Software-Based Quantitative Analysis of Lung Parenchyma in Patients with Systemic Sclerosis May Provide New Generation Data for Pulmonary Fibrosis

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September 16, 2020

Abstract

Objectives: To investigate lung volume and density in patients with SSc and changes in these parameters due to PF, using a software-aided image quantification method, and compare this with a matched healthy control group. Methods: Thoracic high-resolution computed tomography (HRCT) images of patients and controls were analyzed using Myrian XP Lung 3D software. Right, and left lung densities and volumes were calculated separately by a blinded operator. Results were analyzed between subgroups to investigate associations with the clinical features. Results: A total of 135 patients with SSc and 38 healthy controls (HC) were included. Characteristics of the SSc patients were 94 (69.6%) without PF, 85.4% female, mean age 49.8 (15.4) years; 41 (30.4%) with PF, 88.3% female, mean age 50.2 (11.5) years and HC group were 89.5% Female, mean age 52.2 (5.8) years. The right and left lung densities were significantly higher, and right and left lung volumes were significantly lower in the SSc patients with signs of fibrosis than those without and HC ($p<0.001$ and $p<0.001$; $p=0.006$ and $p=0.002$, respectively). After excluding patients with PF, right and left lung densities and volumes differed significantly between diffuse cutaneous SSc, limited cutaneous SSc, and HC ($p=0.002$ and $p<0.001$; $p=0.045$ and $p=0.044$, respectively). Patients who developed PF during follow-up had significantly lower baseline right and left lung densities than those who did not ($p=0.018$; $p=0.014$, respectively). Forced vital capacity and carbon monoxide diffusing capacity showed weak correlation with lung densities and volumes in patients without PF and moderate to high correlation in PF patients. Conclusion: Lung density and volume in SSc patients changed significantly in those with PF and those without. Quantitative information extracted by soft-ware aided methods may contribute more to the detection, screening, and risk prediction in SSc related PF.

Key-Points:

Soft-ware aided quantification of the lung in SSc patients showed decreased lung density and volume in patients with pulmonary fibrosis.

INTRODUCTION

Systemic sclerosis (SSc) is a life-threatening, immune-mediated rheumatic disease characterized by fibrosis of the skin and internal organs and vasculopathy. SSc may affect almost every organ, but usually the skin, lung, heart, gastrointestinal tract, and peripheral circulation.

Lung involvement is one of the leading causes of morbidity and mortality [1]. Postmortem examination reveals signs of pulmonary fibrosis (PF) in approximately 80% of SSc patients [2]. Major risk factors for the development of PF include diffuse cutaneous SSc (dcSSc), African American race, older age at disease onset, shorter disease duration, presence of anti-Scl-70 antibodies, and absence of anticentromere antibodies [3]. It has been reported that there is a close association between thoracic computed tomography (CT) patterns and histopathological findings in surgical lung biopsy specimens which has resulted in the widespread use of

high-resolution computed tomography (HRCT) to identify the lung pathology due to fibrosis [4-5]. Thoracic HRCT scanning plays a central role in detecting lung fibrosis in SSc. Compared to HRCT, pulmonary symptoms, chest radiography, pulmonary function tests, and bronchoalveolar lavage (BAL) have limited diagnostic accuracy and availability, especially when lung disease is less advanced. HRCT may identify abnormalities in up to 44% of the patients with apparently normal chest radiographs [6].

Despite major advances in diagnosis, SSc-related PF is challenging for clinical management because treatment options are still limited. However, it has been suggested that there is a "window of opportunity" when patients are identified at a very early phase of the disease, enabling physicians to prevent or at least slow disease progression with effective medications [7]. This view has highlighted the importance of identification of organ involvement before irreversible fibrosis and organ damage occur. Recent technical advances in radiology and informatics have enabled the extraction of quantitative information, such as volumetric data, morphometric data, or textural patterns, concerning an organ of interest or a lesion within the organ [8]. Many algorithms and software platforms provide image segmentation routines for quantification of lung abnormalities. Lung segmentation is the method used to identify the boundaries of the lung from the surrounding tissue and provide quantitative data to assess the lung parenchyma [9].

The aim of this study was to investigate lung volume and density in patients with SSc and changes in these parameters due to PF, using a software-aided image quantification method, and compare this with a matched healthy control group.

