

Quantitative volumetric assessment of pulmonary involvement in patients with systemic sclerosis

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Background: Computed tomography (CT) is the gold standard for assessing interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). In this study, we performed a quantitative calculation of ILD severity by examining the lung volume of SSc patients.

Methods: The present study was performed retrospectively on 38 patients with SSc who were referred to our clinic. Patients were divided into two groups based on high-resolution computed tomography (HRCT): patients with ILD and patients without ILD. The percentage of lower lobe volume (PLLV) was calculated using HRCT. In addition, we evaluated the PLLV in all patients according to age, diffusing capacity of the lung for carbon monoxide (DLCO) and spirometric findings, and assessed the relationships among these factors.

Results: PLLV of the right lung in patients with ILD was reduced when compared with patients without ILD ($P=0.041$). The PLLV of the right lung in patients with ILD was negatively correlated with age and forced vital capacity (FVC; $P=0.01$ and $P=0.012$, respectively).

Conclusions: The PLLV of the right lung may decrease in SSc patients with ILD. In these patients, the PLLV may be a quantitative parameter indicating damage in the lung.

Keywords: Lung volume; high-resolution computed tomography (HRCT); pulmonary function test (PFT)

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Introduction

Systemic sclerosis (SSc) is a chronic progressive autoimmune disease that may involve the pulmonary, gastrointestinal, cardiac, musculoskeletal, and renal systems, in addition to skin lesions. In SSc patients, lung involvement is high, with previously reported rates of 50–92% (1-3). In such patients, pulmonary hypertension (PH) results in fibrotic lung parenchyma, often with concomitant cardiac involvement, which shortens the lifespan (4-8). SSc has a 50% mortality rate and cardiac and pulmonary complications are the main causes of death (7,9). In SSc patients, lung involvement is prominent in the basal segments, primarily in the form of reticular honeycomb areas and ground-glass densities accompanied by interstitial lung disease (ILD) (3). In

addition, chronic obstructive pulmonary disease symptoms, such as emphysema and pulmonary nodules, may be observed (10-12).

To assess the severity of lung involvement, high-resolution computed tomography (HRCT), pulmonary function tests (PFT) and diffusing capacity of the lung for carbon monoxide (DLCO) tests are used (13-15). However, DLCO and spirometric measures may not be conclusive in the early stages of SSC. In HRCT measurements, fibrosis scales are used to determine the severity of lung involvement (3,16). However, these methods are subjective and do not provide quantitative results for determining severity.

Radiological quantitative parameters are used to

Table 1 Characteristics of study population

Study population	ILD positive group	ILD negative group	Total population	P value
Age (median)	43	37	41	0.817
Gender M/F	2/21	0/15	2/36	–
Diagn year (mean)	3.7	2.46	3.25	0.267
Right PLLV (%) (median)	41.47	47.07	41.91	0.041
Left PLLV (%) (median)	46.1	51.17	49.37	0.044
Total PLLV (%) (median)	42.82	46.31	45.73	0.051
FVC (mL) (median)	2,470	2,570	2,485	0.721
Predicted FVC (median)	85	90	87	0.320
FEV1/FVC (median)	84	81	83	0.51
DLCO (median)	71	81	71	0.164

Diagn year, diagnosed year; ILD, interstitial lung disease; PLLV, percentage of lower lobe volume; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide.

evaluate the severity of ILD in SSc patients. Quantitative studies assessing ILD in SSc patients have been performed previously (13,17). However, to the best of our knowledge, studies of volume reduction in the lower lobes of patients with SSc have not been performed. Because lung involvement in SSc patients is more severe in basal segments, we aimed to show quantitatively that volume loss is a result of fibrosis in the lower lobe.

