Original Article

Correlation of delta high-resolution computed tomography (HRCT) score with delta clinical variables in early systemic sclerosis (SSc) patients

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Background: The correlation of changes (delta: Δ) of high-resolution computed tomography (HRCT) score with the Δ of other clinical variables has not been well studied. The purpose of this study was to determine the correlation of Δ HRCT score with Δ percent predicted forced vital capacity (%pFVC), Δ modified Rodnan Skin Score (mRSS), Δ erythrocyte sedimentation rate (ESR), and Δ percent of oxygen saturation at room air (%SpO_2) in patients with early systemic sclerosis (SSc).

Methods: We used an inception cohort of early-SSc patients seen at the Rheumatology Clinic, Chiang Mai University, Thailand, between January 2010 and June 2014. All patients underwent HRCT at study entry and every 12 months thereafter. Thirty-one SSc patients who underwent pulmonary function test (PFT) within 12 weeks of their corresponding HRCT at baseline and last visit were identified. The extent of ground glass (GG), lung fibrosis (Fib), bronchiectasis (B), and honeycombing (HC) was scored, and then aggregated to produce a total (t) HRCT score.

Results: Mean ± SD age and disease duration from non-Raynaud's phenomenon (NRP) to undergo HRCT at baseline were 52.2±8.8 years and 11.7±7.1 months, respectively. Seventeen (54.8%) patients were female and 20 (64.5%) were classified as dcSSc. The mean ± SD interval between the two HRCT tests was 16.0±7.2 months. The Δ HRCT scores [total fibrosis scores (t-Fib), total bronchiectasis scores (t-B), and total HRCT score (t-HRCT) scores] and Δ mRSS, but not Δ %pFVC, showed significant change over the observation period. We found significant correlation of Δ total honeycombing scores (t-HC) with Δ ESR ($r=-0.44$, $P<0.05$), and Δ t-Fib with Δ %SpO_2 ($r=-0.38$, $P<0.05$). However, no significant correlation of any Δ HRCT scores with Δ %pFVC and Δ mRSS were observed.

Conclusions: In this study, the changes in the HRCT scores were greater than %pFVC; this, along with their correlations with the changes in ESR and %SpO_2, suggest that HRCT scores are a useful and sensitive method for monitoring disease progression in early SSc-related ILD (SSc-ILD).

Keywords: Correlation; high-resolution computed tomography (HRCT); systemic sclerosis (SSc); interstitial lung disease (ILD)

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Introduction

Interstitial lung disease (ILD) is a serious pulmonary complication of patients with systemic sclerosis (SSc). High-resolution computed tomography (HRCT) is a high-sensitivity diagnostic method useful for routine detection and evaluation of ILD complications of SSc patients (1-10). Recently, Suliman *et al*. (11) has proposed using HRCT as an additional imaging investigation for screening and early

diagnosis of SSc-related ILD (SSc-ILD) in anti-centromere, antibody-negative patients with normal FVC values. Annual HRCT screening for early detection of ILD has also been suggested for early-SSc patients with high risk factors, including male gender, presence of anti-Scl-70, or absence of anti-centromere antibodies (4). Currently, HRCT, in conjunction with pulmonary function test (PFT), serves an important role in measuring SSc-ILD, making treatment decisions (10), and predicting treatment outcomes (5,12-14) and mortality (8).

While several HRCT scoring systems have been used to determine the extent of lung involvement in ILD, they basically divide into two quantification types: visual reader-based (4,10,15-17) and computer-based (18-21) scoring; although these have not yet been fully validated. Several researchers have reported a close correlation between visual reader-based and computer-based scores (2,18-20,22). Furthermore, Khanna *et al*. (5) suggested that the choice of staging system in a clinical trial should depend on the study feasibility and available expertise, rather than the quantification method used.

Cross-sectional studies have demonstrated significant correlations of different HRCT scores with other variables, including percent predicted forced vital capacity (%pFVC) (2-4,9,23), percent predicted diffusing capacity for carbon monoxide (%pDLco) (2,3,9), Health Assessment Questionnaire-Disability Index (HAQ-DI) (2), modified Rodnan Skin Score (mRSS) (3), percent of oxygen saturation at room air (%SpO_2) (4,23), and erythrocyte sedimentation rate (ESR) (4).