METHODS

Patient Selection

Medical records of the patients in the SSc cohort of the Rheumatology Department of Kocaeli University School of Medicine were reviewed. Among 164 patients who fulfilled the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/ EULAR) SSc classification criteria between 2007 and 2019 [10], 135 patients with a baseline HRCT evaluation were included in the study. Thirty-eight gender- and age-matched healthy subjects, scanned for different indications from various outpatient clinics were enrolled. Demographic, clinical, and laboratory data were retrieved from medical records, including organ involvements due to SSc, autoantibody status, forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO). The patients were classified into limited cutaneous SSc (lcSSc, n=85) or diffuse cutaneous SSc (dcSSc, n=50) according to LeRoy's criteria [11].

PF was defined based on a range of morphological HRCT findings, including any one of the following: evident ground glass; honey combing; interlobular septal thickening; or traction bronchiectasis. The restrictive pulmonary disease pattern was characterized by a pulmonary function test showing a normal FEV1/FVC value ([?]70%) and at least one of the following: FVC of <70% of predicted normal or DLCO of <70% of predicted normal [12]. In case of doubt about the findings (pneumonia, etc.), pulmonary involvement was confirmed with supportive findings in follow-up HRCTs. Patients with a diagnosis of other respiratory disorders such as asthma or chronic obstructive pulmonary disease, malignancy and significant pulmonary hypertension defined by previous clinical or echocardiographic evidence of significant right heart failure, low cardiac index ([?]2 L/min/m^2 with right heart catheterization) or requiring parenteral therapy with epoprostenol were excluded.

The study was approved by Kocaeli University School of Medicine Ethics Committee, Kocaeli, Turkey, study number GOKAEK-2020/7.24.2020/118.

Image Quantification

Baseline HRCT scans of the patients and controls obtained between 2007 and 2019 were retrieved from the radiology archive. All CT scans were performed non-contrast and volumetric thin-section using a 64-slice multiple-detector CT scanner (Aquilion, Toshiba, Tokyo, Japan). Participants were in the supine position and held a full inspiration during acquisition. Images of 1 mm thickness were presented at window settings designed for lung parenchyma evaluation (width 1,500 Hounsfield units (HU); level – 500 HU). Scans were

analyzed by Myrian XP Lung 3D software (Intrasense SA, Montpellier, France) for lung volume and lobar density quantification. One operator (OC) blinded to the patients' clinical features performed lung volume and density quantification using the Myrian toolbox. Myrian is a medical imaging and computer-aided diagnostic software program used to view, store, reproduce, and export medical images. It is used for 3D imaging involving maximum intensity projection and extremely accurate volume mapping, which utilizes dedicated segmentation algorithms to separate entire vascular pulmonary structures and normal parenchyma and quantify high precision lung parenchyma volume. The software is compliant with DICOM images and shows the 3D images in three planes (axial, coronal, and sagittal). All CT scans were pre-processed using Gaussian smoothing for noise reduction and histogram equalization for contrast enhancement. CT data of the lung was saved as DICOM format, and subsequently imported into Myrian-Xp-Live software. The system automatically identified and extracted image information of the airways, vessels and lung parenchyma, and then generated reconstructed 3D images of the lung. The right and left lungs, as well as the trachea and adjacent vasculature could be clearly observed in all directions. Segmentation of lung volume with an adaptive area was used to divide the left and right lungs. The option of manual correction was used to solve problems caused by individual anatomical variability at each segmentation step. Based on their high density, the pulmonary vessels were extracted from the segmented lung volumes. For the right and left lungs, the densities were measured automatically, with a choice of – 700 or – 900 HU as the characteristic density value of healthy lungs (Figure 1).

Statistical Analysis

Descriptive statistics for clinical and demographic characteristics of the patients are presented as frequency and percentage (%) for categorical variables and mean with standard deviation (mean ± SD) or median with interquartile range (median [Q3–Q1]) according to the distribution of the continuous variables. The normality was assessed both visually and through the Shapiro–Wilk test. The independent samples t-test was used to evaluate the intergroup differences for normally distributed data; lung volumes and densities. For the parameters which were not normally distributed, Mann–Whitney U test (Wilcoxon rank-sum test) or Kruskal–Wallis test was used as appropriate. Pearson Chi-square test was applied to analyze the categorical variables. The Spearman's rank correlation coefficients were used to examine the degree of associations between the right and left lung densities, and right and left lung volumes and FVC and DLCO [13]. The test-retest reliability was assessed by the intraclass correlation coefficient (ICC). The strength of agreement between repeated measures was determined by an ICC of 0.7 or greater, representing a high agreement [14]. Statistical analyses were performed using the SPSS, version 20.0, software (IBM Inc., Chicago, IL, USA) and RStudio, Version 1.2.1335© 2009-2019 (PBC, Boston, MA). Two-sided p values less than 0.05 were considered statistically significant (p <0.05).

