Original Article

Correlation of HRCT Scoring System with PFT Parameters in Interstitial Lung Disease Associated with Systemic Sclerosis Patients

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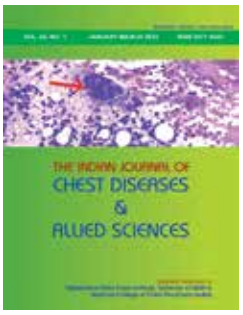

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ABBREVIATIONS USED IN THIS ARTICLE

HRCT = High resolution computed tomography

PFT = Pulmonary function test

ILD = Interstitial lung disease

SSc = Systemic sclerosis

GGO = Ground-glass opacity

NSIP = Non-specific interstitial pneumonia

UIP = Usual interstitial pneumonia

FEV_1 = Forced expiratory volume in one second

FVC = Forced vital capacity

GIT = Gastrointestinal tract

IPF = Idiopathic pulmonary fibrosis

SPSS = Statistical Package for Social Sciences

SD = Standard deviation

Abstract

Objectives. Interstitial lung disease (ILD) with features of pulmonary fibrosis and honey-combing is a significant cause of morbidity and mortality in patients with systemic sclerosis (SSc). High resolution computed tomography (HRCT) is the established non-invasive gold standard technique for the diagnosis of SSc related ILD. The present study was designed to characterise HRCT features of ILD in SSc and to correlate pulmonary function test (PFT) parameters with HRCT semi-quantitative scores.

Methods. This is an observational, cross-sectional study including 36 patients of SSc who underwent HRCT chest. All the patients were females. Severity and extent were assessed using four HRCT features: ground-glass opacity (GGO), mixed GGO and reticular opacity, reticular fibrosis and honey-combing. Thirty-three patients were able to perform PFT. Total HRCT score, inflammatory index and fibrosis index were correlated with PFT parameters.

Results. Interstitial lung disease was found in 33 patients (91.6%), 24 patients (66.6%) had mixed GGO along with reticular inter-lobular septal thickening. Majority of the patients (64%) had non-specific interstitial pneumonia (NSIP) pattern. Usual interstitial pneumonia (UIP) pattern was seen in 25% of the cases. One patient had overlapping features of both UIP and organising pneumonia. There was predominant lower lobe involvement. Among the 33 patients who were able to perform PFT, 85% had abnormal results (predicted forced vital capacity [FVC]<80%). Total HRCT score showed significant negative correlation with PFT parameters — FVC (r=–0.48, P=0.004) and forced expiratory volume in one second (FEV_1) (r=–0.28, P=0.1), respectively. The ratio of FEV_1 and FVC had significant positive correlation with total HRCT score (r=0.5, P=0.002). Inflammatory index and fibrosis index had significant negative correlation with predicted FVC% (P<0.05).

Conclusions. Mixed pattern (GGO and reticular opacity) was the most common HRCT finding. HRCT semi-quantitative scoring system is sensitive in assessing the severity and extent of ILD qualitatively and quantitatively in SSc patients.

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Introduction

Systemic sclerosis (SSc) is a complex, chronic, multi-system autoimmune connective tissue disorder affecting around 15 people per 10 lakh population in the world. It has 3:1 female predilection and typically occurs in third to fifth decades of life.[1] The disease is characterised by vascular obliteration due to endothelial dysfunction, fibrosis of skin and internal organs due to excessive collagen formation and immunologic abnormalities. Among internal organs, lungs, gastrointestinal tract and kidneys are frequently affected.

More than 90% of the patients with SSc have evidence of interstitial lung disease (ILD) at autopsy and 40% of patients show abnormal pulmonary function tests (PFTs).[2] Pulmonary complications, such as ILD and pulmonary hypertension are the most common cardio-pulmonary findings in patients with SSc. These account for approximately 60% of SSc related deaths.[3] The disease is classified into two sub-types — diffuse scleroderma and limited cutaneous scleroderma. Diffuse scleroderma shows anti topoisomerase - I (scl-70) antibody. Limited scleroderma, also known as CREST syndrome is associated with anticentromere antibodies.[4]

Pulmonary function test is important for the evaluation of pulmonary involvement in SSc. It shows a restrictive pattern with a decrease in per cent predicted of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) and increase the ratio of FEV_1/FVC. High resolution computed tomography (HRCT) has higher spatial resolution as compared to routine CT. It is useful for the assessment of different pulmonary diseases and is the established non-invasive gold standard technique for the diagnosis of SSc related ILD. It is a much more sensitive test as compared to traditional chest radiography, particularly in identifying the interstitial pattern in early SSc-related ILD.

