Automatic Quantitative Computed Tomography Evaluation of the Lungs in Patients With Systemic Sclerosis Treated With Autologous Stem Cell Transplantation

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Background/Objective: Interstitial lung disease stands among the leading causes of death in systemic sclerosis (SSc) patients. Autologous hematopoietic stem cell transplantation (AHSCT) has been proven superior to conventional immunosuppressive therapy in severe and progressive SSc. Here, pulmonary quantitative measurements were obtained in high-resolution computed tomography (HRCT) scans of patients with SSc before and after AHSCT.

Methods: The medical records of thirthy-three patients who underwent AHSCT between 2011 and 2017 were evaluated for clinical and tomographic features at baseline (pre-AHCST) and 18 months after the procedure. Quantitative analysis of HRCT images by a fully automated program calculated lung volumes, densities, attenuation percentiles, and vascular volume. Patients were divided into 2 groups, according to changes in forced vital capacity (FVC). The "best response" group included patients that had an increased FVC of 10% or greater, and the "stable response" group included those who had a decreased or an increased FVC of less than 10%.

Results: In the best response group (15 patients), there was reduction ($p < 0.05$) of mean lung density and density percentile values after AHSCT. In the stable response group (18 patients), there were no significant changes in lung volumes and pulmonary densities after AHSCT. Pulmonary HRCT densities showed moderate/strong correlation with function.

Conclusions: Quantitative HRCT analysis identified significant reduction in pulmonary densities in patients with improved pulmonary function after AHSCT. Lung density, as evaluated by the quantitative HRCT analysis tool, has potential to become a biomarker in the evaluation of interstitial lung disease treatment in patients with SSc.

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The present study was approved by the Research Ethical Committee of the University Hospital of Ribeirao Preto Medical School, University of São Paulo. As this was a retrospective observational study based on examinations already performed by the patients, with a clinical indication in the evaluation or follow-up of systemic sclerosis, free and informed consent term was waived. This work was elaborated according to the Brazilian Norms of Research Involving Human Beings.

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Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by skin fibrosis and visceral involvement.[1,2] Interstitial lung disease (ILD) and/or pulmonary hypertension (PH) can be detected in up to 90% of patients.[3] Despite therapeutic increments over the years, cardiopulmonary involvement remains as the main cause of death in SSc patients.[4,5] Autologous hematopoietic stem cell transplantation (AHSCT) has been proven effective in the treatment of patients with severe and progressive SSc. Three randomized studies have shown longer survival, better disease control, and higher quality-of-life scores after AHSCT, when compared with conventional treatment.[6–8] Results are especially encouraging for patients with ILD, because AHSCT promotes at least stabilization, if not improvement, of lung function.[9–11]

High-resolution computed tomography (HRCT) is highly accurate for the evaluation of ILD related to SSc. Main pulmonary findings on HRCT include ground-glass and reticular opacities, traction bronchiectasis, and honeycombing.[12] The most common pattern observed is nonspecific interstitial pneumonia (NSIP) as shown in Figure 1, although usual interstitial pneumonia may be also found in 25% to 40% of cases.[13,14] Other thoracic manifestations include mediastinal lymph node enlargement, esophageal dilatation, and indirect signs of PH, such as right-sided heart disease or enlargement of pulmonary artery and its branches.[15–17]

Quantitative analyses of chest HRCT images have been used in the evaluation of different lung diseases, mainly emphysema,[18] airway diseases such as asthma and cystic fibrosis,[19,20] and ILD.[21] Recent studies have suggested that quantitative HRCT can be considered a biomarker of the natural evolution of respiratory diseases, allowing to assess severity and prognostic risk and to monitor treatment, showing good correlation with pathological findings and functional tests.[22–24] These quantitative and functional imaging techniques can help in therapeutic decisions, especially in patients with heterogeneous clinical conditions and in those who are unable to complete pulmonary function tests.[25,26]

Therefore, in this study, pulmonary quantitative measurements were obtained from HRCT scans of patients with SSc before and after AHSCT, using a fully automated software, in order to correlate with functional pulmonary outcomes.