RESULTS

Patients were divided into two groups; SSc patients with any typical morphological findings of PF on HRCT (n=41) and patients without any typical morphological findings of PF on HRCT (n=94). These were compared with healthy controls (n=38). These three groups were comparable in age and gender distribution (49.8±15.4, 50.2±11.5, 52.2±5.80,p =0.563; female 85.4%, 88.3%, 89.5%, p =0.840, respectively). Baseline demographic and clinical characteristics and laboratory results of the SSc patients with and without PF are shown in Table 1. The patients with PF had more diffuse cutaneous involvement, lower FVC and DLCO, and were more likely to be Scl-70 autoantibody positive. Pulmonary artery diameter was higher in the patients with PF, and more patients had pulmonary artery dilatation when a cut-off value of 30 mm was used (p <0.001 and p =0.002, respectively). Synovitis was more common in patients without PF.

The soft-ware analysis was performed on HRCT images of the 135 patients with SSc and 38 controls (Figure 2). Analysis of the right and left lung density, right and left lung volume derived from the baseline HRCT scanning in SSc patients with PF, SSc patients without PF, and control group was performed (Table 2, Figure 2). Comparison of the lung measurements showed the right and left lung densities were significantly increased, and the right and left lung volumes were significantly decreased in SSc patients with PF than SSc without PF and controls. The pairwise comparisons between the groups revealed there were no differences

between the SSc patients without PF and controls in terms of right and left lung densities (p =1.000 and p =1.000, respectively); there was a significant difference between SSc patients with and without PF in terms of right and left lung volumes (p =0.005 and p =0.003, respectively).

Patients without evidence of PF were sub-grouped into limited (n=71) and diffuse (n=23) cutaneous involvement. This showed that the right and left lung densities (p =0.002 and p <0.001, respectively), and the right and left lung volumes differed significantly between the groups (p =0.045 and p =0.044, respectively) (Table 3).

Sixteen out of 56 (28.6%) patients without any signs of PF at initial evaluation and who had an annual follow-up CT scans developed abnormal imaging after a mean duration of 10±5 years. Baseline lung densities and volumes were compared between these sub-groups. This revealed that the baseline right and left lung densities were significantly lower in the patients who developed signs of PF during follow-up than those who did not (p =0.016 and p =0.014, respectively) (Table-4).

The correlation between FVC and DLCO and lung densities and volumes in patients with and without PF was analyzed separately. Spearman rank correlation demonstrated negative correlation between the FVC and left lung density (r =-0.230, p =0.043) and positive correlation between FVC and right and left lung volumes (r =0.331,p =0.003; r =0.299, p =0.008, respectively) in the patients without PF signs while DLCO correlated only with left lung volume in these patients (r = 0.248, p =0.032). In the patients with PF, FVC correlated negatively with right and left lung densities (r = -0.601, p =0.001; r = -0.507,p =0.005, respectively) and positively with left lung volume (r = 0.500, p =0.006). Similarly, DLCO correlated negatively with right and left lung densities (r =-0.487, p =0.012;r = -0.393, p =0.047, respectively) and positively with left lung volume in these patients (r = 0.402, p =0.042) (Table 5).

Intra-observer variability

All HRCT aided measurements were performed by an experienced radiologist (O.C.) who was blinded to the patients' clinical features. In our study, the intraobserver variability was as follows: ICC= 0.877 (95% CI 0.741-0.941) for right lung density, ICC=0.887 (95% CI 0.743-0.948) for left lung density; ICC=0.940 (95% CI 0.870-0.972) for right lung volume and ICC=0.922 (95% CI 0.838-0.963) for left lung volume. The interobserver variability was calculated by making the measurements by a scond operator (D.T.K.) and as follows: ICC= 0.857 (95% CI 0.700-0.932) for right lung density, ICC=0.872 (95% CI 0.648-0.946) for left lung density; ICC=0.940 (95% CI 0.870-0.972) for right lung volume and ICC=0.928 (95% CI 0.828-0.967) for left lung volume.

DISCUSSION

In this study the change in lung density and volume due to pulmonary fibrosis in patients with SSc evaluated by a soft-ware aided image segmentation method was investigated. According to the study hypothesis, fibrosis of lung tissue should lead to increased lung density and reduced lung volume due to decreased ventilation [15]. Consistent with this hypothesis, it was shown that right and left lung densities were higher in SSc patients with signs of fibrosis than SSc patients without pulmonary fibrosis and healthy controls.