Materials and methods

Patients

The records of 45 patients diagnosed with SSc, who presented to our clinic between July 2008 and June 2014, were reviewed retrospectively. The study was approved by the Ethics Committee of our institution. The patients were diagnosed with SSc and evaluated according to the criteria of the American Rheumatism Association (18). All patients satisfied the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion) (weighted 9), skin thickening of the fingers, (only count the higher score); puffy fingers (weighted 2), sclerodactyly of the fingers (weighted 4), fingertip lesions, (only count the higher score); digital tip ulcers (weighted 2) or fingertip pitting scars (weighted 3), telangiectasia (weighted 2), abnormal nail fold capillary pattern (weighted 2), pulmonary arterial hypertension and/or ILD; (maximum score is 2) pulmonary arterial hypertension (weighted 2) ILD (weighted 2), Raynaud's

phenomenon (weighted 3), SSc-related autoantibodies (maximum score is 3): anticentromere antibody, anti-topoisomerase I antibody (also known as anti-Scl-70 antibody), or anti-RNA polymerase III antibody. The maximum possible score is 19, and patients with a score of 9 or higher are classified as having SSc (19). HRCT examinations of patients diagnosed with SSc were evaluated. Seven cases were excluded from the study; two patients could not be evaluated due to motion artifacts, two had emphysema, which caused volume increase in the upper lobe lung, two had a previous tuberculosis infection, and one patient was previously exposed to asbestos, which caused volume loss in both lungs. In total, 38 patients were included in the study; 2 patients were male (5.3%) and 36 were female (94.7%). The HRCT scan was evaluated for GGO and ILD pattern including reticular intra-interlobular thickening, honeycomb cysts, traction bronchiectasis, bronchiolectasis. HRCT scans the distribution of ILD was categorized as upper, middle, or lower zone predominant. Patients were divided into two groups according to the results of HRCT examination: there were 23 patients with ILD and 15 patients without ILD. The median age of patients with ILD (43 years) was not significantly different from that of patients without ILD (37 years; $P=0.698$). The demographic data and echocardiograms of all patients were obtained from the archives of our hospital (Table 1).

HRCT scanning protocol

All views were obtained with patients in the supine position using Toshiba Activion 16 equipment (Toshiba Medical

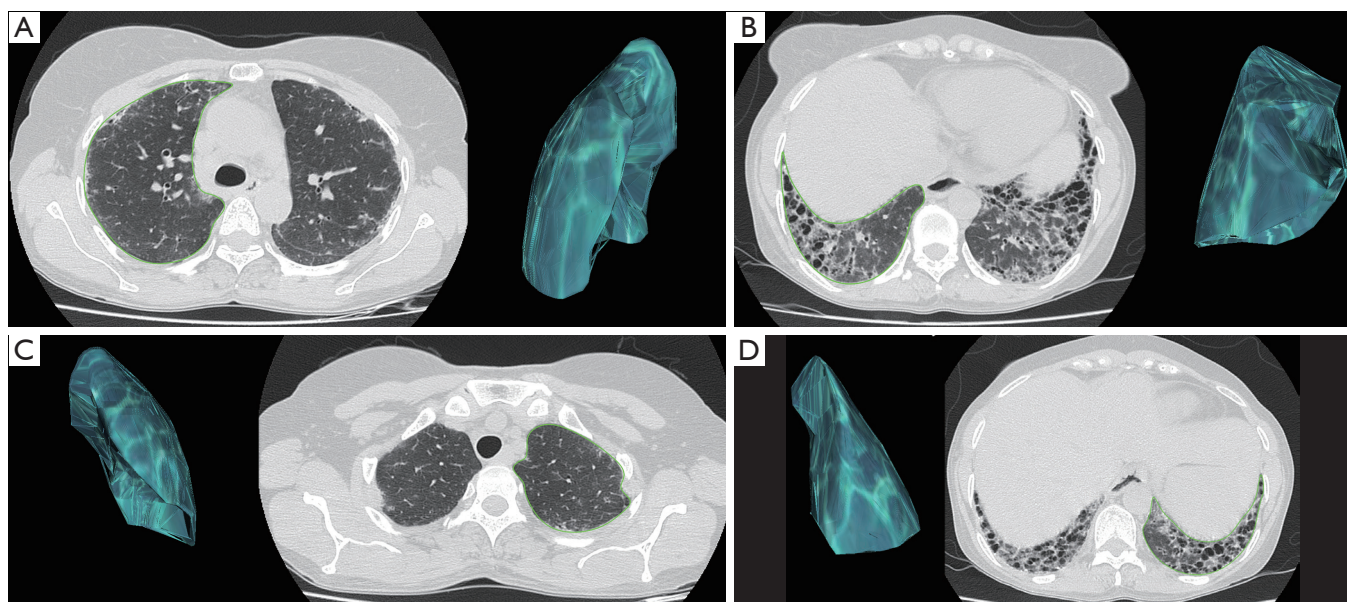


Figure 1 The marked boundaries of the lung lobes in axial images; volume calculations were performed by combining the volumes of these areas [right upper lobe + middle lobe (A), right lower lobe (B), left upper lobe (C), left lower lobe (D)].