PATIENTS AND METHODS

Patients Population

In this medical records, observational study, 53 patients with SSc who underwent AHSCT at our institution, between January

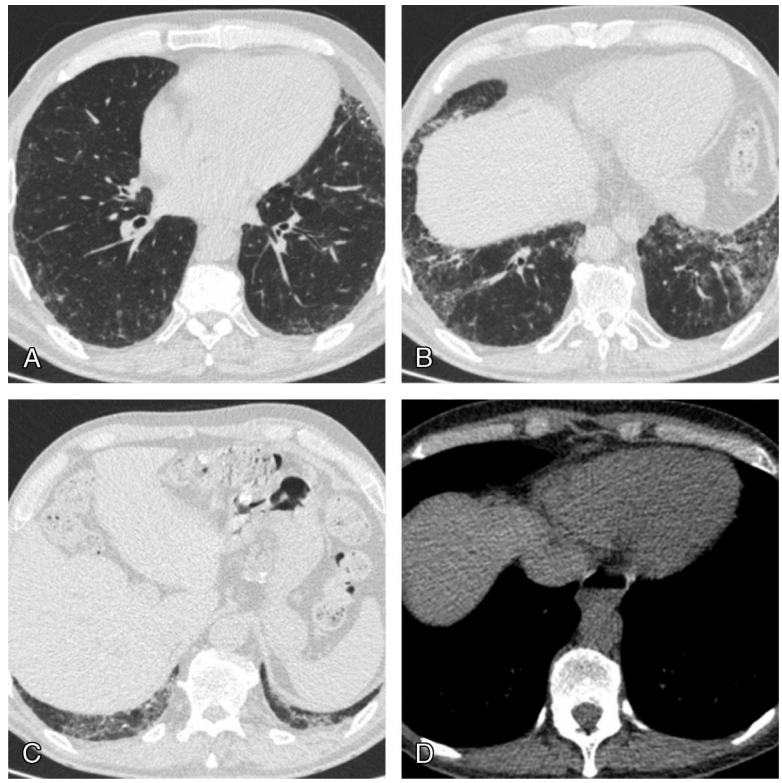

FIGURE 1. High-resolution computed tomography images of patients with SSc showing reticulations, ground-glass opacities, and traction bronchiectasis indicating an NSIP pattern (axial slices in lung window in A–C) and esophageal dilation (mediastinal window in D).

2011 and May 2017, were included. The transplantation protocol and inclusion and exclusion criteria have been previously reported.[27] Briefly, autologous hematopoietic stem cells were mobilized from the bone marrow to the peripheral blood with 2 g/m^2 of cyclophosphamide plus granulocyte colony-stimulating factor and subsequently harvested by leukoapheresis. Patients were subsequently treated with total dose of 200 mg/kg cyclophosphamide plus 4.5 mg/kg rabbit antithymocyte globulin in 5 days, followed by infusion of unmanipulated, previously cryopreserved autologous hematopoietic stem cells.

Pulmonary Function Tests

As part of standard care, all enrolled SSc patients had completed imaging and functional evaluations at the baseline (pre-AHSCT) and at 6, 12, and 18 months after AHSCT. Patient records were assessed for demographic data (sex, age), date of AHSCT, and pre- and post-AHSCT clinical information, including pulmonary function test results.

Considering the 18-month post-AHSCT time point, patients were divided into 2 groups, according to pulmonary response to treatment. Patients who had an increase of at least 10% in forced vital capacity (FVC) from baseline values were classified as the "best response" group, whereas those whose FVC changed less than 10%, in any direction (decline or increase), were labeled as the "stable response" group.[26]

High-Resolution Computed Tomography

All examinations included in this study were performed in multi–detector-row computed tomography (CT) scanners (Brilliance CT Big Bore 16 [Philips, Amsterdam, Netherlands] or Aquilion Prime 160 [Toshiba, Tokyo, Japan]) using the same high-resolution protocol as defined by the American Thoracic Society/European Respiratory Society[28,29]: volumetric acquisitions without intravenous administration of iodinated contrast medium, with 1-mm thickness acquisition at full inspiration and end expiration. Other typical acquisition parameters were as follows: kVp of 120, automatic mAs modulation (typically between 110 and 130), gantry rotation of 0.3 to 0.7 second, and radiation exposure of less than 5 mSv. The volumetric acquisitions were reconstructed with soft/standard filter and 1-mm thickness for quantitative evaluation. The HRCT pattern of ILD was defined as consensus by 2 radiologists according to the American Thoracic Society/European Respiratory Society 2018 guideline[28] based only on images from the baseline examination.

