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Original Article

Tomographic Fibrosis Score in the Patients with Systemic Sclerosis-Associated Interstitial Lung Disease

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Abstract

Background: Various visual semi-quantitative staging systems based on high-resolution computed tomography are used to evaluate inflammatory rheumatologic disease-associated interstitial lung disease. We aimed in this retrospective study to evaluate whether tomographic fibrosis score, a new visual semi-quantitative staging system, was a predictor of mortality and the relationship between tomographic fibrosis score and respiratory function tests in patients with systemic sclerosis-associated interstitial lung disease.

Methods: The patients who have been followed up at a single-center rheumatology clinic for the last 5 years and met the American College of Rheumatology / European League Against Rheumatism (ACR-EULAR) 2013 systemic sclerosis classification criteria were included in the study. Clinical data were obtained retrospectively from patient records, including patients' characteristics, pulmonary function test (forced vital capacity), diffusing capacity of the lung for carbon monoxide test, high-resolution computed tomography results, medication history, and serological test results. High-resolution computed tomography of the patients diagnosed with interstitial lung disease were assessed for the study. The radiologists scored the extent of parenchymal abnormalities (ground glass opacification, reticulation, honeycombing, and consolidation) and calculated tomographic fibrosis score and also traction bronchiectasis score for each patient.

Results: Fifty-two patients (46 female, median age 60 (Q1-Q3:47-66) years) were included in this study. The median disease duration, follow-up time, interstitial lung disease duration, and time from systemic sclerosis diagnosis to interstitial lung disease diagnosis were 80 (59-143) months, 78 (50-119) months, 63 (43-81) months, and 4 (0-58) months, respectively.

The median tomographic fibrosis score and traction bronchiectasis score of the patients were 3.08% (1.33-8.06) and 0 (0-2), respectively. There was a moderate direct correlation between tomographic fibrosis score and traction bronchiectasis score ($r = +0.472$, $P < .001$). Additionally, there was a moderate inverse correlation between tomographic fibrosis score and diffusing capacity of the lung for carbon monoxide at diagnosis ($r = -0.554$, $P = .011$).

During the follow-up period, 12 (23%) patients died. Kaplan–Meier Test ($P = 0.009$) and Cox regression analysis (B: 4.673, 95% confidence interval, 1.321-16.529, $P = .017$) revealed that tomographic fibrosis score ≥ 5% was associated with mortality. Multivariate analysis was not performed due to the small number of patients.

Conclusion: An inverse relationship was found between tomographic fibrosis score and diffusing capacity of the lung for carbon monoxide at diagnosis. The odds ratio for mortality was 4.7 when tomographic fibrosis score was ≥5%. Tomographic fibrosis score may be useful for predicting mortality and respiratory function in patients with systemic sclerosis-associated interstitial lung disease.

Keywords: interstitial lung disease, pulmonary fibrosis, pulmonary function test, computed tomography, mortality

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Introduction

Systemic sclerosis (SSc) is a chronic multisystemic autoimmune connective tissue disease characterized by progressive fibrosis of the skin and internal organs and vascular dysfunction.[1] Pulmonary involvement is common in patients with SSc and is the leading cause of disease-related death. The most common pulmonary involvements are interstitial lung disease (ILD) and pulmonary hypertension (PH).[2]

Interstitial lung disease is a heterogeneous group of lung diseases characterized by involvement of the pulmonary parenchyma by varying degrees of inflammation and/or fibrosis. The prevalence of ILD in SSc is up to 91%.[3]

High-resolution computed tomography (HRCT) has become the gold standard for the diagnosis of SSc-associated ILD (SSc-ILD) in recent years, as it correlates very well with biopsy findings. Biopsy, an invasive procedure, is not routinely recommended for the diagnosis of SSc-ILD unless another cause of lung disease such as malignancy is considered.[4]

High-resolution computed tomography is also used to evaluate the extent and pattern of lung involvement in patients with connective tissue disease. Studies have shown that especially the extent of fibrosis is associated with poor prognosis and mortality in SSc-ILD. Different HRCT staging systems have been developed to quantify the extent of fibrosis as semi-quantification by visual assessment or quantification using computer-aided methodology.[5]

Various visual semi-quantitative staging systems such as radiological fibrosis score have been proposed to date.[6] In this study, a new visual semi-quantitative staging system, tomographic fibrosis score (TFS), which is the sum of scores for ground glass opacity, reticulation, and honeycombing, was used.