Systems, Tokyo, Japan) with the following parameters: Kv, 120; mAs, 300; slice thickness, 5 mm; and detector collimation, $16 \times 1 \text{ mm}^2$. HRCT images were created using 1 mm reconstructions.

HRCT measurement

All HRCT measurements were performed by a thoracic radiology specialist with 5 years of experience (MG. Ç), using OsiriX 4.0 software (OsiriX Foundation, Geneva, Switzerland) with our picture archiving and communication system (PACS) on an iMac27 Mid 2011 (Apple Inc., Cupertino, CA, USA) workstation. All measurements were confirmed by a thoracic radiology specialist with 7 years of experience (Goya C). Measurements for each lobe were performed at 5 mm intervals, forming a complete series. On axial images, the parietal pleura (and fissure) were used as the border and measurements were then obtained (Figure 1). Lobe volume was calculated automatically by combining the areas in all sections using the OsiriX program. The following areas were measured in each patient: the right upper and middle lobes, lower lobe of the right lung, upper lobe of the left lung and lower lobe of the left lung. The percentage of lower lobe volume (PLLV) was calculated as follows:

$$\text{PLLV of the right lung} = \left[\frac{\text{lower lobe volume}}{\text{upper lobe}} \right] \times 100\%$$

$$+ \text{middle lobe} + \text{lower lobe volume}] \times 100\%$$

$$\text{PLLV of the left lung} = \left[\frac{\text{lower lobe volume}}{\text{upper lobe} + \text{lower lobe volume}} \right] \times 100\%$$

$$\text{Total PLLV of the lung} = \left[\frac{\text{right} + \text{left lower lobe volume}}{\text{right lung} + \text{left lung volume}} \right] \times 100\%$$

PFT and carbon monoxide (co) tests

All spirometric measurements were performed using a Vmax 22 Series spirometer (Viasys Healthcare, Yorba Linda, CA, USA) according to the American Thoracic Society (ATS) standards (20), and forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and the FEV1/FVC ratio were recorded. Predicted values of FVC, FEV1 and the FEV1/FVC ratio according to gender and height were used to determine respiratory function.

Each patient's total lung function was measured using a body box plethysmograph (Vmax 22 Series, Viasys Healthcare) and ATS/European Respiratory Society (ERS) standard criteria. The lung volumes and predicted CO diffusing capacity of each patient were measured using the single breath wash-out technique and by adjusting blood hemoglobin values, respectively (21).

Statistics

Patient data, including the number of cases, were recorded

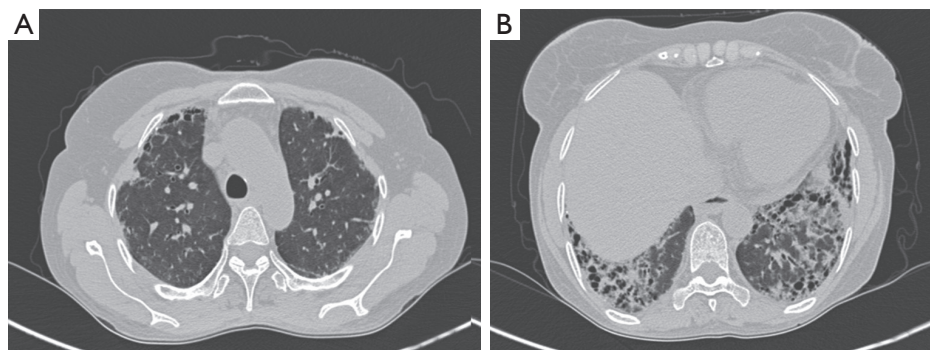


Figure 2 Lung involvement in a 49-year-old female with systemic sclerosis (SSc). Reticular fibrosis areas were observed in the peripheral areas of the upper lobe (A) and common reticular honeycomb areas in the lower lobe (B) on high-resolution computed tomography (HRCT) images.