However, to our knowledge, only one study has reported significant correlation between 12-month changes of computer-aided HRCT scores with changes of %pFVC, %pDLco, and mRSS (3), using data obtained from clinical trials (12). Therefore, this study aimed to determine the correlation of changes (delta: Δ) of our visual reader-based HRCT score (4) with the Δ of other clinical variables—Δ %pFVC, Δ mRSS, Δ ESR, and Δ %SpO_2, from our previous inception cohort study.

Methods

Patients

This study was recruited from our previous inception cohort study (4) at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Thailand. This study included all consenting, consecutive, adult (≥18 years), early-diagnosed SSc patients [disease duration ≤3 years from the onset of the first non-Raynaud's symptom attributable to SSc including swollen skin, skin thickening, digital pitting scar, digital ulcer or arthritis (non-Raynaud's phenomenon: NRP)], from January 2010 to June 2014. All patients fulfilled the 1980 classification criteria of SSc (24); they were classified as dcSSc or lcSSc according to LeRoy and Medsger's classification criteria (25). Patients were excluded if they had an overlap syndrome [SSc with rheumatoid arthritis or SSc with systemic lupus erythematosus (SLE)].

The onset of SSc was defined as the time of the first NRP, as reported by the patient. Disease duration was calculated as the interval between disease onset and the time at study entry. At cohort entry, we recorded demographic data, clinical manifestations, routine laboratory tests, tests for antinuclear and anti-centromere antibodies (by immunofluorescence on Hep2 cells) and anti-Scl-70 antibodies (enzyme linked immunosorbent assay; ELISA), and current medications. Self-reported functional status was determined by the Thai-version of a health assessment questionnaire (HAQ) (26).

All participants underwent HRCT, echocardiograph, and PFT at study entry, and annually thereafter. Patients were seen at regular intervals of one to three months; complete data, including clinical manifestations and routine blood tests, were recorded every 6 months. Patients received all medical treatments as recommended by the attending rheumatologist, following standards of care. ILD was determined by HRCT. Estimated systolic pulmonary artery pressure (SPAP) was determined by echocardiography.

Data were obtained from the subgroup of our previous inception cohort of SSc patients who underwent PFT within 12 weeks of their corresponding HRCT at baseline and last visit. Patients were excluded if they had ILD due to a condition other than SSc. The Research Ethics Committee, Faculty of Medicine, Chiang Mai University, approved this study. All participants gave informed consent at the time of cohort entry according to the Declaration of Helsinki.

Chest HRCT scoring system

Our previous visual reader-based HRCT scoring system (4) was used to determine the extent and severity of ILD using one of two MDCT platforms—Somatom Definition, Siemens, Forchheim, Germany or Aquilion 16, Toshiba, Tochigi-Ken, Japan. Volumetric scans were performed with a high spatial resolution (1-mm thick) and interval image reconstruction in the supine position with deep

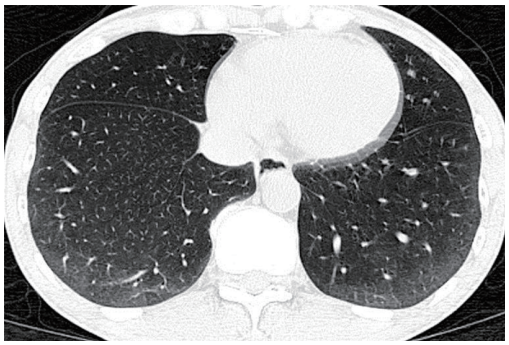


Figure 1 Axial high-resolution computed tomography (HRCT) image in a 56-year-old man with dcSSc reveals bilateral subpleural ground glass (GG) opacities in basal lungs, compatible with early nonspecific interstitial pneumonitis (NSIP) pattern.