We aimed in this retrospective study to evaluate whether TFS was a predictor of mortality and the relationship between TFS and respiratory function tests in patients with SSc-ILD.

Material and Methods

Study Population

The patients who were followed up at a single-center rheumatology clinic for the last 5 years and met the ACR-EULAR 2013 SSc classification criteria were included in the study.

The SSc-ILD patients older than 18 years and with no other comorbidities that could cause ILD were included in the study. The diagnosis of ILD was made when patients had chronic pulmonary symptoms and evidence of ILD on HRCT.

Written informed consent was obtained from all patients participating in the study.

The study was approved by the ethics committeeof Izmir Katip Celebi University (approval number: 27/5/2021 – 286).

Patient Assessment

Clinical data were obtained retrospectively from patient records. We evaluated patients' characteristics, pulmonary function tests, HRCT results, medication history, and serological test results.

The disease duration was defined as the time from the date of diagnosis to the date of death or the date on which the study was performed. It would be more appropriate to take the beginning of this period from the time of the first symptom onset, such as the Raynaud phenomenon. However, this was not preferred in this study because patients could not clearly remember the first symptom and onset time, which could reduce the reliability of this information.

The follow-up time was defined as the time period from the first admission of the patient to our rheumatology clinic to the date of death or the date on which the study was performed.

The ILD duration was defined as the time period from the first diagnosis of ILD with HRCT to the date of death or the date on which the study was performed.

Pulmonary function tests (PFTs) and diffusing capacity of the lung for carbon monoxide (DLCO) test performed at the time of ILD diagnosis on HRCT (within no more than 90 days) and at the time of study or death (within no more than 90 days) were evaluated. Forced vital capacity (FVC) values were used as PFTs.

The patients were evaluated for the presence of a diagnosis of PH. Since right-sided cardiac catheterization is the gold standard in the diagnosis, the data of the patients who underwent right-sided cardiac catheterization with the suspicion of PH were taken into account. The latest criteria (mean pulmonary artery pressure (mPAP) > 20 mm Hg at rest) were used to identify cases of PH.

High-Resolution Computed Tomography Assessment

High-resolution computed tomography, on which the diagnosis of ILD was first made, was assessed for the study. The HRCTs of the patients were first evaluated independently by 2 radiologists (a 4-year radiology resident and a senior radiologist with 21 years of chest radiology experience), who were blinded to the lung function data and other clinical indicators of disease severity. In case of different results, they reached a common conclusion by discussion.

While evaluating HRCTs, 6 anatomical levels were determined. The levels were as follows: (i) the aortic arch, (ii) the carina, (iii) the pulmonary venous confluence, (iv) the middle of the third and fifth levels, (v) 1 cm above the dome of the right hemidiaphragm, and (vi) 2 cm below the dome of the right hemidiaphragm.

The radiologists assessed the extent of parenchymal abnormalities (ground glass opacification, reticulation, honeycombing, and consolidation) at each of the 6 levels for each patient. They used a dedicated 3D Imaging Syngo Workstation (Siemens Healthcare, Erlangen, Germany) to analyze and score the images. The extent of each parenchymal abnormality and all lung parenchyma were manually delineated and calculated. As it is challenging to distinguish between reticulation and ground glass opacification, the 2 abnormalities were calculated together. The total score for each parenchymal abnormality was obtained by summing the calculated scores of all 6 levels.

