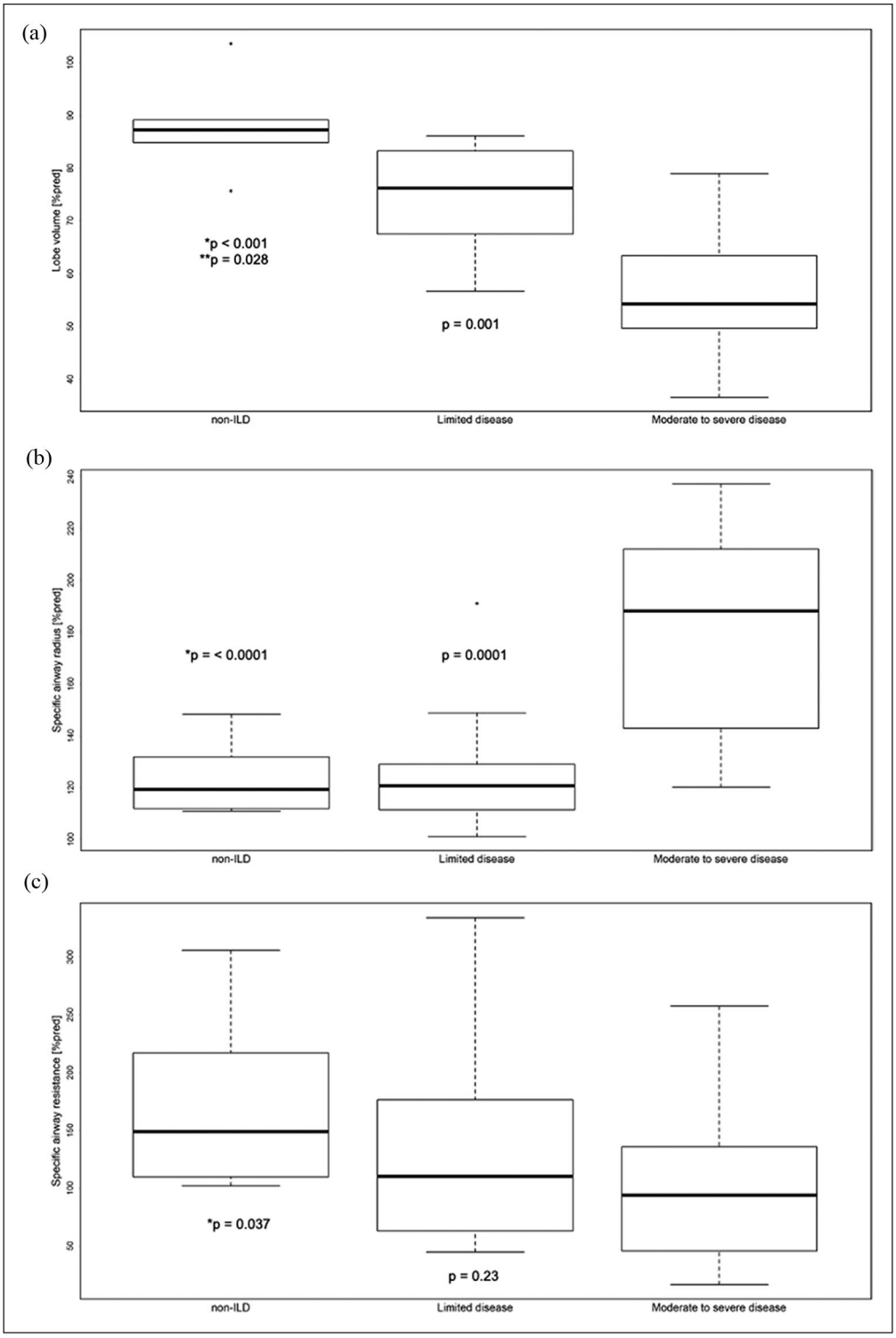


**Figure 4.** Baseline differences in non-ILD, limited, and moderate to severe diseases (inter-group) for (a) FRI determined volumes, *p*-value is the least square mean difference at baseline between limited and moderate to severe disease groups: **p*-value between non-ILD and moderate to severe disease and ***p*-value between non-ILD and limited disease, (b) specific image-based airway radius (siRADaw), *p*-value: least square mean difference at baseline between limited and moderate to severe disease group - **p* value: between non-ILD and moderate to severe disease and (c) specific image-based airway resistance (siRaw), *p*-value: least square mean difference at baseline between limited and moderate to severe disease group - **p* value: between non-ILD and moderate to severe disease.