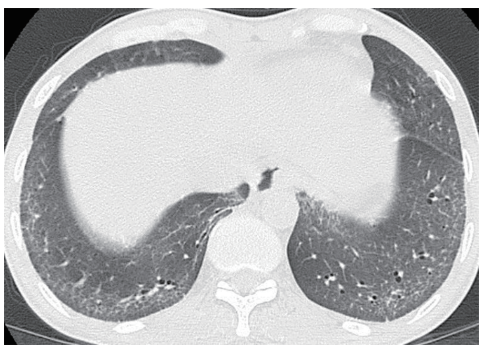


Figure 2 Axial high-resolution computed tomography (HRCT) image in a 53-year-old man with dcSSc reveals ground glass (GG) opacity, fine reticulation (Fib) and mild traction bronchiectasis (B) involving bilateral peripheral and posterior compartment of basal lungs and sparing of bilateral posterior subpleural regions, compatible with early fibrotic nonspecific interstitial pneumonitis (NSIP) pattern.

inspiration. Sampling the HRCT with 1-mm thick slices during expiration was constructed with at least six levels in order to cover the whole thorax. To exclude ground glass (GG) opacity from dependent atelectasis, prone inspiratory HRCT was performed to cover the suspected area. All images were reviewed by an experienced thoracic radiologist of 20 years (Juntima Euathrongchit), blinded to clinical and laboratory data. Soft-copy DICOM images were retrieved and reviewed with a picture archiving and communication system-PACS (Synapse FUJI-PACS; software version 4.2.200, Stamford, USA).

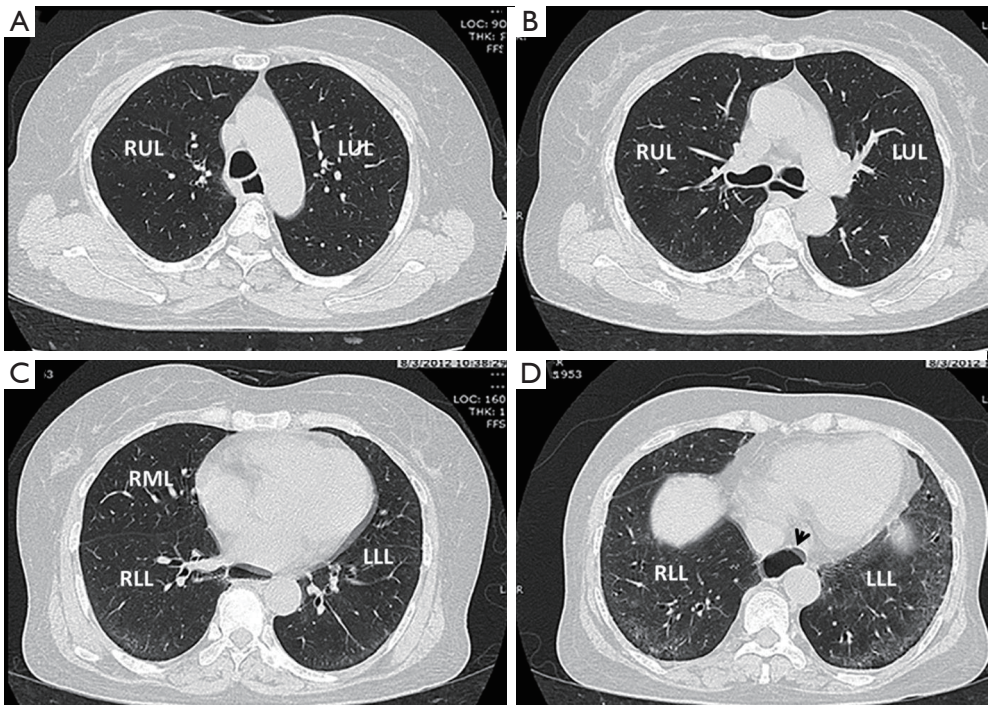
We used HRCT to categorize the pattern of the lung parenchyma findings representing ILD that were unexplainable by other causes. Parenchymal abnormalities were classified into four categories: ground-glass opacity (GG), lung fibrosis (Fib), bronchiectasis (B), and honeycombing (HC). The corresponding radiographic definitions were: ground-glass opacity (GG)—faint parenchymal opacity with preserved underlying bronchovascular structure without architectural distortion; Fib—thickening of interlobular septae or intralobular septae and traction B; B—dilatation of bronchial tree with peribronchial wall thickening; and HC—clustered air-filled cyst.

The radiographic definition of nonspecific interstitial pneumonitis (NSIP) and usual interstitial pneumonitis-usual nonspecific interstitial pneumonitis (UIP) on HRCT were modified from previous reports (27,28). The corresponding radiographic definitions were: NSIP—GG and reticular opacities (inter- or intralobular septal thickening) with or without micronodules, microcystic HC, and traction B (*Figures 1-3*); and UIP—reticular opacities and volume loss with macrocystic HC, traction B, and focal GG. NSIP distribution showed relatively symmetrical involvement of peripheral, subpleural, and basal lungs with subpleural sparing (*Figure 3*). UIP distribution was similar to NSIP, with its extent increasing from the apex to basal lungs (*Figure 4*).