Tomographic fibrosis score of each patient was calculated by dividing the sum of the ground glass opacity, reticulation, and honeycombing areas by the total lung area and multiplying by 100. In addition, when consolidation areas were added to the sum of the ground glass opacity, reticulation and honeycombing areas, the total lung area involved in that patient was obtained. The percentage of total lung area involved was calculated by dividing the total lung area involved value by the patient's total lung area and multiplying by 100.

The radiologists also evaluated the traction bronchiectasis score (TBS) by assigning a score to traction bronchiectasis at each of the 6 levels. The scores were as follows: 0 = none; 1 = mild; 2 = moderate; or 3 = severe. The sum

Main Points

- Interstitial lung disease (ILD) causes significant morbidity and mortality in patients with systemic sclerosis (SSc).
- In SSc patients, high-resolution computed tomography (HRCT) has become the gold standard for diagnosing ILD, as radiological findings on HRCT correlate well with biopsy findings.
- Semi-quantitative staging systems based on HRCT have been developed for the evaluation of ILD.
- In this study, an inverse relationship was found between tomographic fibrosis score (TFS), a new visual semi-quantitative staging system, and diffusing capacity of the lung for carbon monoxide at diagnosis in SSc-associated ILD patients.
- The odds ratio for mortality was 4.7 when TFS was ≥5%.

of the scores at all 6 levels was the patient's TBS, with a maximum score of 18.

The HRCT scans of the patients were also examined to identify HRCT patterns and craniocaudal and mediolateral distributions of abnormalities.

Statistical Analysis

The categorical variables of the patients were given as frequency and percentage. All continuous variables were given as median with interquartile range (Q1-Q3) due to the small number of patients in the groups. When evaluating the differences and correlations among the groups, non-parametric tests (chi-square or Fisher's exact test, Mann–Whitney *U* test, and Spearman correlation coefficients) were used.

Receiver operating characteristic (ROC) curve analysis was used to determine cut-off values with maximum joint sensitivity and specificity. Candidate predictive factors for mortality were tested by Kaplan–Meier (with Log-rank) and Cox regression analysis.

Statistical analyses were performed using Statistical Package for the Social Sciences Statistics software version 22.0 (IBM SPSS Corp.; Armonk, NY, USA).

A *P*-value smaller than .05 was considered statistically significant.

Results

The medical records of 146 SSc patients were screened retrospectively, of which 66 patients were diagnosed with ILD. Fourteen patients were excluded due to either unavailability of HRCT images or the presence of another lung disease. The remaining 52 patients were included in the study.

The characteristics of the patients are given in Table 1. The median disease duration, follow-up time, ILD duration, and time from SSc diagnosis to ILD diagnosis are also given in Table 1. Fifteen (29%) patients were diagnosed with SSc and ILD at the same time.

The patients were evaluated in terms of the drugs they used at any time during the follow-up period. The drug use rates were as follows: corticosteroid 81% (42), acetylsalicylic acid 64% (48), nifedipine 90% (47), sildenafil 14% (7), bosentan 15% (29), ilioprost 36% (19), hydroxychloroquine 52% (27), azathioprine 56% (29), methotrexate 29% (15), mycophenolate mofetil 25% (13), cyclophosphamide 36% (19), and rituximab 10% (5).

Table 1. The Characterics of the Patients with Systemic Sclerosis

Characteristics	
Female/male	46 (88%)/6 (12%)
Age (years)	60 (47-66)
Age at SSc diagnosis (years)	50 (38-61)
Limited/diffuse SSc	15 (29%)/37 (71%)
Digital ulcer presence	22 (42%)
Esophageal dilatation presence (as HRCT finding)	30 (58%)
Autoantibody positivity	
Anti-Scl-70 antibody	26 (50%)
Anti-centromere antibody	11 (21%)
Disease duration (months)	80 (59-143)
Follow-up time (months)	78 (50-119)
ILD duration (months)	63 (43-81)
Time from SSc diagnosis to ILD diagnosis (months)	4 (0-58)

The frequencies are given as numbers and percentages. The continuous variables are given as median with interquartile range (Q1-Q3).
HRCT, high-resolution computed tomography; ILD, interstitial lung disease; SSc, systemic sclerosis.