Quantitative CT Analysis

Quantitative automated analysis of HRCT images was performed with the scientific program Yacta version 2.7 (University of Heidelberg, Heidelberg, Germany).[30] The Yacta program can be installed on a Windows-based computer and works fully automatic, requiring no user intervention at any point of analysis. The software anatomically separates lung parenchyma, airways, and blood vessels of the entire lung, right and left lungs, and at pulmonary lobes using attenuation thresholds and anatomical recognition algorithms. Among analysis results, the Yacta software provides quantitative values of lung volumes and densities and histogram of parenchyma density (including mean, percentiles, and emphysema quantification) and of pulmonary vascular volume (PVV) for each lobe (Fig. 2).

In this study, the following quantitative CT measurements were evaluated in baseline and post-AHSCT examinations of SSc patients: pulmonary volume (mL); mean pulmonary density (in Hounsfield units [HU]); percentiles of lung densities: P10th, P40th, P50th, P80th, and P90th (HU); and PVV (mL).

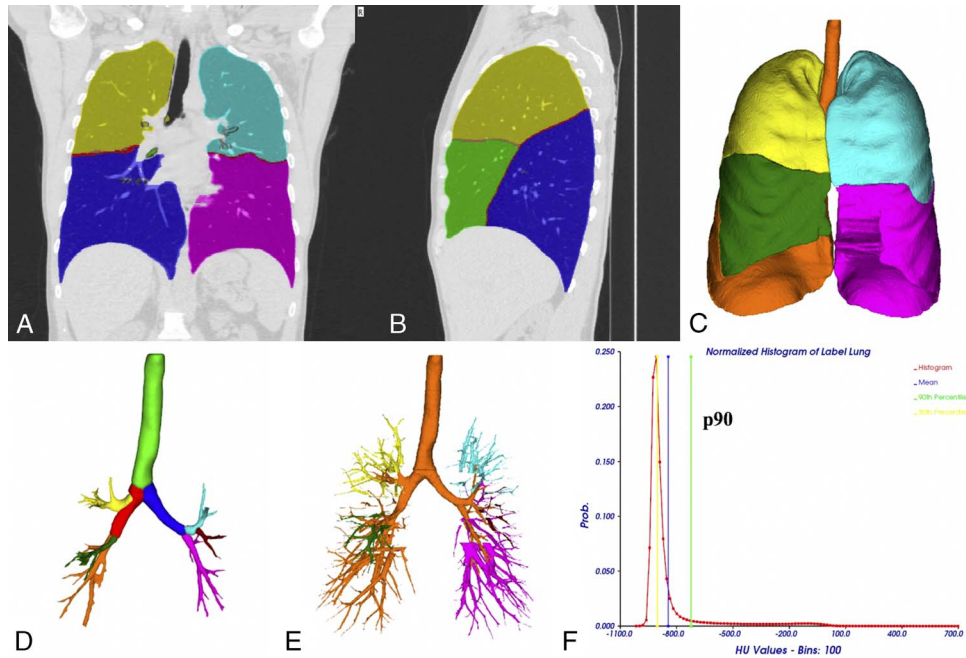

FIGURE 2. Example of the automatic segmentation performed by Yacta software with identification of pulmonary fissures and separation of pulmonary lobes in images represented in A, B, and C (yellow = right upper lobe, green = medium lobe, dark blue = right lower lobe, blue clear = upper left lobe; pink = lower left lobe). In D, segmentation of the tracheobronchial tree is observed, and in E, segmentation of pulmonary vasculature is shown. In F, density histogram of the lungs, including percentile 90 (p90), is highlighted.