The extent of pulmonary parenchymal abnormality was scored from each lobe [right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), and left lower lobe (LLL)] using a Likert scale (0=absent; 1=1–25%; 2=26–50%; 3=51–75%; 4=76–100%) modified from Kazerooni *et al*. (15). The total (t)-GG, total fibrosis scores (t-Fib), total bronchiectasis scores (t-B), and total honeycombing scores (t-HC) were calculated by summing all of the scores from all five lung lobes, ranging from 0–20. All scores were aggregated to produce a total HRCT score, ranging from 0–80 (*Figures 3*,*4*).

Statistical analysis

The data were presented as percentage or mean ± SD. Comparison of continuous variables within the same population between baseline and last HRCT were analyzed using a repeated-measure mixed model that controlled for duration. The delta variables (Δ) were calculated as T2 values (last visit) minus T1 values (baseline); T2–T1. The correlation of Δ HRCT scores with Δ PFT results and Δ of the clinical variables—mRSS, ESR, and $\%SpO_2$—were performed using Spearman's rank correlation coefficients. P values <0.05 were considered statistically significant.



HRCT scoring system	RUL	RML	RLL	LUL	LLL
Ground glass (GG) opacity	0	0	2	0	2
Fibrosis (Fib)	0	0	1	0	1
Bronchiectasis (B)	0	0	0	0	0
Honeycombing (HC)	0	0	0	0	0
Total HRCT score	6				

Figure 3 Four high-resolution computed tomography (HRCT) images in a 58-year-old man with dcSSc at level of aortic arch (A); carina (B); inferior pulmonary vein (C) and lung base (D) reveals bilateral peripheral ground glass (GG) opacities with fine reticulation (Fib) and relative subpleural sparing, which compatible with early fibrotic nonspecific interstitial pneumonitis (NSIP) pattern. There was esophageal dilatation (arrow head).

Statistical analyses were performed using Stata for Windows version 13.0 (Texas, USA).

Results

Demographic and clinical characteristics

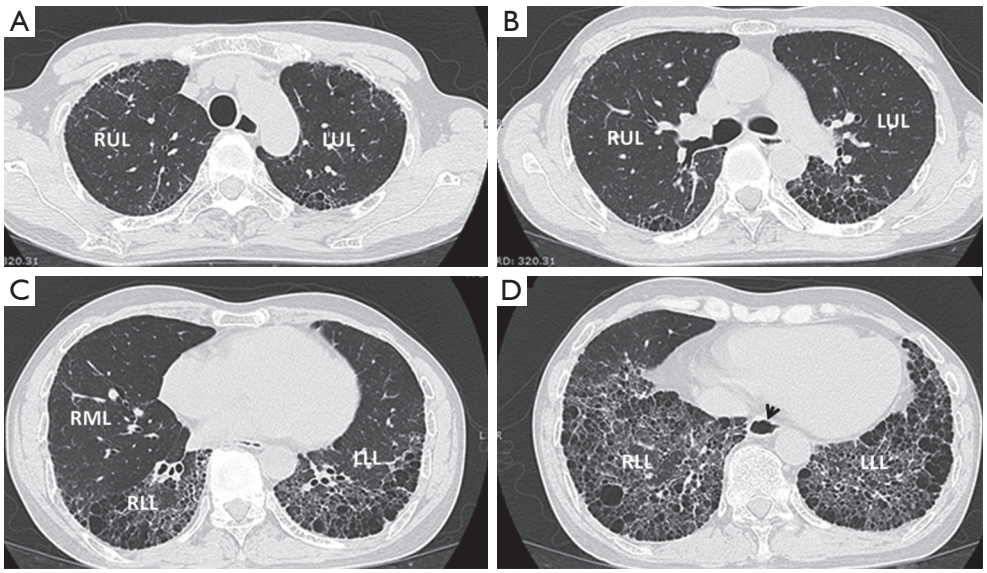
Of the 117 early-SSc patients initially enrolled, 86 were excluded (3 did not undergo HRCT at study entry, 1 later developed an overlapping syndrome with SLE, and 82 did not have available PFT results within 12 weeks of their corresponding HRCT at either baseline or last visit), leaving a cohort of 31 patients for final analysis. The characteristics of the study population are summarized in *Table 1*. The mean interval between the two HRCT tests was 16.0±7.2 months.