When the variables (both categorical and continuous) were compared according to gender, there was no difference other than the time from SSc diagnosis to ILD diagnosis. This period was longer in males (3 (0-35) months and 127 (4-163) months; *P* = .041).

The median FVC at diagnosis of ILD (dx FVC) and at the time of study or death (final FVC) were 77% (65-92) (n = 39) and 78% (48-96) (n = 44), respectively. The median DLCO at diagnosis of ILD (dx DLCO) and at the time of study or death (final DLCO) were 57% (43-77) (n = 20) and 61% (42-78) (n = 37), respectively.

High-resolution computed tomography pattern of lung involvement was nonspecific interstitial pneumonia pattern in 28 (54%) patients. Craniocaudal distribution of lung involvement was as upper 3 (6%), lower 45 (86%), and diffuse 4 (8%). Mediolateral distribution of lung involvement was as peripheral 51 (98%) and diffuse 1 (2%).

The parenchymal abnormalities, TFS, and TBS of the patients with SSc are shown in Table 2. Since only 1 patient had consolidation, this value was not included in the calculation. Therefore, total lung involvement was not calculated. Six (12%) patients had honeycombing (136, 34, 27, 15, 10, and 9 mm^2) and 24 (46%) patients had traction bronchiectasis.

The median TFS and TBS of the patients were 3.08% (1.33-8.06) and 0 (0-2), respectively. There was a moderate direct correlation between TFS and TBS ($r = +0.472$, $P < .001$). Tomographic fibrosis score cut-off value for TBS presence was 3.62 (71% sensitivity, 79% specificity, *P* = .023).

Table 2. The Parenchymal Abnormalities and Tomographic Fibrosis Score of the Patients with Systemic Sclerosis

Parameter	
Parenchymal abnormality	
Ground glass opacity with reticulation (mm^2)	30 (12-80)
Honeycombing area (mm^2) (n = 6)	0 (0-0)
Ground glass opacity with reticulation and honeycombing area (mm^2)	34 (14-90)
TFS (%)	3.08 (1.33-8.06)
TBS (0-18) (n = 24)	0 (0-2)
Total lung area (mm^2)	1100 (990-1181)

The continuous variables were given as median with interquartile range.
TBS, traction bronchiectasis score; TFS, tomographic fibrosis score.

There was also a moderate inverse correlation between TFS and dx DLCO ($r = -0.554$, $P = .011$), but no correlation between TFS and dx FVC ($P > .05$). Tomographic fibrosis score cut-off value for dx DLCO < 60% was 6.82 (70% sensitivity, 90% specificity, $P = .023$).

The patients were compared according to their TFS values by dividing them into 2 groups as both <5%/≥5% and <10%/≥10%. When the threshold was 5%, there was a difference between the 2 groups in terms of TBS. When the threshold was 10%, there was also a significant difference in terms of not only TBS but also dx FVC and dx DLCO (Table 3). In addition, all patients (n = 9) in the TFS ≥ 10% group were diffuse SSc ($P = .036$).

No relationship was found between the time from the SSc diagnosis to ILD diagnosis and TBS, dx FVC, dx DLCO, HRCT pattern, esophageal dilatation presence, SSc involvement type, and digital ulcer presence ($P > .05$).