Statistical Analysis

All data were analyzed using the statistical analysis program GraphPad Prism, version 7.0 (GraphPad Software, San Diego CA). Baseline and 18-month post-AHSCT data were selected for statistical analysis. The Shapiro-Wilk normality test was used to verify the normality of data distribution. For data with normal distribution, comparisons between groups were performed with unpaired *t* test, while analysis of each group was done with paired *t* test. For data with nonnormal distribution, comparison between groups was performed using Mann-Whitney *U* test, whereas pre- and post-AHSCT analysis was done with Wilcoxon test. Correlation analysis between quantitative CT parameters and function was done with Pearson coefficient for normal distribution data, or with Spearman correlation coefficient for nonnormal distribution data. $p < 0.05$ was considered statistically significant.

RESULTS

Patients

All patients met the 1980 American College of Rheumatology and/or the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc diagnosis.[31] Data from 53 patients were initially included for analysis in the present study. Twenty patients were excluded because of irregular follow-up, absence or insufficient quality of HRCT scans, or inadequate lung function tests at evaluated time points, resulting in a final cohort of 33 patients. In the studied population, the predominant pattern of ILD was NSIP, accounting for 61% of the baseline HRCT classification, followed by an alternative diagnosis without specific categorization, which was observed in 12% of the patients. Only 1 patient had a usual interstitial pneumonia pattern. The best response group consisted of 15 patients (11 females), with mean age of 32.1 (SD, 13.5) years. The stable response group consisted of 18 patients (14 females), with mean age of 37.5 (SD, 9.6) years. At baseline, there was no significant difference in age, sex, and pulmonary function test values between groups (Table 1).

Posttransplantation Evaluation

In the best response group, statistical analysis showed significant increase in absolute and predicted values of FVC at 18 months, when compared with pre-AHSCT (baseline), whereas in the stable response group there was no significant change in these parameters (Table 2). It is also important to comment that no patient had FVC reduction greater than 10% after AHSCT in both groups.

The Yacta program was able to segment and analyze all HRCT images of the 33 patients included in this study, measuring total lung volume, mean lung density, and density percentiles for lungs and lobes separately. There were minor segmentation errors in 4 examinations because of marked esophageal dilatation or excessive gas content in the gastric fundus or transverse colon, which were interpreted by the software as part of the lungs. Such errors were corrected manually in the Yacta program.

At baseline, the best response and the stable response groups showed similar values for lung volume and lung densities evaluated by quantitative CT ($p > 0.05$). Table 2 presents the results of the automatic analyses of pulmonary volumes and densities in HRCT at baseline and 18-month post-AHSCT. There were no significant changes in lung volumes at 18 months after AHSCT, when compared with baseline values, in both groups. In the best response group, mean lung density decreased at 18 months after AHSCT. Percentile analyses in this group of patients, from P10 to P90, also showed decreased lung density at 18 months, when compared with pre-AHSCT. In the stable response group, there were nonsignificant changes of mean and percentile lung densities 18-month posttransplantation as evaluated with quantitative CT analysis. When vascular volumes were analyzed by Yacta

TABLE 1. Demographic and Clinical Features (Baseline Values) of Patients With SSc Who Underwent AHSCT

Characteristic	"Best Response" Group	"Stable Disease" Group
Patients n	15	18
Female n (%)	11 (73%)	14 (78%)
Age, y	32.1 (13.5)	37.5 (9.6)
FVC, L	2.46 (0.81)	2.75 (0.62)
FVC%	68.4 (17.9)	72.5 (15.8)
Tiffeneau index, %	113.9 (9.6)	113.4 (8.4)
FEV_1 (L)	2.21 (0.72)	2.41 (0.54)
FEV_1%	77.5 (19.0)	81.9 (18.3)
DLCO	61.0 (10.8)	77.7 (19.3)

Values are expressed as mean ± SD. "Best response" group: patients who had an increase ≥10% of FVC compared with baseline after 18 months; "stable disease" group: patients who had changes less than 10% on FVC in any direction.

DLCO indicating diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in first second; FEV_1%, predicted FEV_1; FVC%, predicted FVC; Tiffeneau index, FEV_1/FVC ratio.

software, nonsignificant reductions were observed at 18 months after AHSCT, also in both groups of patients.