The most common radiological appearance of lung disease in SSc is diffuse lung parenchymal disease characterised by prominent ground-glass opacities (GGOs) and fine interstitial reticular marking in juxta-pleural, posterior and basilar areas of lungs, which may progress to pulmonary fibrosis causing architectural distortion of the lung parenchyma. Non-specific interstitial pneumonia (NSIP) is a common pattern observed on the HRCT chest of SSc patients.

The coarseness of fibrosis and proportion of GGO is similar in patients with SSc and NSIP; but significantly different from that of idiopathic pulmonary fibrosis (IPF).[5] Since lung involvement plays a fundamental role in the prognosis of SSc, various scoring systems have been used to quantify ILD on HRCT chest findings.[6] In the present study, we have evaluated the semi-quantitative scoring system initially proposed by Ooi *et al*[7] to assess severity and extent of the disease.

Material and Methods

The present study was a cross-sectional, observational including 36 female patients referred from the Departments of Medicine and Dermatology to Department of Radiodiagnosis of our hospital. Patients with clinical diagnosis of SSc having pulmonary involvement were included in the study. Pregnant females and patients having active chest infection or history of pulmonary tuberculosis were excluded. PFT was done for all the study patients. Other investigations done were chest radiography, as an initial imaging modality and relevant blood investigations as required.

High-resolution computed tomography chest, using Siemens SOMATOM™ definition flash 128-slice dual source CT scanner with appropriate protocols was performed in the supine position and with full inspiration, as end-inspiratory sections give fine details of lung parenchyma and allow reliable reconstruction of volumetric images. Thin axial sections were taken from the lung apex to lung base without intravenous contrast. Prone sections were obtained to distinguish gravity dependent changes, wherever indicated. Slice thickness of 5mm with 1mm reconstruction and 0.7mm increment was used. According to the semi-quantitative scoring method formulated by Ooi *et al*[7], all HRCT findings, like GGO, mixed ground-glass and reticular opacity, reticular fibrotic changes alone and honey-combing were assessed in each of the six lobes (considering lingula as a separate lobe) of the lungs and expressed as percentage of each lobe affected as – 0 for 0%, 1 for 1%–25%, 2 for 26%–50%, 3 for 51%–75% and 4 for 76%–100% area involved.[7]

The extent of lobar involvement was calculated as percentage of each lobe affected for each HRCT abnormality. Total score was obtained by adding individual lobar scores for all the four HRCT abnormalities and correlated with the PFT parameters. Inflammatory index was derived using the score of GGO and mixed pattern and fibrotic index was found from the scores of reticular opacities only or honey-combing changes as described by Ooi *et al*.[7]

Out of 36 patients, three patients could not perform the PFT test due to excessive facial skin involvement. All pulmonary function parameters were expressed as percentage predicted values, except FEV_1/FVC ratio. Abnormal lung function was considered when predicted FVC and FEV_1 value were <80% and FEV_1/FVC was <75% or >85%.

Statistical Analysis

The data was entered in Microsoft Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS). Categorical variables were presented in number and percentage and continuous variables were presented as mean ± standard deviation (SD) and median. Quantitative variables were compared using the student's t-test. A P value of <0.05 was considered statistically significant.

Results

All patients were females, age ranged from 13 to 61 years (mean 36.3±10.2 years) and in the third to fifth decade (86% patients) predominance (Table 1). All the patients had clinical complaints of skin thickening and tightness, barring a few. Mean duration of skin manifestations was 5.3±5.9 years. Other than skin thickening, dyspnoea and dry cough were the frequently associated symptoms. Clinically respiratory complaints were found in 94% of patients with a mean duration of 9.1±7.9 months. The remaining patients had no respiratory symptoms, but had deranged PFT. Acral cyanosis with classical Raynaud's phenomenon and fingertip ulcerations were found in 15 (42%) patients.