When patients were compared in terms of the involvement types of SSc, TFS (3.43 (1.97-10.04) and 1.20 (0.69-6.43); $P = .024$) and TBS (1 (0-2) and 0 (0-0); $P = 0.033$) were found to be higher in diffuse type. Final FVC (74 (63-86) and 84 (70-103); $P = 0.006$) was worse in the diffuse type. While the NSIP pattern was more common (68%) in the diffuse type, non-NSIP patterns were more common (80%) in the limited type, and the difference was significant ($P = .002$). Unlike the limited type (33%), most of the patients with diffuse type involvement had esophageal dilatation on HRCT (68%) ($P = .024$). In addition, all but 1 of the 6 patients with honeycombing were with diffuse type involvement.

The patients with digital ulcers (n = 22) had longer disease duration (72 (57-84) months and 145 (77-171), $P = .001$). All 6 patients with honeycombing had digital ulcers. The patients with digital ulcers also had lower final DLCO (65 (48-84) and 47 (27-70), $P = .047$).

The patients with esophageal dilatation (n = 30) had higher TBS (0 (0-0) and 2 (0-2.5), $P < .001$) and lower final FVC (88 (74-103) and 56 (42-89), $P = .006$) and final DLCO (76 (61-93) and 50 (32-70), $P = .007$).

During the follow-up period, 12 (23%) patients died. The causes of death of the patients were pulmonary disease (6), renal disease (1), cardiac disease (1), infection (3), and cancer (1). We used all-cause death for survival analysis in this study.

Table 3. The Comparison of TBS, FVC, and DLCO Values of the Patients by Dividing into 2 Groups According to TFS Values as 5% and 10% Below and Above

	TFS < 5% n = 31 (60%)	TFS ≥ 5% n = 21 (40%)	*P*	TFS < 10% n = 43 (83%)	TFS ≥ 10% n = 9 (17%)	*P*
TBS	0 (0-1)	2 (0-3)	.001	0 (0-2)	2 (0.5-5)	.017
dx FVC (%predicted)	77 (68-95)	77 (64-84)	.544	81 (69-95)	63 (56-75)	.012
dx DLCO (%predicted)	66 (51-77)	44 (28-79)	.123	72 (52-78)	29 (26-41)	<.001

The continuous variables are given as median with interquartile range (Q1-Q3). DLCO, diffusing capacity of the lung for carbon monoxide; dx, diagnosis; FVC, forced vital capacity; TBS, traction bronchiectasis score; TFS, tomographic fibrosis score.

During the follow-up period, 9 patients underwent catheterization due to echocardiographic findings suggestive of PH, of which 5 (10%) were diagnosed with PH (mPAP > 20 mmHg). Among these patients, 3 (60%) died, all of whom died due to pulmonary causes.

Final FVC and final DLCO were worse in patients who died (Table 4).

Five (16%) of the 12 patients who died were in the TFS < 5% group (n = 31) and 7 (33%) were in the TFS ≥ 5% group (n = 21). When survival analysis was performed with Kaplan–Meier test, mortality was significantly higher in the TFS ≥ 5% group for disease duration ($P = .009$).

Cox regression analysis also revealed that being in the TFS ≥ 5% group was associated with mortality (B: 4.673, 95% CI, 1.321-16.529, $P = .017$). However, we did not perform multivariate analysis due to small number of patients.

The cut-off TFS and TBS values were calculated for the patients' risk of death. But they were not statistically significant ($P = .071$ and $P = .287$, respectively).

Discussion

Semi-quantitative staging systems based on HRCT have been developed for the evaluation of ILD, which causes significant morbidity and mortality in patients with SSc. In this study, the relationship between TFS, a new visual semi-quantitative staging system, and pulmonary function and mortality was investigated in SSc-ILD patients. An inverse relationship was found between TFS and dx DLCO. The odds ratio for mortality was 4.673 when TFS was ≥5%.