Comparison of quantitative CT and functional parameters for all patients (n = 33) showed significant correlation values between lung densities and function in both baseline and 18-month post-AHSCT analysis, with moderate/strong negative relationships (Table 3). Stronger negative correlations were obtained in the comparison between P90 of lung density and values of FVC at 18-month posttransplantation, showing that a higher amount of high attenuation areas (HU) in lung parenchyma correlates with lower values of FVC after treatment (Fig. 3).

DISCUSSION

In this study, SSc patients who underwent AHSCT in our center were evaluated for pulmonary function and quantitative CT, before and after transplantation. A fully automatic quantitative analysis program was used to measure pulmonary volumes and densities in chest HRCT images. Patients were divided into 2 groups according to lung function (FVC) outcomes after AHSCT. Patients in the best response group, who improved at least 10% in FVC from baseline, showed significant reduction in pulmonary density parameters at 18 months after transplantation. Lung densities on CT showed moderate/strong negative correlation with pulmonary function on baseline and posttransplantation examinations.

High-resolution CT plays key role in the diagnosis of ILD in SSc patients and is the imaging method of choice for assessing lung involvement.[32] An analysis of the European Scleroderma Trials and Research showed that ILD was present in up to 53% of a cohort of 3656 SSc patients.[33] In initial studies, 100% of autopsied patients had pulmonary involvement,[34] whereas up to 90% of patients had interstitial abnormalities on HRCT,[35] and only 40% to 75% presented alterations in pulmonary function tests.[36] It is well established that cardiopulmonary disease is the main cause of morbidity and mortality in SSc[36,37]; therefore,

TABLE 2. Main Functional and Quantitative CT Parameters (Lung Volumes and Densities) in Patients With SSc, Before and After AHSCT

Parameter	Baseline	18 mo Post-AHSCT	*p* value
"Best response" group			Baseline vs. 18 mo
FVC, L	2.46 ± 0.78	3.02 ± 0.84	0.0001[a]
FVC%	68.4 ± 17.34	81.93 ± 19.56	0.001[a]
Total lung volume, mL	3492.8 ± 1112.8	3792.47 ± 1123.13	0.07
Mean lung density, HU	−761.67 ± 40.9	−786.13 ± 34.31	0.01[a]
P10, HU	−885.67 ± 28.18	−898.27 ± 27.91	0.02[a]
P40, HU	−842.27 ± 36.98	−862.8 ± 33.39	0.01[a]
P50, HU	−825.47 ± 40.49	−849.47 ± 35.53	0.01[a]
P80, HU	−703.93 ± 65.60	−741.4 ± 54.40	0.008[a]
P90, HU	−530 ± 68.99	−576.8 ± 52.16	0.005[a]
Vascular volume, mL	66.47 ± 21.37	57.6 ± 10.77	0.06
"Stable disease" group			Baseline vs. 18 mo
FVC, L	2.75 ± 0.61	2.75 ± 0.61	0.93
FVC%	72.44 ± 15.33	71.72 ± 17.36	0.65
Total lung volume, mL	3880.78 ± 911.43	4079.67 ± 830.53	0.05
Mean lung density, HU	−764.61 ± 67.16	−780.72 ± 42.05	0.14
P10, HU	−885.28 ± 47.21	−896.05 ± 26.51	0.18
P40, HU	−844.61 ± 62.50	−861.22 ± 34.87	0.08
P50, HU	−827.72 ± 70.45	−846.72 ± 39.02	0.08
P80, HU	−708.67 ± 103.8	−732.11 ± 75.20	0.11
P90, HU	−545.44 ± 94.95	−559.22 ± 76.91	0.23
Vascular volume, mL	70.39 ± 29.86	66.83 ± 21.91	0.24

Values expressed as mean ± SD. "Best response" group: patients who had an increase ≥10% of FVC compared with baseline after 18 months; "stable disease" group: patients who had reduction, stability or increase <10% on FVC.

[a]$p < 0.05$ was considered statistically significant.

P10–P90 indicates percentile distribution of lung densities.