The finding that progressive disease in SSc-ILD is correlated with siRADaw (i.e. airway volumes) is particularly noteworthy. In a recent study using FRI, similar correlations between airway and lobar volumes and FVC decline were observed in a cohort of 66 IPF patients.[15] IPF is another fibrotic lung disease, where the lower lobes are most affected

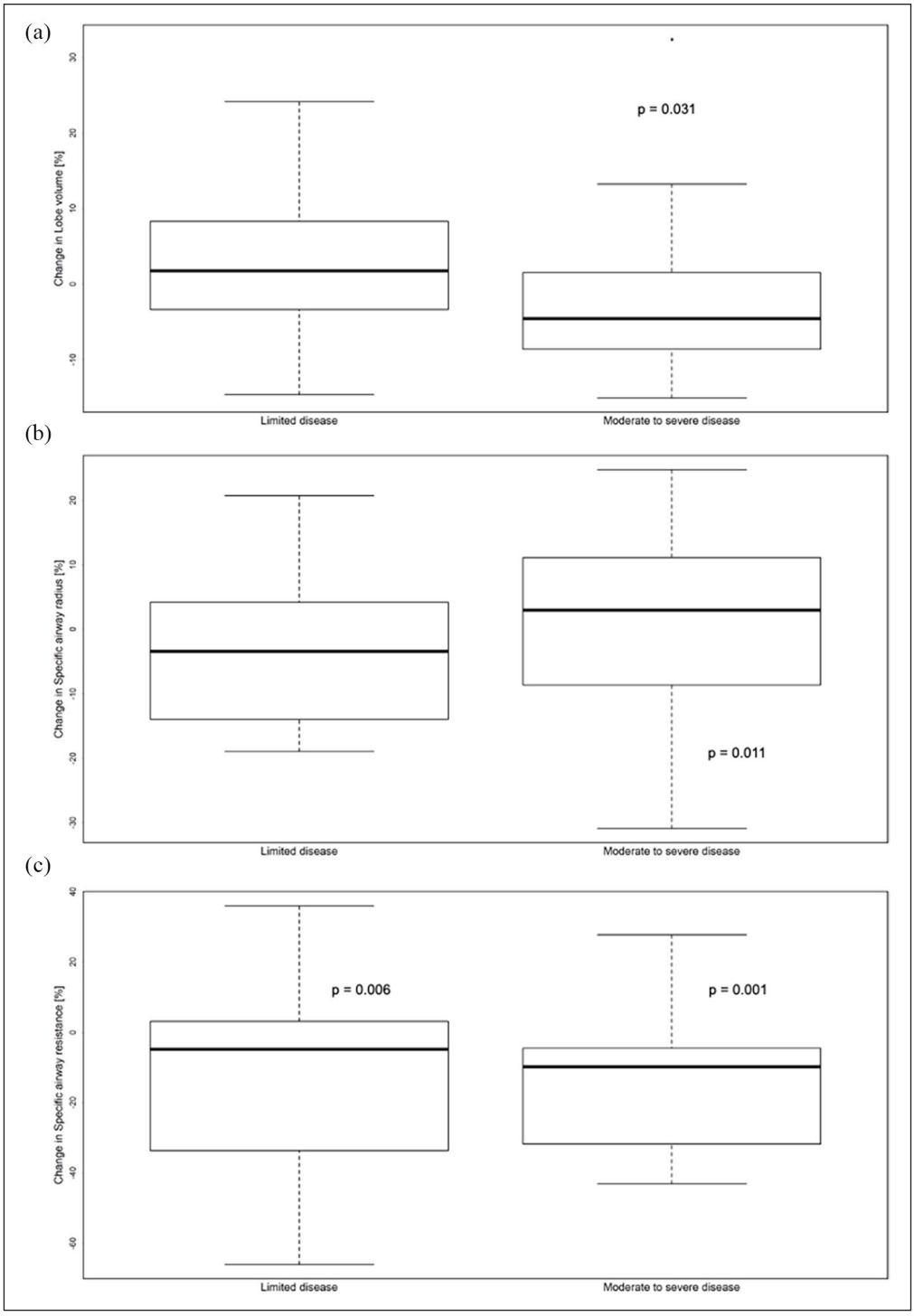


**Figure 5.** Relative changes from baseline to follow-up in limited and moderate to severe diseases (intra-group) for (a) FRI determined lower lobe volumes, (b) specific image-based airway radius (siRADaw), and (c) specific airway resistance (siRaw). *p*-value is the least square mean differences between baseline and follow-up.

throughout disease progression.[23] In the aforementioned study, airway dilation is hypothesized to result from a combination of the well-documented traction bronchiectasis as well as the re-distribution of intra-pulmonary pressure due to increased stiffness of the alveolar region.[15] Traction bronchiectasis in fibrotic lung disease shows to be a clear indicator of mortality and remains a significant predictor of a poor outcome, independent of other associated parenchymal interstitial lung disease patterns.[24] Evidence for the relation between the extent of traction bronchiectasis and

mortality in SSc-ILD in particular is less compelling, although this relation is well described for a broader group of patients suffering from connective tissue disease–related interstitial lung disease (CTD-ILD).[25,26] Fibrotic extent, and presumably by extension of the presence of traction bronchiectasis, is important in SSc-ILD because of correlation with progressive disease[27] and its observed responsiveness to treatment interventions.[6,28]

Another qCT method (Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER)) showed similar associations between tissue changes interpreted as a surrogate marker of ILD extent and mortality. CALIPER is a computer vision–based technique that includes volumetric local histogram and morphologic analysis to provide quantitative assessment of pulmonary parenchymal disease on HRCT data. CALIPER-determined pulmonary vessel volume (PVV) in CTD-ILD patients (a large proportion of whom suffered from SSc-ILD) shows predictive power for mortality.[29] Jacob et al.