Majority of patients (55%) had FVC in the range 61%–80% of the predicted value, 30% cases were in the range of 41% to 60% of the predicted value, while 15% of cases had normal FVC values (>80%). This suggests that the majority of patients had mild to moderate decrease in FVC%. None of the patients had FVC below 40% or a very severe decrease in PFT parameters. Moderate decrease in FVC% was found in patients who had respiratory symptoms for more than one year (Table 2). The patients with respiratory symptoms for less than one year had mild decrease in the predicted FVC%. Almost all the patients showed a restrictive pattern of lung function with a FEV_1/ FVC of >85%. Mean and SD of the % predicted values of PFT in the study was 67±10.6 for FVC, 68.3±8.7 for FEV_1 and 102.3±8.7 for FEV_1/FVC, respectively.

Chest radiography was not found to be a sensitive modality in evaluating ILD, particularly in the early stages of the disease (Table 3). Only 44% of the patients showed diffuse or zonal abnormality. Among them, 75% had lower zone involvement and 25% had diffuse lung involvement. No significant upper and middle zone involvement was seen in 32 patients. Most common chest radiograph finding was fine or coarse reticular opacity. Variable degree of lung volume loss was observed on radiography.

High-resolution computed tomography of chest showed ILD in 33 (91.6%) cases. Idiopathic interstitial pneumonia (IIP) pattern was noted on HRCT in all the ILDs cases. Twenty-four patients (66.6%) had mixed GGO along with reticular inter-lobular septal thickening, while reticular fibrosis was seen in five (13.8%) cases (Figures 1-3). GGO was seen in four (11%) cases only. Eight (22.2%) cases had honey-combing and 14 (38.8%) cases had traction bronchiectasis.

Table 1. Baseline profile and pulmonary function data

Age Group (years)	Number of Patients (%)
10-20	2 (6)
20-30	10 (28)
30-40	14 (30)
40-50	7 (10)
50-60	2 (6)
60-70	1 (3)
IIP Pattern	
NSIP	23 (64)
UIP	9 (25)
Organising pneumonia	1 (3)
No abnormality	3 (8)
Duration of cutaneous manifestation	
<5	25 (69.4)
6–10	8 (22.2)
>10	3 (8.4)
Duration of respiratory symptoms	
No complaints	2 (6)
<6 months	13 (36)
6–12 months	12 (33)
>12 months	9 (25)
Forced vital capacity	
>80%	5 (15)
61%–80%	18 (55)
41%–60%	10 (30)
<40%	0

Table 2. Correlation of duration of respiratory symptoms with forced vital capacity

Duration of Respiratory Symptoms	FVC			
	>80%	60%–80% (mild)	40%–59% (moderate)	<40% (severe)
	(Number of Patients)			
<6 months	3	8	2	0
6-12 months	1	6	2	0
>12 months	1	2	6	0

Table 3. Pulmonary function tests and radiological imaging findings

FEV_1/ FVC	Number of Patients (%)
70%–85%	2 (6)
86%–100%	18 (55)
>100%	13 (39)
Lung zone involved	
Upper	0
Middle	0
Lower	12 (75)
Diffuse	4 (25)
Predominant chest radiograph finding	
Reticular	16 (44)
Reticulo-nodular	0
No abnormality detected	20 (56)
HRCT chest findings	
Only GGO	4 (11)
Mixed GGO + Reticular inter-lobular septal thickening	24 (66.6)
Only reticular fibrosis	5 (13.8)
Honey-combing	8 (22.2)
Traction bronchiectasis	14 (38.8)
HRCT chest score	
0–5	13 (37)
6–10	17 (46)
11–15	6 (17)
(Mean HRCT score) FVC% predicted	
>80% (4)	5 (14)
60%–80% (5.5)	18 (50)
<60% (8.8)	10 (28)
Could not perform (11.6)	3 (8.4)

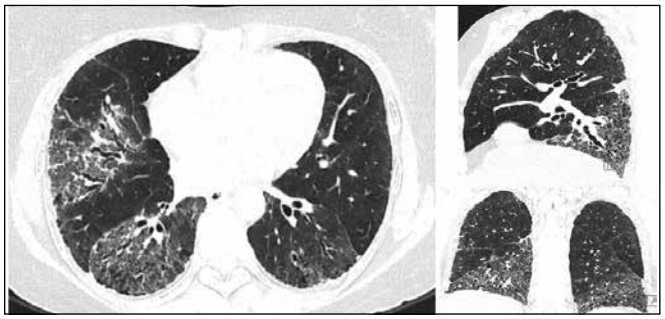

Figure 1. A 45-year-old female with a diagnosis of systemic sclerosis. HRCT(axial, sagittal and coronal reformatted images) showing peripheral and basal predominant GGO with intra- and inter-lobular septal thickening and traction bronchiectasis suggestiveof NSIP.