Comparison of HRCT scores, PFT, and clinical variables between initial and last visit

After controlling for the different intervals between initial and last HRCT, we found that Δ t-Fib, Δ t-B, Δ total HRCT score (t-HRCT), and Δ mRSS showed significant differences over a mean ± SD interval of 16.0±7.2 months; in contrast, Δ %pFVC, Δ ESR, and Δ %SpO_2 showed no significant differences (*Table 2*).

The correlation of Δ HRCT scores with Δ of other clinical variables

At baseline visit (n=31), we found significant negative correlation of %pFVC with total ground glass scores (t-GG) (r=–0.43, P<0.05), t-Fib (r=–0.56, P<0.01), t-B (r=–0.43,



HRCT scoring system	RUL	RML	RLL	LUL	LLL
Ground-glass (GG) opacity	0	1	1	0	1
Fibrosis (Fib)	1	1	3	1	3
Bronchiectasis (B)	0	1	3	1	3
Honeycombing (HC)	0	1	3	1	3
Total HRCT score	28				

Figure 4 Four high-resolution computed tomography (HRCT) images in a 48-year-old man with dcSSc at level of aortic arch (A); carina (B); inferior pulmonary vein (C) and lung base (D) reveals peripheral diffuse coarse reticulation (Fib), honeycombing (HC) and traction bronchiectasis (B) in both lower lobes, and minimal ground glass (GG) opacity at RML, which compatible with usual nonspecific interstitial pneumonitis (UIP) pattern. There was esophageal dilatation (arrow head).

P<0.05), t-HRCT scores (r=–0.52, P<0.01), HAQ (r=–0.43, P<0.05), and ESR (r=–0.41, P<0.05). Furthermore, we observed significant correlation of t-HRCT scores with HAQ (r=0.37, P<0.05), ESR (r=0.38, P<0.05), and %SpO_2 (r=–0.47, P<0.01). However, we found no significant correlation of mRSS with %pFVC, HRCT scores, HAQ, and ESR.

At last visit, the correlation of Δ HRCT scores with Δ FVC, Δ %pFVC, Δ mRSS, Δ ESR, and Δ %SpO_2 are shown in *Table 3*. We found significant negative correlations of Δ t-HC with Δ ESR (r=–0.44, P<0.05) and Δ t-Fib with Δ %SpO_2 (r=–0.38, P<0.05). However, we observed no significant correlation of any Δ HRCT scores with Δ %pFVC or Δ mRSS.

Discussion

To date, HRCT is an important measure of the extent of SSc-ILD that can be used to screen for early ILD complications (4,11), initiate treatment decisions (10), and predict treatment outcomes (5,12-14) and mortality (8) in patients with SSc-ILD. Both visual reader-based (4,10,15-17) and computer-based (18-21) HRCT scores have been developed to determine the extent of ILD. Visual reader-based HRCT scores correlated well with computer-based HRCT scoring (2,18-20,22), PFT results (2,9,19,20,23), and other clinical variables (20,23) in cross-sectional studies. Furthermore, changes in computer-based HRCT scores measuring SSc-ILD provide a sensitive outcome measure of disease progression and response to treatment (3). However, visual reader-based HRCT scoring remains an essential diagnostic tool in treatment centers with HRCT scoring expertise, but where computer-aided scoring software is not a feasible option, as suggested by Khanna *et al*. (5).