[30] explain this phenomenon by worsening fibrosis that causes an increase in vessel size and numbers in non-fibrotic regions of the lung, which is picked up by increase in CALIPER PVV, acting as a surrogate marker of ILD extent. We might expect, therefore, that siRADaw ought to show the same association with mortality.[15] In addition, quantitative lung fibrosis (QLF) makes use of texture-based analysis for scoring changes in lung fibrosis and interstitial lung disease using validated qualitative and quantitative methods.[11] QLF has provided pioneering work in the domain of SSc-ILD as an endpoint in clinical trials, supporting the results of PFT changes.[6,31]

Future studies should compare these qCT methods between themselves to better understand these disease markers. While various qCT methodologies differ considerably, they all share the benefit of minimizing observer subjectivity in interpretation of serial HRCT changes. This form of objective analysis may overcome the issue of the interobserver variability and could provide more consistent prognostic indexes.[30,32,33]

This study has several limitations. The number of patients is rather low. Repeatability of FRI measurements still has to be proven in SSc-ILD or other fibrosing ILD. The data have been retrospectively analyzed and virtually all patients had some form of background therapy, probably interfering with natural disease progression. This cohort comprised many patients suffering from diffuse cutaneous scleroderma. This is probably due to the recruitment from a single center (specialized scleroderma clinic). This issue poses limitations on the generalizability of our data. In addition, because of the slow progression of ILD in SSc[7,34] and low mortality rate in this cohort, we were not able to define clinically meaningful short-term changes in FRI parameters in relation to other clinical endpoints (i.e. evolution in respiratory-related patient-reported outcome, FVC changes in the longer term or mortality). Furthermore, the effect of comorbid pulmonary hypertension (often associated with SSc) on disease progression was not taken into account.[5] Despite this, a clear signal was seen from this small patient group. These initial observations support FRI as a useful qCT method to overcome the difficulties other larger clinical trials and observational studies faced[7,17,28] by reducing follow-up time and sample size.