In SSc patients, HRCT has become the gold standard for diagnosing ILD, as radiological findings on HRCT correlate well with biopsy findings. Therefore, unless a different diagnosis such as malignancy is considered, biopsy, an invasive procedure, is usually not required not only in SSc-ILD patients but also in CTD-ILD patients.[4] The extent and pattern of lung involvement are also evaluated with HRCT.[5]

High-resolution computed tomography staging systems have been developed to quantify the extent of not only fibrosis but also the other parenchymal abnormalities such as ground glass opacity. These systems are also used to predict prognosis, especially mortality in patients with ILD.[7] These systems are based on visual assessment by the radiologist or computer-aided diagnosis methods.[5,8] In both methods, ground glass opacity and honeycombing are also evaluated together with fibrosis. Although the future is in computer-aided diagnosis, it is not possible for everyone to reach it today and well-validated packages are not yet available. On the other hand, visual assessment of the extent of fibrosis is semi-quantitative and has limitations because of the high intra- and interobserver variability.[9,10] However, this method can be performed anywhere by a radiologist with experience in pulmonary HRCT assessment. In addition, the development of semi-quantitative methods will also be helpful for the development of computer-aided diagnosis.

Several visual semiquantitative staging systems have been proposed to date. Kazerooni et al[11] scored the extent of ground glass opacity and reticulation (fibrosis) using thin-section

Table 4. Final Pulmonary Function Tests of Surviving and Deceased Patients with Systemic Sclerosis-Associated Interstitial Lung Disease

	Surviving (n = 40)	Deceased (n = 12)	*P*
Final FVC (%predicted)	85 (69-99)	46 (34-60)	<.001
Final DLCO (%predicted)	64 (47-80)	27 (23-57)	.032

The continuous variables are given as median with interquartile range (Q1-Q3). DLCO, diffusing capacity of the lung for carbon monoxide; dx, diagnosis; FVC, forced vital capacity.

computed tomography (i.e., HRCT) in their study published in 1997. Each lobe of the lung was scored on a scale of 0-5 for both ground glass opacity and fibrosis depending on the percentage of each lobe involved and the type of finding. They performed this scoring first with 3 selected sections (limited), then with the whole lung (complete) and compared the results of these techniques in terms of correlation with the underlying histopathology of idiopathic pulmonary fibrosis. As a result, they found that the scores obtained from both the simplified limited and the complete lung evaluation were correlated with the histopathological findings.

In 2008, Goh et al[7] proposed a different scoring system. They calculated the total extent of ILD in terms of the involved area by identifying 5 levels. They used ground glass opacity and reticulation (fibrosis and honeycombing) together in the calculation. They also graded the coarseness of reticulation according to the presence of fine intralobular fibrosis and/or honeycombing.

Takei et al[6] proposed the radiological fibrosis score in 2018. In this scoring, in which 6 levels were evaluated, reticulation and honeycombing areas were taken into account for the radiological fibrosis score. When ground glass opacification and consolidation areas were added to this score, the total interstitial disease score was obtained. In addition, TBS was calculated out of 3 for each level and the mean of 6 levels was taken as final TBS.

In our study, we calculated TFS by evaluating reticulation, ground glass opacity and honeycombing areas. Since it is difficult to distinguish, we evaluated reticulation and ground glass opacity together, like Goh's study. However, unlike Goh's study, we used 6 levels instead of 5, as in Takei's study. In Goh's study, the total extent of ILD was rounded to the nearest 5% in each of the 5 sections. The global extent of disease on HRCT was then computed as the mean of the scores, and the coarseness of reticulation was scored on a scale of 0-3. As in Takei's study, we calculated the area involved, including honeycombing, in square millimeters and proportioned it to the total lung area and obtained the percent involved area, namely TFS. We did not grade the coarseness of reticulation in our study. We also calculated TBS, like Takei et al. However, instead of calculating the final TBS by averaging the TBS values for the six levels, we obtained the final TBS by summing points of all 6 levels (out of 3 for each level; maximum 18).