Although parenchymal changes related to fibrosis were detected in approximately 80-100% of SSc patients in early autopsy studies [2,16], it is known that lung involvement in SSc varies between 40-60% when assessed by HRCT studies [17-19]. In line with the literature, it was expected that lung densities would be decreased in the patients without fibrosis-related morphological changes on HRCT compared to healthy subjects indicating sub-clinical and sub-radiological lung involvement. However, lung densities showed no difference between the patients without signs of fibrosis and controls. It hs previously been shown that PF is closely related to anti-topoisomerase antibody positivity and diffuse cutaneous involvement, and thus patients without fibrosis-related morphological changes on HRCT were analyzed after subgrouping them into limited and diffuse cutaneous sub-types [15,18,20]. Our results showed that in dcSSc patients, even if there were no signs of interstitial lung disease (ILD) in HRCT, lung densities were higher than those of lcSSc and control patients. This result suggested that early changes in lung density may appear before the architectural

distortion on HRCT in dcSSc compared to lcSSc patients. Numerous studies have confirmed that patients with lcSSc or dcSSc have distinct autoantibody profiles, patterns of organ involvements, progression, and outcomes [21-22]. There is still controversy whether the two subtypes of SSc represent truly distinct diseases or merely different extremes of one disease spectrum [23]. We suggest that the two subtypes differ in terms of lung density in radiologically non-apparent disease, although the clinical significance of this is unknown.

The annual follow-up HRCT scans of the 56 patients without any morphological signs of fibrosis on HRCT were evaluated and it was found that 16 (28.6%) of the patients developed abnormal imaging after a mean of ten years from baseline scans. It was shown that the baseline right and left lung densities were significantly lower in the future PF developers than the non-developers. However, there is little evidence to support the predictive value of decreased lung density for PF development in the future. Therefore its role as a parameter in assessing and monitoring newly diagnosed patients should be investigated in larger cohorts. Considering the heterogeneity of systemic sclerosis-associated interstitial lung disease (SSc-ILD), the potential absence of symptoms in early or mild disease, and the potential impact of ILD on outcomes in patients with SSc, our results may contribute to prediction models in SSc-ILD [24].

There was a weak correlation between lung volumes and left lung density and both FVC and DLCO in patients without PF. However, the association became stronger in PF between the densities and left lung volume and both FVC and DLCO. Based on our results, the gradual development of a relationship with the effect of fibrosis-related changes in the lung parenchyma was evident.

Interestingly, the expected decrease in lung volumes due to fibrosis were inconsistent in some subgroup analyses. We believe that this variability may be due to a change in compensatory capacity of the lungs in response to any volume-decreasing pathology. Thus, due to this possible confounder, the main focus of the study was lung density and we believe that use of lung volume as a measurement parameter may be misleading.

One of the most important limitations of our study was that follow-up HRCT scans were not performed in all patients at regular intervals due to the retrospective design. Thus, we refrain from making precise comments about the time to the onset of PF, especially in patients with dcSSc. The small sample size was another limitation, leading to unreliable statistical analysis in some of the subgroup comparisons.

Conclusion

To the best of our knowledge this was the first study to use software aided methods for a deeper analysis of HRCT data which is often routinely gathered in SSc patients. It was demonstrated that lung density decreased in patients with any signs of PF compared to those without PF and healthy controls. It was also shown that, even in the absence of signs of pulmonary fibrosis in HRCT, lung density was decreased in patients with dcSSc compared to both lcSSc patients and healthy controls. Decreased baseline lung density may be a predictive parameter for future PF in SSc patients although this proposal requires validation in larger patient groups. The methods described herein may contribute to the use of software-assisted machine learning techniques in assessing lung parenchyma in SSc.

Acknowledgments The authors thank all investigators for their contribution to the study. The corresponding author certifies that all authors approved the entirety of the submitted material and contributed actively to the study. We would like to thank Mr. Jeremy Jones, of the Kocaeli University Academic Writing Department, for the revision of the English in this paper.

Funding No funding.

Conflict of interest None of the authors has financial or non-financial conflicts of interest to disclose.

Ethical approval This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Author Contributions : DTK acquired the clinical data, contributed to experimental plan design, performed all the statistical analysis and drafted the manuscript. OC contributed to the acquisition of HRCT

data. AK contributed to the acquisition of clinical data. AY and AC contributed to critical revision of the manuscript.

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