In order to address the shortcomings and limitations mentioned above, use of FRI in a longitudinal prospective study of a larger cohort is warranted. The CTD-ILD working group, under the aegis of the Outcome Measures in Rheumatology (OMERACT) initiative, strongly recommends that future research should be focused on refinement of the measurement of disease progression. This could be done by integrating FVC change with a morphological measure of disease progression (such as serial HRCT) and exploration of strategies to integrate measures of disease progression with changes in dyspnea and quality of life in individual patients.[18,34] FRI parameters (siRaw, siRADaw, percentage of fibrotic tissue, and predicted lobe volume—all measured at TLC) seem promising at playing a vital role in resolving this issue.

## Conclusion

FRI—in terms of lower lobe volumes, siRaw, and siRADaw—can differentiate between moderate to severe and limited diseases, predict disease progression, and is able to detect short-term changes in SSc-ILD, independent of disease severity. These novel findings should be prospectively validated in earlier disease and other SSc-ILD cohorts, in conjunction with other measures of disease progression.

### Authors' note

This research adds a new perspective on the quantification of disease progression in interstitial lung disease in systemic sclerosis, using a detailed quantitative CT analysis method (functional respiratory imaging).

### Acknowledgements

The Editor/Editorial Board Member of Journal of Scleroderma and Related Disorders (JSRD) is an author of this paper; therefore, the peer review process was managed by alternative members of the Board and the submitting Editor/Board Member had no involvement in the decision-making process.

### Author contributions

J.C., M.L., J.D.B., and D.K. contributed to the conceptualization and data curation. J.C., M.L., D.B., C.V.H., W.D.B., D.V., P.C., J.D.B., and D.K. contributed to the formal analysis. J.C., M.L., J.D.B., and D.K. contributed to the investigation and methodology. The funding acquisition is not applicable for this study. J.C. contributed to the project administration. M.L., D.B., C.V.H., and J.D.B. contributed to the resources and software. J.C., M.L.,

D.B., C.V.H., W.D.B., D.V., P.C., J.D.B., and D.K. contributed to the validation. J.C. contributed to the visualization. J.D.B. and D.K. contributed to the supervision. J.C. contributed to the writing—original draft. J.C., D.V., P.C., W.D.B., B.R.L., J.D.B., and D.K. contributed to the writing—review and editing. J.C., M.L., D.B., C.V.H., W.D.B., D.V., P.C., B.R.L., J.D.B., and D.K. contributed to the final approval of the manuscript.

## Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.L., D.B., C.V.H., and B.R.L. are the employees of FLUIDDA Inc. D.V. reports personal fees and non-financial support from Boehringer Ingelheim, outside the submitted work. J.C., P.C. and W.D.B. have nothing to disclose. J.D.B. is the shareholder and employee of FLUIDDA Inc. D.K. reports personal fees from Actelion, personal fees from Astra Zeneca, grants and personal fees from Bayer, grants and personal fees from BMS, grants and personal fees from Boehringer Ingelheim, personal fees from Chemomab, personal fees from CiVi Biopharma, Inc., personal fees from Corbus, personal fees from CSL Behring, personal fees from Cytori, personal fees from Eicos, personal fees from EMD Serono, grants and personal fees from Genentech/Roche, personal fees from GSK, personal fees from Horizon, grants from NIH NIAID, grants from NIH NIAMS, grants from Pfizer, grants and personal fees from Sanofi-Aventis/Genzyme, personal fees from UCB Pharma, during the conduct of the study, and personal fees from AstraZeneca, outside the submitted work. He is the chief medical officer of Eicos Sciences, Inc.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Dr D.K. is funded by the NIH/NIAMS K24 AR063120 and Drs D.V., P.C., and D.K. are funded by the NIH/NIAMS R01 AR-07047 (awarded to Dr D.K.).

## ORCID iDs

Johan Clukers https://orcid.org/0000-0003-0021-8870

Cedric Van Holsbeke https://orcid.org/0000-0003-0248-841X

## Supplemental material

Supplemental material for this article is available online.

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