TABLE 3. Correlations of Lung Densities (Automatically Measured on CT Images) and FVC Values for All Studied Patients With SSc, Before and 18 Months After AHSCT

CT Parameters	Baseline FVC	Baseline FVC%	Post-AHSCT FVC	Post-AHSCT FVC%
Mean lung density	−0.3841[a]	−0.3568[a]	−0.6523[a]	−0.4436[a]
P10	−0.3790[a]	−0.3298	−0.6107[a]	−0.3481[a]
P40	−0.3830[a]	−0.3561[a]	−0.6261[a]	−0.3915[a]
P50	−0.3734[a]	−0.3540[a]	−0.6299[a]	−0.3965[a]
P80	−0.3680[a]	−0.3507[a]	−0.6186[a]	−0.4191[a]
P90	−0.4226[a]	−0.3692[a]	−0.6676[a]	−0.5093[a]

[a]$p < 0.05$ was considered statistically significant.

FVC% indicates predicted FVC; P10–P90, percentile distribution of lung densities; r = correlation coefficient.

new, accurate, and reproducible methods for evaluation of pulmonary involvement are warranted.

Previous studies have shown that AHSCT leads to improvements in functional capacity, with increased FVC values in SSc patients.[6,7,38] The majority of patients evaluated in this study showed stability or improvement of the respiratory function, demonstrated by higher values of FVC after 18 months of transplantation, corroborating previous published results. The ASSIST study, for example, showed improvement of pulmonary function and involvement of the skin 12 months after AHSCT, with sustained improvement up to 24 months.[7]

The main finding of this study was the significant reduction in pulmonary density values measured in HRCT of patients in the best response group after AHSCT, showing correlation with pulmonary function, which was stronger for the parameter related to higher-density pulmonary areas (namely, 90th percentile). We believe that this result reflects the regression of inflammatory manifestations (lung opacities) in the background of the chronic pulmonary fibrotic disease, corroborating the improvement in FVC. Inflammation usually precedes fibrosis and is potentially reversible; therefore, early treatment may benefit patients with ILD.[32] To date, there is no treatment capable of reversing well-established pulmonary fibrosis, but there is evidence that it may be possible to reduce and even stabilize progression.[39] Thus, control of inflammation and prevention of fibrosis progression are currently the most realistic goals in treatment of SSc patients with ILD.[32] Precise and reproducible biomarkers are needed to identify and monitor response to treatment.

Previous studies have quantitatively analyzed HRCT chest images in SSc and ILD patients.[26,40,41] However, no study has used a fully automatic program capable of performing pulmonary, lobar, vascular, and airway segmentation, evaluating in a more precise manner the tomographic characteristics of the pulmonary parenchyma.[42,43] Previous studies have evaluated the performance of computer-aided methods for quantifying ILD in SSc patients, demonstrating strong correlation with conventional visual scores and significant negative correlation with pulmonary function tests (FVC and carbon monoxide diffusion).[44] Quantitative ILD HRCT analysis can also identify patients with SSc with severe oxygen desaturation during the 6-minute walk test without significant