Previously, we showed that visual reader-based HRCT scoring correlated well with %pFVC, ESR, and %SpO_2 in an inception cohort study of 113 early-SSc patients with mean disease duration from NRP to first HRCT of

Table 1 Baseline clinical characteristics of the study population

Variables	Total (n=31, %)
Demographics	
Age (years)	52.3±8.8
Female gender	14 (45.2)
dcSSc	20 (64.5)
Disease duration (months)	11.7±7.1
Clinical characteristics	
ILD	22 (70.9)
NSIP	17 (77.3)
UIP	5 (22.7)
SPAP (mmHg) (n=23)	30.5±6.9
Dyspnea	
NYHA class I/II/III (n)	4/20/7
Arthritis	6 (19.4)
Large joint contracture	4 (12.9)
Small joint contracture	7 (22.6)
Tendon friction rub	4 (12.9)
Myositis	5 (16.1)
GERD	6 (19.4)
Dysphagia	10 (32.3)
HAQ	0.7±0.6
Laboratory investigation	
Hemoglobin (g/dL)	12.9±1.5
Creatinine (mg/dL)	0.8±0.2
Creatine kinase (IU/L)	233.6±192.4
Anti-Scl-70 antibody	25 (80.6)
Anti-centromere antibody	2 (6.5)
Medication used	
Baseline	
Prednisolone	7 (22.6)
Dose ≤7.5 mg/day	4 (57.1)
Other immunosuppressants*	9 (29.0)
Last visit	
Prednisolone	23 (74.2)
Dose ≤7.5 mg/day	22 (95.6)
Other immunosuppressants#	22 (70.9)

Values are presented in mean ± SD or n (%). *, cyclophosphamide (n=4), azathioprine (n=2), mycophenolate mofetil (n=2), methotrexate (n=1); #, cyclophosphamide (n=8), azathioprine (n=6), mycophenolate mofetil (n=5), methotrexate (n=3); ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonitis; UIP, usual nonspecific interstitial pneumonitis; SPAP, estimated systolic pulmonary artery pressure; NYHA, New York Heart Association functional class; GERD, gastroesophageal reflux disease; HAQ, Thai-version of a health assessment questionnaire.

1 year (4). Our findings showed, in agreement with others (2,9,19,22), although using different scoring systems, that the extent of ILD measured by visual reader-based HRCT significantly correlated with %pFVC (2,9,19,23). However, we did not investigate the long-term changes in our visual reader-based HRCT scoring with changes in other clinical variables.

Therefore, in this study, we analyzed a subgroup of our previous inception cohort population; those with paired results of HRCT and PFT at study entry and last visit, with a mean observation period of 16 months. Twenty-two of 31 (70.9%) patients had ILD at study entry and last visit. No new ILD complications were detected during the observation period. At study entry, our results showed, in agreement with Salaffi *et al.* (2), although using different scoring systems, that visual reader-based HRCT scores showed significant correlation with %pFVC, but not mRSS. In contrast, Kim *et al.* (3) found significant correlation of HRCT score with mRSS using computer-based HRCT scoring. Different study populations and HRCT scoring methods may explain these discrepancies.

In this study, over the 2-year observation periods of early-SSc patients, the change in HRCT scores—consisting of t-Fib, t-B, and t-HRCT scores—increased significantly, while Δ mRSS decreased significantly; in contrast, Δ %pFVC, Δ ESR, and Δ $\%SpO_2$ were fairly stable. Kim *et al.* (3) demonstrated greater changes in computer-based HRCT scores—from fibrotic to either a GG or normal pattern—in the cyclophosphamide group compared to the placebo group of SSc-ILD patients (mean disease duration of 3 years) from a Scleroderma Lung Study-I (SLS-I) during a follow-up period of 12 months. Furthermore, in SLS-I, the changes in 12-month %pFVC and mRSS were higher in the cyclophosphamide group compared with the placebo group (12). Our findings, as supported by others (3,12), showed that changes in HRCT scores (3) and mRSS (12) provided a sensitive indication of disease progression and response to treatment in early-SSc patients. However, our observation of no significant change in %pFVC differed from a previous study (12), which may be due to different study populations and study design. Another possible explanation may be the low sensitivity to change of PFT results compared with HRCT scores for early detection of lung disease progression, similar with the low sensitivity of PFT to detect early ILD compared with HRCT, as reported by Suliman *et al.* (11).

We found significantly negative correlations of Δ t-HC with Δ ESR, reflecting that greater changes in HC scores were associated with less remaining inflammation.