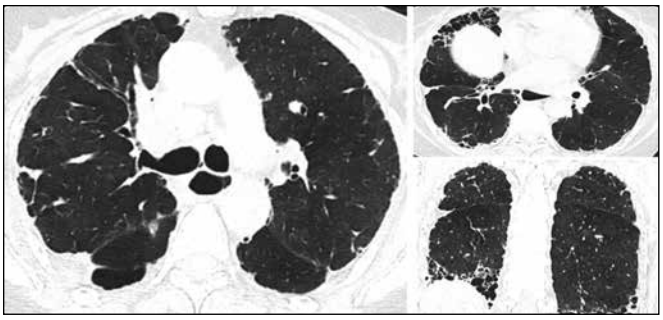

Figure 2. A 61-year-old female systemic sclerosis patient. HRCT (axial and coronal reformatted images) showing peripheral and patchy consolidation with bronchiectasis. In the lower sections inter-lobular septal thickening with honey-combing are also seen. Oesophagus is dilated. This was categorised as organising pneumonia. Features of UIP are also present.

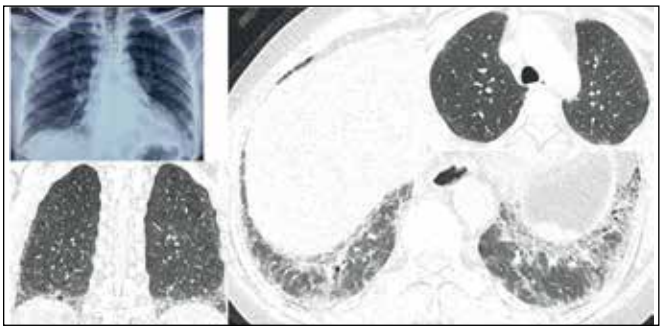

Figure 3. A 45-year-old female systemic sclerosis patient. Chest radiograph (postero-anterior view) showing mild bilateral basal reticulations. HRCT (axial and coronal reformatted images) showing GGO with inter- and intra-lobular reticulations in the posterior and basal regions of the bilateral lower lobes with bronchiolectasis, suggestive of NSIP.

In SSc patients, NSIP pattern was found to be the more common. Twenty-three (64%) patients had NSIP, nine (25%) had usual interstitial pneumonia (UIP) and one (3%) had organising pneumonia with overlapping features of UIP. Bilateral lower lobe predominance was noted in almost all the patients in terms of the extent disease and severity of the lesions (Table 4).

HRCT Scoring

Chest HRCT findings were assessed and scored by two radiologists independently according to the semi-quantitative scoring method described by Ooi *et al*.[7] In case of discrepancy in the report of the observers, consensus was evolved. Chest HRCT findings, such as GGO, mixed pattern, reticular fibrosis only or honey-combing were scored as disease severity. All the lobes, with lingula counted as a separate lobe, were evaluated and scored as percentage of lobar involvement. Total score was obtained by adding all the lobar scores of all the abnormalities. Three cases did not show any

Table 4. Cephalo-caudal distribution of disease

Chest HRCT Findings	Number of Patients					
	Right Lung			Left Lung		
	Upper Lobe	Middle Lobe	Lower Lobe	Upper Lobe	Middle Lobe	Lower Lobe
Only GGO	4	3	6	4	3	6
Mixed GGO and Reticular	13	14	21	12	9	21
Only reticular opacity	6	8	8	6	7	9
Honey-combing	5	6	7	2	6	7

abnormality on HRCT and were scored as zero, 17 cases had HRCT score between 6–10, 13 had between 0–5 and six had between 11–15. On comparison between total HRCT score and FVC% predicted, it was found that the mean of total HRCT score for the cases with >80% FVC was less than means of total HRCT score for cases with <60% and 60%–80% FVC values.