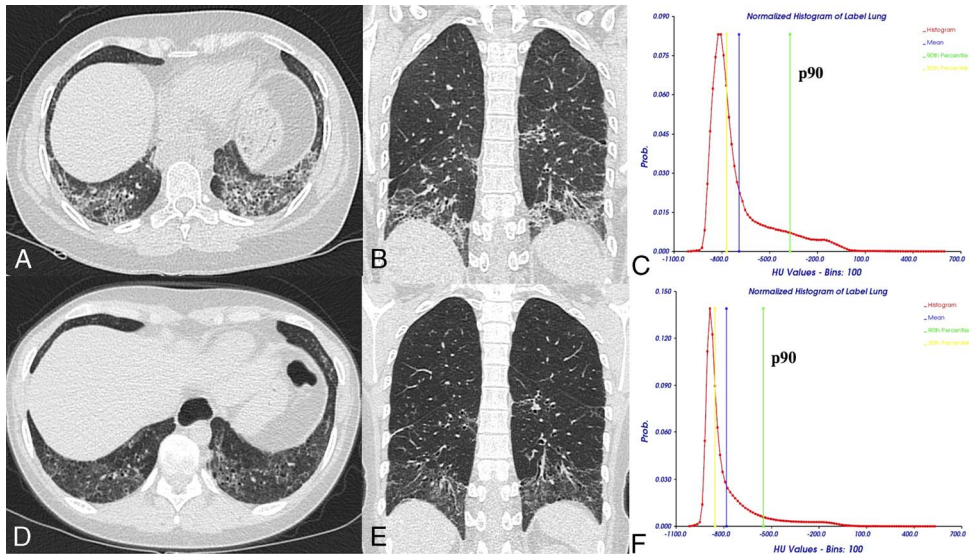

FIGURE 3. Representative images of a 28-year-old woman with SSc and pulmonary interstitial disease (NSIP pattern) included in the best response group. High-resolution computed tomography images (A, axial; B, coronal, lung window) and histogram of densities (C) are shown before AHSCT. In D, E, and F, HRCT images (D, axial; E, coronal, lung window) and the histogram of densities (F) 18 months after AHSCT, showing reduction of pulmonary opacities with concurrent changes in histogram pattern, with reduced lung densities, including p90, and narrowing of the distribution curve of density values. In this patient, FVC increased from 1.97 L to 2.42 L, and the p90 value decreased from –462 HU to –558 HU. Color online-figure is available at http://www.jclinrheum.com.

intraobserver and interobserver variability.[45] In addition, 85th percentile pulmonary density was previously described as a potential indicator of the presence of PH in SSc patients with ILD.[46] Similar to what is demonstrated in this study, but using different methodology, a previous report has shown that quantitative HRCT analysis of lung volumes and densities in patients with SSc and ILD has good correlation with pulmonary function and clinical evaluation after AHSCT.[26]

Mean PVV, as evaluated by HRCT, was not significantly reduced after AHSCT, in any of the studied groups. This parameter was included in analysis because previous studies have suggested a role of pulmonary vascular measurements in diagnostic and prognostic evaluation of patients with ILD[47] and in characterization of PH.[43] Further investigation will be necessary to fully address the role of pulmonary vasculature as evaluated by CT in patients with SSc.

Although medical records review at a single center, this study was able to associate imaging and functional outcomes of transplanted SSc patients. Our results are comparable to those from other international centers.[26] A larger cohort of patients would probably allow the use of more powerful statistical tools, correlations, and comparisons. Nevertheless, in this study, unequivocal reduction of lung density measurements after AHSCT in the group of patients with better functional pulmonary outcomes was shown. Despite a few processing errors, easily detected and readily corrected, the Yacta software applied to clinical routine HRCT images may be considered a reliable tool, fully automatic and robust. Future studies may address reproducibility and application in different scenarios and even evaluate such densities percentile data in a lobar level, which may have a better statistical correlation when compared with the whole lung. Pulmonary function tests, which are standard of care for SSc patients' lung evaluations, were used in our study as comparison for the evaluations of quantitative CT. However, one must consider that pulmonary function tests are observer- and patient-dependent and therefore subject to variation and inaccuracy. In addition, results of carbon monoxide diffusion tests, a more sensible pulmonary function measurement, were not available for analysis in all patients.

In conclusion, this study corroborates the feasibility of quantitative HRCT analysis as a tool to assess ILD in SSc, including its role to monitor response to treatment of pulmonary involvement, as a complementary evaluation to pulmonary function tests, or even as a replacement in cases in which a patient cannot adequately perform them. With development of increasingly faster CT scanners and exponential improvements in image quality and reduced exposure to radiation, we believe that differences between acquisition techniques and imaging processing will become less important, enhancing the applicability of quantitative HRCT in clinical routine.

KEY POINTS

(1) HRCT images of the lungs can be evaluated in an objective and quantitative manner using an automated software.
(2) Increase in FVC after AHSCT correlates with reduction of lung densities as automatically evaluated by HRCT.
(3) Quantitative CT analysis may represent a biomarker in treatment evaluation of ILD in patients with SSc undergoing AHSCT.

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