While developing a new scoring system, we aimed to facilitate daily clinical use. Therefore, HRCT evaluation was performed by a senior radiologist with 21 years of chest radiology experience and a 4-year radiology resident. We also evaluated TBS, as traction bronchiectasis has both diagnostic and prognostic implications. The presence and severity of traction bronchiectasis have been shown to be an independent predictor of higher mortality irrespective of the HRCT pattern.[12]

The median TFS of the patients was 3.08% (1.33-8.06) in the study. This median value was lower when compared to the results in other studies. Since our scoring system is different, it may not be very accurate to compare it with other studies, but at least it might be informative. For example, in the study by Takei et al,[6] the total interstitial disease extent, which can be considered similar to TFS, was 10.8 (range: 6.2-21.4). We also chose smaller threshold values (5% and 10%) to categorize the patients into groups for TFS values. While determining these values, we considered the median and quartile values. The groups became more applicable to our patients with these threshold values. Goh et al[7] chose 20% as the threshold value for limited or extended involvement of lung. If we had a threshold value of 20% like Goh, only 2 of our patients would exceed this value. Although ILD is present in 80% of SSc patients in HRCT, only 30%-40% of patients are clinically evident.[13] In our clinic, patients with SSc are evaluated for ILD even before clinical manifestations. This approach may lead to early diagnosis of ILD. The fact that approximately one-third of our patients were diagnosed with SSc and ILD at the same time may be the reason why lung involvement is not yet extensive and lower than in other studies. The presence of honeycombing in only 6 (12%) of our patients may also be related to this reason. In the previous studies, the prevalence of honeycombing was reported as 17%-49.3%.[14]

Traction bronchiectasis was present in 24 patients and the median TBS was 0 (0-2). There was a moderate direct relationship between TFS and TBS ($r = +0.472$, $P < .001$). Tomographic fibrosis score cut-off value for TBS presence was 3.62 (71% sensitivity, 79% specificity, $P = .001$). In our study, no relationship was found between TBS and mortality. Of course, this result does not indicate that TBS does not contribute to mortality.

Pulmonary function tests and DLCO tests are important in evaluating the severity and prognosis of ILD. However, in some cases, such as in SSc-ILD, they may have limitations in terms of accuracy due to the coexisting pulmonary vascular changes and chest wall skin.[15] Therefore, HRCT has become an important tool to provide a more comprehensive evaluation of the extent and prognosis of ILD and is often used in conjunction with PFTs and DLCO.[16] In this study, we evaluated the relationship between TFS and PFT and DLCO in our patients. We used FVC as the PFT and evaluated the values of both FVC and DLCO at the time of ILD diagnosis and at the study endpoint or time of death. We found a moderate inverse relationship between TFS and dx DLCO ($r = -0.554$, $P = .011$). Tomographic fibrosis score cut-off value for dx DLCO < 60% was 6.82 (70% sensitivity, 90% specificity, $P = .023$). We did not detect a similar relationship between TFS and dx FVC. However, when it was evaluated according to subgroups of TFS, dx FVC values were also worse along with dx DLCO in TFS ≥ 10% group (Table 3). In addition, the final FVC and DLCO values of patients who died were lower as expected (Table 4). Diffusing capacity of the lung for carbon monoxide is known to be a more sensitive marker of early lung damage in ILD, while changes in FVC may occur later in the disease process.[17] This could result in a stronger correlation between TFS and DLCO compared to TFS and FVC. However, further studies would be needed to confirm this hypothesis.

Most of the patients in our study (71%) had diffuse type skin involvement. Nonspecific interstitial pneumonia was the most common HRCT pattern (68%) in this patient subgroup. Tomographic fibrosis score and TBS were higher and final FVC was worse in the diffuse type SSc. All of the patients (n = 9) in the TFS ≥ 10% group were diffuse SSc patients ($P = .036$). Diffuse skin involvement was present in 5 of 6 patients with honeycombing detected. Esophageal dilatation was observed on HRCT in 68% of diffuse SSc patients. Traction bronchiectasis score, final FVC, and DLCO values were worse in all our patients with esophageal dilatation (58%). The underlying reason may be diffuse type involvement. It has been generally assumed that the SSc-ILD is more severe in patients with diffuse SSc. Different results have been reported in the literature in terms of parenchymal abnormalities and esophageal dilatation depending on the type of skin involvement. In the study of Patiwetwitoon et al,[14] no difference was found according to the type of skin involvement in terms of parenchymal abnormalities and esophageal dilatation. On the contrary, there are studies reporting that parenchymal abnormalities such as honeycombing are more in the limited type. These

discrepancies were attributed to the heterogeneity of the study population and the different HRCT scoring methods used.