Total HRCT score was higher in patients having lower FVC values, demonstrating a negative correlation between PFT parameters and disease extent and severity on HRCT. An inverse trend was noted between FVC% and total HRCT score, with few outliers, a few patients with FVC value >80% had high total HRCT score. This anomaly was probably due to less severe, though extensive disease, thereby affecting the overall HRCT score. Cases with early pulmonary involvement showed GGO only with or without some fine reticulations. This is likely to be due to inflammatory alveolitis in chronic autoimmune connective tissue diseases, like SSc. This is also the basis for inflammatory index among the patients having high HRCT score with normal or mildly decreased FVC value. Another group of patients who had a lower total HRCT score with mixed pattern images had predicted FVC value <80%. This suggested the restrictive pattern of the ILD with underlying lung fibrosis. GGO in these patients could be due to fine alveolar fibrosis.

There was a significant negative correlation between predicted FVC% and total HRCT score (r=–0.48, P=0.004). A tendency towards negative correlation was also found between FEV_1% and total HRCT score (r=–0.28, P=0.1). This reflects decreased lung function when there is increased total HRCT score, which represents the extent of lung involvement. The FEV_1/FVC ratio had positive correlation with HRCT score (r=0.5, P=0.002). Patients with increased FEV_1/FVC values had higher total HRCT score demonstrating restrictive nature of the disease.

Mean and median of inflammatory index score were 6.1±3.5 and 6, respectively. It was inversely related to % predicted FVC (r=–0.39, P=0.08). Mean and median of fibrosis index were 10.5±3.0 and 9, respectively with an inverse relation to FVC (r=–0.40, P=0.04) showing a significant association. Duration of the disease and clinical features did not show any significant correlation between PFT and total HRCT score.

Discussion

Interstitial lung disease was found in 33 (91.6%) out of 36 of cases on HRCT. Bastos *et al*[8] noted changes suggestive of ILD findings in 94% cases, while Solomon *et al*[3] and Bocchino *et al*[9] reported in 90% of SSc patients. In the study by Ooi *et al*[7], 86.7% patients had ILD while Moorthy *et al*[10] observed in 85% of the cases.

Strollo and Goldin[1] in 2010 showed the disease prevalence in the 3rd to 5th decade. In comparison to Ooi *et al*[7] (mean age 48.5±13.4); there was an earlier age of presentation of patients in our study 36.3±10.2 years (age range 13 to 61 years); 86% were between third to fifth decade. Patients included in our study were all females demonstrating a marked female predominance, same observations were made by other workers.[8,12] Valeur *et al*[14] labelled *juvenile* SSc when the age of the patient was less than 16 years and they reported 3% to 10% of total cases were of juvenile SSc. In the present study one patient (2.8%) belonged to the juvenile age group who had oesophageal dilatation along with Raynaud's phenomenon. In the study by Valeur *et al*[13], 72% to 84% cases had Raynaud's phenomenon and 65% to 69% cases had gastrointestinal symptoms.

Mean predicted FVC% in our study was 67.1% with a standard deviation of 10.6 and mean FEV_1 was 68.4±8.7 and FEV_1/FVC ratio was 102.3±8.7. Khanna *et al*[14] also had similar findings of mean FVC% as 67.7%. In our study a restrictive pattern of ILD in SSc was observed in 90% of the cases, as there was a decrease in both % predicted FVC and FEV_1 with an increase in the FEV_1/FVC ratio. Goh *et al*[15] observed a mean FVC of 77.6±18.6, FEV_1 of 78.7±21.4; higher values than our study. The reason for this difference in observations might be due to more severe patients or less number of patients in our study.

Only 44% of the patients had chest radiograph abnormalities in our study. Fine or coarse reticular opacity was the most common radiological finding involving lower lung zones predominantly. Three of these cases had diffuse lung field involvement. Schurawitzki *et al*[16] also noted that only 39% cases had findings on chest radiograph; most had interstitial opacification and 26% of cases had equivocal radiological findings, while Bastos *et al*[8] reported this in 25% to 53% cases.