Table 2 Comparison of calculated HRCT scores and other variables between the initial (T1) and last (T2) HRCT (n=31)

Variables	Initial visit (T1)	Last visit (T2)	Absolute Δ (T2–T1)	P value
HRCT Scores				
Total ground glass	3.2±3.3	2.7±2.4	0.5±2.1	0.203
Total fibrosis	4.0±3.5	4.3±3.3	0.3±1.9	0.041*
Total bronchiectasis	2.4±3.3	2.9±3.6	0.5±1.2	0.031*
Total honeycombing	0.7±2.2	1.0±2.3	0.3±0.8	0.053
Total HRCT score	10.3±10.2	11.0±9.9	0.7±3.8	0.002*
Pulmonary function test				
FVC	2.2±0.7	2.3±0.7	0.1±0.4	0.181
%pFVC	69.0±15.9	73.8±15.4	4.8±12.8	0.081
FEV_1/FVC	87.0±7.4	86.4±8.2	–0.7±6.3	0.713
Clinical variables				
mRSS	15.4±9.9	10.5±6.9	–4.9±6.5	0.029*
ESR	34.0±25.3	28.2±21.7	–5.8±22.3	0.360
$\%SpO_2$	96.7±2.6	97.2±1.6	0.6±2.6	0.081

Values are presented in mean ± SD; delta (Δ=T2–T1). P values are from a repeated-measures mixed model that controlled for duration; *, duration showed significant effect with Δ (T2–T1) values; HRCT, high-resolution computed tomography; FVC, forced vital capacity; %pFVC, percent predicted forced vital capacity; FEV_1, forced expiratory volume in 1 s; mRSS, modified Rodnan Skin score; ESR, erythrocyte sedimentation rate; $\%SpO_2$, percent oxygen saturation at room air determined by digital probe pulse oximetry.

Table 3 Spearman's rank correlation coefficients of Δ HRCT scores with Δ other variables

Variables (n=31)	Δ t-GG	Δ t-Fib	Δ t-B	Δ t-HC	Δ t-HRCT
Δ FVC	–0.07	–0.09	0.03	–0.16	–0.03
Δ %pFVC	–0.09	–0.16	0.05	–0.15	–0.05
Δ mRSS	0.05	–0.08	0.01	–0.02	–0.01
Δ ESR	–0.02	–0.09	–0.29	–0.44*	–0.33
Δ $\%SpO_2$	0.14	–0.38*	–0.19	–0.26	–0.15

*, P<0.05; t-GG, total ground glass scores; t-Fib, total fibrosis scores; t-B, total bronchiectasis scores; t-HC, total honeycombing scores; t-HRCT, total HRCT score.

Furthermore, Δ t-Fib showed negative correlations with Δ $\%SpO_2$, reflecting that greater changes in fibrotic scores were associated with poorer oxygen saturation. To our knowledge, limited data exists on the correlation of change in HRCT score and change in ESR or $\%SpO_2$. However, our study observed no significant correlations of Δ HRCT scores with Δ %pFVC and mRSS, in contrast to Kim *et al.* (3); again, different study populations and HRCT scoring methods might be a possible explanation.

A major limitation of this study was the small sample size of early-SSc patients with sufficient PFT data at either cohort entry or last visit to correspond with the available HRCT data, given the limited availability of PFT at our institution. Another important limitation was that only a single experienced chest radiologist (blinded to clinical and laboratory data) read all of the HRCT results, although this is similar to some previous studies (4,17,23,29). Kazerooni *et al.* (15) has shown good inter-observer agreement in measuring the extent of pulmonary fibrosis; therefore, we do not think that the readings from a single radiologist bias the findings of this study. Our findings should also be interpreted with caution, given the limited follow-up period of 2 years; it is unknown whether the observed correlation persisted over longer periods. Furthermore, the use of immunosuppressive drugs after detection of ILD in our study cohort might have affected the change

of HRCT score and PFT results compared to those not given immunosuppressive drugs. However, our study is the first to investigate the long-term relationship between the changes of simple, visual reader-based HRCT scores with the changes in other clinical variables commonly used in daily practice to monitor disease progression of early-SSc patients.

Conclusions

We found that greater changes of our visual reader-based HRCT scores, rather than %pFVC, along with their correlations with changes in ESR and $\%SpO_2$, suggested that visual reader-based HRCT scoring was a useful and sensitive method for monitoring disease progression in early SSc-ILD. A larger study population with longer follow-up is needed to confirm our findings.

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Footnote

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

Ethical Statement: The study was approved by Research Ethics Committee, Faculty of Medicine, Chiang Mai University of No. 09NOV271015 and written informed consent was obtained from all patients.

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