In the study, 12 (23%) of the patients with SSc-ILD died. Consistent with the literature, the most common cause of death was pulmonary disease.[2] We used all causes of death for survival analysis. We did not exclude patients with PH from the study (3 deaths).

Nonspecific interstitial pneumonia is the most common histopathological and radiological (based on HRCT) pattern in SSc-ILD.[18,19] Consistent with this information, the most common pattern in our study was NSIP (54%). The previous studies have not shown a clear association between radiological patterns and disease progression, mortality, and PFTs in patients with SSc.[20] No relationship was found between these patterns and mortality or PFTs in our study either. In addition, it is not always easy to distinguish between radiological patterns. The interobserver agreement for the identification of radiological patterns based on qualitative assessment was relatively poor in the previous studies. Therefore, for clinical practice, quantitative assessment of the HRCT parenchymal patterns (such as reticulation, ground glass opacity, honeycombing, and consolidation) may be feasible and reproducible.[16] Several studies have reported that HRCT parenchymal patterns were more accurate indicators of the severity of underlying pathological processes in the lung and were associated with mortality.[5] Furthermore, advantages of using the combined extent of parenchymal abnormalities (e.g., the combined extent of reticulation and honeycombing) have been reported, including ease of calculation without the need to distinguish individual parenchymal patterns. It has also been reported that these combined evaluations are also predictors of mortality.[21,22]

In the study, mortality was significantly higher in the group with TFS ≥ 5%, according to the survival analysis performed with Kaplan–Meier test ($P = .009$). It was found that the risk of mortality increased approximately 4 times when TFS was ≥5% (B: 4.673, 95% CI, 1.321-16.529, $P = .017$). However, in our study, no statistically significant cut-off value for TFS with regard to mortality was obtained ($P = .071$). In addition, multivariate analysis was not performed in our study due to the small number of patients. However, it may be possible to obtain a significant cut-off value and perform multivariate analysis, if a study is conducted with a larger number of patients.

In the study by Takei et al,[6] the cut-off value for radiographic fibrosis score to overall survival was 14.2% (81.8% sensitivity, 73.3% specificity). Goh et al[7] suggested a threshold of total disease extent of approximately 20% for survival. Although we could not give the optimal cut-off value for survival in our study, we found that TFS ≥ 5% poses a risk for mortality. We mentioned earlier why our threshold values are lower than other studies.

There were some limitations in our study. It was a retrospective study conducted at a single center. Some data could not be accessed because the information was obtained from the patient file. Since the number of patients was small, multivariate analysis was not performed for possible factors that could have an effect on mortality. Instead of evaluating with a single HRCT, a longitudinal study design could be used to evaluate changes in HRCT over time. Although we aimed to propose a practical method, it may still not be very simple. Simpler methods can be developed, such as identifying the levels that provide the most information and using fewer number of levels than the proposed six.

In conclusion, semi-quantitative HRCT staging systems, which are accessible and can be easily used anywhere in daily practice, are used to detect the extension of parenchymal abnormalities and to predict prognosis in SSc-ILD patients. Tomographic fibrosis score, a new scoring system, has been found to be related to DLCO. When TFS was ≥5%, mortality is increased 4.7 times in SSc-ILD patients. Further studies are needed to reveal the temporal variation of TFS and its relations with respiratory function and prognosis and to make it more practical.

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