On HRCT, 23 (64%) patients showed an NSIP pattern and nine (25%) had a UIP pattern in our study, which is in contrast with earlier studies.[5,17-19] One patient in our study had peripheral patchy consolidations with features of reticular fibrosis and honey-combing. This was categorised under organising pneumonia.GGO was noted in 28 (77.7%) patients in our study; however only GGO as an abnormality was found in 11% of the cases, in contrast with other workers.[2,20] Shah *et al*[21] had observed GGO in 66% of cases and GGO alone in 7% of cases. Few patients with only GGO or associated with fine reticulation (17%) had better lung function results (predicted FVC >70%) but higher total HRCT score. This paradox may be explained by the early pulmonary involvement and inflammatory alveolar infiltrates which affects lung function less severely than fibrosis.[2,7] Majority of the patients with GGO and fine reticulations had moderately deranged PFT with consistently higher total HRCT score. The GGO in these cases may be due to fine alveolar fibrosis as HRCT does not have sufficient spatial (anatomical) resolution to separately identify these two features in patients with extensive GGO.[21]

Shah *et al*[20] on follow-up scan in patients with GGO found that only 7.5% cases had significant improvement. Rest of the patients were associated with irreversible disease which they labelled as fibrosing alveolitis. Pandey *et al*[2] postulated a high likelihood of fine fibrosis in the areas of GGO instead of inflammatory alveolitis. Hence, they suggested that GGO could not be considered a reliable indicator to predict active inflammation and/or reversible disease. One patient in our study diagnosed as possible UIP had developed early honey-combing within the areas of GGO. This suggests underlying fine reticular fibrosis in the areas of GGO instead of inflammatory alveolitis. Similar findings were also reported by Remy-Jardin *et al*.[22]

Reticular opacity and honey-combing were present in nine patients, suggesting inter-lobular and intra-lobular septal thickening. They were associated with traction bronchiectasis and bronchiolectasis. Honey-combing represents irreversible end-stage lung fibrosis) leading to lung parenchymal architectural distortion and moderate to severely decreased PFT with higher HRCT score.[2] Of three patients who could not perform PFT, two had a UIP pattern with honey-combing suggesting severe disease associated with honey-combing and coarse reticular fibrosis. This was in agreement with the observations of Ooi *et al*.[7] Traction bronchiectasis was seen in 14 (38.8%) cases in our study, in contrast with Ibrahim *et al*[23]. In almost all the patients in our study, lower lobe predominance of ILD was observed. Further there was predilection of posterior and basal region involvement in all the cases with ILD in our study, as also observed by Remy-Jardin *et al*.[22]

There was a significant negative correlation between the predicted FVC% and the total HRCT score (r=–0.48, P=0.004). A negative correlation was observed between FEV_1% and total HRCT score (r=–0.28, P=0.1). This result was in agreement with the results of Bellia *et al*.[17]

Mean and median of inflammatory index score were 6.1±3.5 and 6, respectively and it was inversely related to % predicted FVC (r=–0.39, P=0.08). Mean and median of fibrosis index were 10.5±3.0 and 9, respectively with an inverse relation to FVC (r=–0.40, P=0.04) showing a significant association. This was in agreement with the results of earlier studies.[7,23]

Most common extra-pulmonary finding in our study was oesophageal dilatation. Oesophagus was considered as dilated when infra-aortic oesophagus measured ≥9mm in coronal diameter.[24,25] Of 36 patients, 21 (58.3%) had this finding. Pandey *et al*[24] noted oesophageal dilatation in 58% of SSc patients. Another common extra-pulmonary HRCT chest feature was dilated main pulmonary artery. In our study, only five cases (13.8%) had this feature with a main pulmonary artery diameter of >29mm. Similar observations, were reported by other workers.[23,25] Mediastinal lymphadenopathy was found in seven (19.4%) cases in our study while Bhalla *et al*[26] and Ibrahim *et al*[23] observed in 60% and 76.7% of their patients, respectively.

Conclusions

Systemic sclerosis commonly occurs in middle aged females; the presenting complaint being diffuse skin thickening over the limbs and face and dyspnoea on exertion with or without dry cough as the primary respiratory symptom. PFT reveals restrictive pattern. The limitations of chest radiography may overcome by HRCT chest. Non-specific interstitial pneumonia pattern is the most common ILD found in SSc. HRCT has a significantly high diagnostic accuracy in detecting the presence or absence of ILD, especially in the early stages of the SSc. HRCT semi-quantitative scoring system is valuable in assessing the disease severity and its extent. It correlates significantly with PFT. HRCT as an imaging modality along with clinical findings can directly help in the treatment and prognostic assessment in very early or sub-clinical pulmonary disease.

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