Table 2 Correlation of PLLVs with PFTs in pulmonary involvement

Lung percentage	FVC		FEV1/FVC		DLCO	
	Spearman's rho	P value	Spearman's rho	P value	Spearman's rho	P value
Right PLLV (%)	0.536	0.012	-0.041	0.860	0.115	0.628
Left PLLV (%)	0.579	0.006	-0.037	0.873	0.076	0.750
Total PLLV (%)	0.539	0.012	-0.062	0.792	0.121	0.61
N	21		21		20	

N, number of patients; PLLV, percentage of lower lobe volume; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide.

using SPSS for Windows (ver. 18.0; SPSS Inc., Chicago, IL, USA) and Microsoft Excel software (Microsoft Corp., Redmond, WA, USA). Because the PLLVs of the two groups were not normally distributed, the Mann-Whitney U test was used. In all patients, correlations between the PLLV values of the left and right lungs were assessed using the Spearman correlation test. Spearman correlation analysis of the PLLV of the right lung, age, DLCO and PFT results of patients with ILD was performed. A P value <0.05 was considered to indicate statistical significance.

Results

In SSc patients, lung involvement is prominent in the basal segments, primarily in the form of reticular honeycomb areas and ground-glass densities accompanied by ILD (Figure 2). Table 1 shows the characteristics of the study population, including the median values of the demographic data, PLLV rate, PFT results and DLCO measurements. ILD was seen in 23 patients, and GGO was seen in 3 patients. ILD distribution was seen lower lobe predominant

in the all patients with ILD (Figure 2). The PLLV of the right lung was correlated with the PLLV of the left lung and total lung (Spearman correlation coefficient, 0.846; $P < 0.001$ and 0.977; $P < 0.001$, respectively). Based on HRCT, the media PLLV of patients with ILD (41.47%) was significantly reduced compared with patients without ILD (47.07%; $P = 0.041$). A negative correlation between the PLLV of the lung and age was observed in the patients with ILD (Spearman correlation coefficient, -0.527; $P = 0.01$). A positive correlation between the PLLV of the lung and FVC was also observed in the patients with ILD (Spearman correlation coefficient, 0.536; $P = 0.012$). The FEV1/FVC ratio and predicted DLCO results did not demonstrate a significant correlation with the PLLV of the affected lung (Table 2).

Discussion

According to our results, the PLLV was decreased in SSc patients with ILD compared to those without ILD. Moreover, in patients with lung involvement, the PLLV rate decreased as age increased. Pulmonary fibrosis indicates

irreversible damage in patients with SSc. In the literature, a decrease in lower lobe volume due to SSc is considered as a prognostic factor (16,22). A number of techniques have been developed to measure pulmonary fibrosis, including visual inspection, and Goh, Wells and Warrick scores, which are all semi-quantitative methods (16,23,24). The major limitation of these methods concerns inter-observer discrepancies. The PLLV can provide a simple, quantitative parameter for assessing pulmonary sclerosis in patients with SSc.

In our study, the PLLV of the lung and FVC were correlated. A decrease in FVC is expected in restrictive lung disease, and in our study was correlated with the PLLV of the lung. According to the literature, FVC values are decreased with fibrosis. FLV can be graded using pulmonary fibrosis scales in patients with SSc (3,25). A 70% reduction of FVC is considered as a critical limit. Patients with an FVC reduction of more than 70% have a decreased likelihood of survival (15,16). In our study, the PLLV of the lung was not correlated with the FEV1/FVC ratio; a lack of correlation between these parameters might be due to poor patient compliance with the FEV1/FVC ratio measurement test.

In this study, the predicted DLCO and PLLV values were not correlated. In the literature, differences in the degree of interstitial lung involvement and predicted DLCO results have been reported in patients with SSc. DLCO results that differ from predictions may be explained by the influence of numerous factors, including the prevention of obstructive disease in accordance with CO distribution, emphysema, chest deformity, obesity, PH, anemia-polycythemia and alveolar-capillary thickness (21,26,27). Although Goh and colleagues (16) found that DLCO values were associated with PH, in other studies pulmonary fibrosis and PH were found to be related (22,28).

The most important limitation of our study was we did not measure sclerosis in the upper and middle lobes. The small study population, small number of male participants, manual drawing of the lung border and long duration required for volume calculation (although automatic segmentation programs may also be used) are additional further limitations.

Conclusions

In summary, PLLV values were significantly lower in SSc patients with ILD than in those without ILD. PLLV may be a quantitative parameter indicating damage in the lung. We believe the method described herein can be used for future large-scale studies on this issue.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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